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A Motor Theory of Reading: The interaction of visual and auditory language

Author

Kaestner, Erik

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A Motor Theory of Reading:
The interaction of visual and auditory language

A dissertation submitted in partial satisfaction of the requirements
for the degree of Doctor of Philosophy

in

Neurosciences

by

Erik Jordan Kaestner

Committee in Charge:

Professor Eric Halgren, Chair
Professor Victor Ferriera
Professor Vikash Gilja
Professor Phillip Holcomb
Professor Ksenija Marinkovic
Professor Bradley Votyek

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The Dissertation of Erik Jordan Kaestner is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

Chair

University of California San Diego

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DEDICATION

Emily, you have provided more support during my work the last 6 years than I had any right to hope for. To quote a better wordsmith than myself, 'You are like nobody since I love you.'

Ray and Beth, thank you for an upbringing that provided all of the freedom of opportunity and all of the freedom from want that a child could ever want.

Eric Halgren, John Polich, James Brewer, Sara Mednick, Sean Drummond, Christine Harris, and James Kulik. Each of you gave a chance to a young man that probably didn’t deserve it. I hope that the work contained herein goes at least some way toward justifying that trust.

EPIGRAPH

There is a curvature in the landscape, a color and shape that constantly frustrate the eye anxious for symmetry or linear simplicity…Every few miles of road the landscape changes; it always surprises, offering ever new vistas that surprise the eye and call the imagination. This landscape has a wild yet serene complexity.

- John O’Donohue

I am tired of knowing nothing and being reminded of it all the time.

- F. Scott Fitzgerald

The most exciting phrase to hear in science, the one that heralds new discoveries, is not “Eureka” but “Huh, that’s funny…”

- apocryphal

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Chapter 1, in part, is currently being prepared for submission for publication of the material. The dissertation/thesis author was the primary investigator and author of this material. Eric Halgren is senior author. Additional co-author's include Chad Carlson, Orrin Devinsky, Werner Doyle, and Thomas Thesen.

Chapter 2, in part, is currently being prepared for submission for publication of the material. The dissertation/thesis author was the primary investigator and author of this material. Eric Halgren is senior author. Additional co-author's include Lucia Melloni, Orrin Devinsky, Werner Doyle, Xiaojing Wu, Daniel Friedman, Patricia Dugan, Thomas Thesen.

Chapter 3, in part, is currently being prepared for submission for publication of the material. The dissertation/thesis author was the primary investigator and author of this material. Eric Halgren is senior author. Additional co-author's include Ksenija Marinkovic, Lucia Melloni, Orrin Devinsky, Sydney Cash, Werner Doyle, Daniel Friedman, Patricia Dugan, and Thomas Thesen.

Chapter 4, in part, has been published in Advanced Functional Materials in 2017. The dissertation/thesis author was a co-primary investigator. Eric Halgrenwas a co-senior author. Additional co-authors include Mehran Ganji, John Hermiz, Nick Rogers, Joseph Snider, George Malliaris, Ilke Uguz, Milan Halgren, Atsunori Tanaka, Sang Heon Lee, David Barba, Daniel Cleary, Sydney Cash, Shadi Dayeh.

Chapter 5, in part, has been submitted for publication of the material as it may appear in Language, Cognition and Neuroscience. The dissertation/thesis author was the primary investigator and author of this material. Eric Halgren will be senior author. Additional co-authors include Adam Morgan, Joseph Snider, Meilin Zhan, Xi Jiang, Victor Ferreira, Roger Levy, and Thomas Thesen.

VITA

Education

2009 B.A. with Highest Honors, Psychology	UCSD
2018 Ph.D., Neurosciences	UCSD

Research Experience

Ph.D Candidate (September 2011 – Present)
Supervisor: Eric Halgren, Ph.D. Professor, UCSD Department of Radiology.

Staff Research Assistant (December 2009 – June 2011)
Supervisor: James Brewer, M.D., Ph.D. Associate Professor, UCSD Departments of Neuroscience and Radiology.

Research Volunteer (September 2009 – January 2011)
Supervisor: Sean Drummond, Ph.D. Associate Professor, UCSD, Department of Psychiatry.

Research Volunteer (March 2009 – June 2009)
Supervisor: Sara Mednick, Ph.D. Assistant Professor, University of California, Riverside, Department of Psychiatry.

Undergraduate Research Assistant (September 2008 – June 2010)
Supervisor: John Polich, Ph.D. Professor, The Scripps Research Institute, Molecular and Integrative Neurosciences Department.

Publications (= co-first author)*

Kaestner E. & Polich J. (2011). Affective recognition memory processing and event-related brain potentials. *Cognitive, Affective, and Behavioral Neuroscience, 11*, 186-198.

Seibert T., Murphy E., Kaestner E., & Brewer J. (2012). Resting fMRI interregional correlations in Parkinson's disease and Parkinson-related dementia. *Radiology, 263*, 226-34.

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Kaestner E., Wu X., Devinsky O., Doyle, W., Friedman D., Dugan P., Melloni L., Thesen T., Halgren E. (In Preparation). The Precentral Gyrus Contributions to Early Time-Course of Grapheme-to-Phoneme Conversion

Kaestner E., Marinkovic K., Devinsky O., Doyle W., Friedman D., Dugan P., Melloni L., Cash S., Thesen, T., Halgren E. (In Preparation). The Separation and Overlap of Lexico-Semantic Processing in Auditory and Visual Language: An Intracranial Study of Single-Word N400 Effects.

Berry K., Kaestner E., Friedman D., Dugan P., Devinsky O., Thesen T., Halgren E. (In Preparation). Observation of Lip Movements during Speech Evokes Early Activation of Mouth Motor Cortex: ECoG Evidence for Mirror Neuron Involvement in Visual Speech Perception.

Conference Presentations

Kaestner E., McKenna B., Brown G., & Drummond S. (2010). Assessing vulnerability of attention in working memory during sleep deprivation using fMRI. Journal of Sleep and Sleep Disorder Research (abstract), 33, Program No. 0085.

Kaestner E. & Polich J. (2010). Affective recognition memory processing and event-related brain potentials. Society for Physiological Research Abstracts, *Psychophysiology* (abstract), 47.

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Teaching, Outreach, and Administrative

Introduction to Statistics. TA, UCSD (2007), Tim Rickard, Ph.D.
Introduction to Psychology. TA, UCSD (2012), Troy Chenier, Ph.D.
Animal Behavior & Communication. TA, UCSD (2013), James Nieh, Ph.D.
Introduction to Cognitive Neuroscience. TA, UCSD (2013), Cory Miller, Ph.D.
Mind, Brain, & Behavior. TA, UCSD (2015), Mark Kritchevsky, M.D.
Research Methods II. TA, UCSD (2015), Evan Raiewski, Ph.D.

Neurosciences Outreach Program, Classroom Volunteer, UCSD (2011-2017).
Neurosciences Outreach Program, Teacher Training Program, UCSD (2013-Present).
NeuWriteSD, Blogger, UCSD (2013-2016).

Triton Psychology Report, Editor-in-Chief, (2009), Supervisor: Victor Ferreira, Ph.D.

Awards

2012-2015	National Science Foundation Graduate Research Fellowship
2015	Rik and Flo Henrikson Interdisciplinary Collaboratories Award

ABSTRACT OF THE DISSERTATION

A Motor Theory of Reading:
The interaction of visual and auditory language

by

Erik Jordan Kaestner

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Professor Eric Halgren, Chair

Reading is learned in the presence of an already formed auditory language network. However, unlike auditory language reading is a recent cultural invention made possible by an extensive period of learning. Understanding the relationship of visual language with auditory language is key to understanding the novel human construct of reading. Articulatory motor movements are a potential bridge between the existing auditory language network and the developing visual reading network. Children who vocalize while learning to read and who understand the relationships between letters and sounds learn at a faster and more successful

rate. However, in neuroanatomical models of silent reading the precentral gyrus, associated with articulatory motor movements, is largely omitted.

The first section of the dissertation presents evidence that the precentral gyrus is involved in the dorsal reading route, putatively in grapheme-to-phoneme conversion. Chapter 1 presents evidence from a speeded semantic decision task. Word-level linguistic effects in the Precentral Gyrus and significant early phase-locking activity between the Fusiform and Precetral Gyrus were identified. Chapter 2 presents evidence from a Match/Mismatch task between sequentially presented graphemes and phonemes. Again, the precentral gyrus is implicated as a central hub by the combination of letter-specific effects, Mismatch effects, and significant connectivity with the Fusiform Gyrus. Chapter 3 examines the overlap and separation of Visual and Auditory language using a semantic decision task performed in each sensory modality. We find that while the Visual language processing that was present significantly overlaps with Auditory language processing, only a fraction of the Auditory language network is recruited during Visual language processing.

The second section details methodological advances to aid in the study of language using intracranial iEEG. Chapter 4 details the use of carbon-based electrodes to increase the possible spatial resolution that iEEG can measure while retaining high signal-to-noise ratio. Chapter 5 details a multimedia tablet which was created to facilitate increased data collection on patients without increasing the effort necessary from either patients or staff. By increasing the possible spatial resolution and the possible amount of data collected, these two chapters demonstrate how to build upon the work in the first three chapters.

INTRODUCTION

Reading has been of intense scientific interest since the beginning of modern cognitive neuroscience with lesion studies into language in the 1800s[1,2]. How the brain turns lines and curves on a page into a rich context of meaning is of particular interest because reading is a very recent development in the human history. The first visual representations of meaning being written down occurred only ~5000 years ago[3]. The ability to read and write has been confirmed to have been developed independently in at least three locations 1000s of years apart, suggesting the development of script may be a consistent consequence of the human brain and the cultural milieu it creates. That learning visual language reorganizes the human brain[4] but that language already exists in a complete form as auditory representations has led to persistent questions about the relationship between language perceived visually and language perceived auditorily. Reading appears to have developed from an opportunistic species leveraging their visual acuity, flexible cortical representations, and an already evolved auditory language system to gain a valuable new skill. Improving our understanding of precisely how the visual and auditory language systems overlap, separate, and interact is the goal of this work.

A key problem has complicated answering this question across the past century-and-a-half. The study of language is perhaps unique in that it can only be truly studied in humans. Some recent studies have found elementary language-like activity may exist in animals as well. For example, there are claims that chimpanzees can be taught the meaning of individual words in sign language[5] or that baboons can learn the statistics of written letter combinations[6]. These studies may demonstrate that the rudiments of language exist in non-humans, but surely the depth and complexity of language which makes it such an indispensable tool is exclusive to human beings. Therefore, studying fully developed and operating language is only possible in human beings, drastically limiting the research methodologies available.

This introduction will provide an overview of the evidence from the main methodologies available to understand visual language processing: Modeling, behavior, extracranial electrophysiology (EEG), lesions, blood-oxygen level dependent (BOLD) imaging, and intracranial electrophysiology (iEEG). The novel research comprising this work will focus entirely on iEEG. This is a comparatively rare methodology, but leverages high spatio-temporal resolution of neural activity allowing it to make complementary additions to the theories built by the more common methodologies.

Two main findings, and many smaller findings, will be explored in this work. They are mentioned briefly here and will be expanded upon in the work below.

First is the role of articulatory motor representations of phonemes, i.e. spoken output, and their role as an early contributor to representations of visual language. The theory that articulatory speech motor representations contribute to reading as a theory dates back to at least the 1970s[7] but quickly fell out of favor[8]. In 4 major reviews of BOLD neuroimaging across 25 years of visual language study the contribution of motor cortex to silent reading is mentioned in only a single sentence[9–12]. Here we present evidence from converging methodologies that the motor cortex is a key part of the visual language network.

Second, the neural representations underlying visual language processing in the dorsal reading route overlap to a significant but not total degree with auditory language. Language representations across the brain consist of uni-modal areas near the relevant primary sensory cortex, followed by regions with overlapping language representations. However the spatial resolution of iEEG demonstrates that often, language representations are in neighboring rather than overlapping cortex. This strongly supports models of reading which have primarily separate visual and auditory language representations by modality rather than models which focus on a-modal language representations[13–15].

Language Hierarchy: A Simultaneous Sequence of Language Representations

Language is typically described as a hierarchy which proceeds from smaller to larger units, such as from lines to letters to words to sentences. There is significant controversy about the timing and interaction of these putative hierarchical levels of identification and processing.

Although the simple model and terms elaborated upon in this section are underspecified, these broad outlines guide the more rigorous implementations of computational modeling which will be discussed in the next section. Cognitive neuroscience is dedicated to understanding the information processing computations that explain our abilities and experiences[16]. This includes understanding both the goal of the cognitive system under study and its method of achieving that goal. The goal under study in this work is the understanding of a single written word. The key contribution this work will make to these goals is biologically constraining the location of the neural representations used to achieve this goal, both in location and timing. For example, if it is found that speech production motor cortex at ~200ms is critical for representations of the letter-level, this would entail different expected computations and relationships to other levels in the hierarchy than if this computation was suspected to be located in the posterior superior temporal gyrus at ~400ms. These findings will combine with increased understanding of the neural activity in each region to refine the existing computational models for reading which for now are built almost entirely on behavioral data.

A neural representation can be understood as a pattern of activity representing a single entity. For example, a representation of the letter ‘T’ would be identified by finding a pattern of neuronal activity preferentially associated to a ‘T’ and nothing else. There are three spatial levels of these representation relevant for current cognitive neuroscience: The macro-map (>10,000um), the meso-map (1000-10,000um), and the micro-map (50-1000um)[17]. Macro-maps (>10,000um) are currently associated with representations of an overall category of stimuli, such as neighboring cortical patches for faces, buildings, objects, and letters[18]. Meso-maps (1000-10,000um) are associated more with specific aspects of the overall category being represented. At a most basic sensory level this could be different tones being represented in different cortical patches within a larger macro-patch responsive to tones[19]. Micro-maps are associated with representing individual features which make up an object, such as the decoding of lines in visual cortex[20]. Micro-maps are a very underdeveloped construct in human neuroscience due to methodological difficulties of working at such a fine spatial specificity.

Therefore, we will deal mainly with macro-maps and meso-maps in this work, concerned with locating overarching neural representations such as letters or words (macro-maps) and characterizing the putative cognitive operations in these areas (meso-maps). As the micro-map, or even individual neurons, provides the most precise information about cognitive operations, it is the ultimate goal for modeling the neurobiology of reading. With regards to micro-maps, this work will report recent methodological advances that will grant cognitive researchers the ability to work at the micro-map level moving forward. The focus at the macro- and meso-level leads to difficulty of precise interpretation, due to knowing only about differential activity and needing a variety of paradigms and rigorous controls to better understand how a particular patch of cortex behaves. An example is the finding that during sentence reading, an unsuitable syntactic construction (such as the word ‘recently’ in the sentence ‘A RECENTLY PRINCESS…’) causes differential activity at a time (~120ms) and a place (primary visual cortex) associated with visual sensory processing. Given that whether a word’s syntactic suitability is a relatively high-order concept in language hierarchy, this is surprising. However, the activity was based on how closely the word matched the expected sensory characteristics of the expected syntactic category[21], restoring activity at this time and location to its expected sensory level in processing hierarchy. This emphasizes how finding differential activity in a single paradigm does not provide the full picture of the underlying neural operations.

Below, we expand upon the proposed macro-map of visual language hierarchy used throughout the field. The language hierarchy proceeds from sensory processing to letters (‘B’ ‘OO’ ‘K’) to words (‘BOOK’) to sentences (‘READ THE BOOK’) to a larger narrative full of context. The levels in this hierarchy encompass a vast and daunting set of empirical findings and theoretical ramifications supported by cognitive operations in large portions of the brain[11].

The present work is restricted to the lower levels of the hierarchy, focusing on individual words and their constituent parts.

Visual Sensory Processing: Fast Categorization in Parallel

Before any language processing, the brain must understand what it is looking at. Early processing of visual information begins as the retina perceives patterns of light and transmits this information to V1 for processing of elementary visual features. The first response to stimuli in V1 in primates occurs at ~40ms followed by a posterior-to-anterior sweep with responses beginning in the anterior inferior temporal gyrus by ~100ms. At this early latency it is possible to see category-specific preferential responses to stimuli such as faces[22]. This speed is impressive given visual processing contains information about a large number of features including color, luminance, texture, motion, eccentricity, and bias. Despite the large amounts of information the same object can be presented from multiple viewing angles under different lighting conditions and with other sensory variations and still be reliably identified and represented neurally. This is referred to as invariant representations and is typically taken as the transition from sensory to higher-level processing. These representations appear to have a macro-map/meso-map relationship, with a super-ordinate category such as 'animate' containing separable regions preferentially responsive for faces and bodies[23]. Orthographic stimuli are processed preferentially among these category-specific representations, in an area of sensory processing specialized for foveal stimuli which is consistent with letters sensory characetristics[24]. This quick, parallel categorizing and identifying ability present in the visual sensory processing is important to how the brain rapidly and flexibly turns sequential lines and curves into letters and words.

The sensory aspect of reading can be thought about as the visual system perceiving the physical structure of multiple letters simultaneously, extracting the critical features (lines and curves), and then somewhere comparing these features to internally stored, i.e. learned, representations of possible letters[25]. Simple sensory features such as background contrast of the words or stimulus degradation affects early visual areas involved in visually perceiving letters but not language areas later and further anterior letter-preferential responses[26,27]. Of particular interest in the transition from sensory to language is the lack of a word length effect. Shorter and longer words are identified at the same latencies, but only after a period of education suggesting this parallel decoding of letters is a learned ability not a default sensory process[28]. Taken together, letters are foveated, critical features extracted, and an early and simultaneous transition from visual sensory stimuli to learned invariant language representations.

Graphemes: Transition from Visual Sensory to Visual Language

The smallest unit of visual script with meaning is a grapheme, which can be a single letter or a combination of letters (such as letters which represent a sound like ‘SH’ or a orthographic unit like ‘-ED’ as a suffix). Subtle sensory differences such as between ‘b’/‘d’ or ‘e’/’c’ profoundly change the identity of a letter string[29]. We are very quickly able to recognize letter identity regardless of their size, font, case, and position, the before mentioned invariant representation of a letter. A study which found that when comparing line shapes and letters matched on luminance, contour length and features, early visual areas from V1-to-V4 were identified that showed a preference for letters. Further the strongest letter responses overlapped with sensory areas that preferred line junctions as opposed to line segments[30]. That this transition between the lines and curves of the letter sensory experience to a confined domain of symbol representations early in the visual stream at ~160ms[31] demonstrates just how early we move from sensory processing to the language system.

Given how quickly the visual sensory aspects of reading cease to matter is a key point in the debate regarding visual and auditory language. One theory is that visual language could be learned entirely as a visual exercise, independent of the established auditory language system. This view gains traction from the recent report that a baboon could learn reading[6]. Baboons share many characteristics of human’s visual processing prowess[32], though their visual object-recognition processing does have subtle differences[33], but baboons lack the developed auditory language system of humans. They are restricted to a relatively a small set of possible vocalizations[34]. The baboons learned to discriminate words from pseudowords, and displayed increased accuracy as the pseudowords were statistically further from being word-like, suggesting knowledge of the individual letters and their sequences rather than a reliance on whole-word form identification (i.e. using 'B' 'O' 'O' 'K' to get to 'BOOK' like a human instead of just memorizing the visual symbols in whole-word form). This would suggest that the primate visual system is predisposed to be able to represent visual letter clusters as words even without an auditory language system to build upon. However, strong phonology theorists point out that the baboons overall abilities with these graphemes are still below human abilities[35].

Phonemes: Are Auditory Units Useful for Visual Language?

The speed at which visual language begins has led many to suppose that the visual language system is capable of operating without input from the auditory phoneme system. One potential connection between visual and auditory language would be in grapheme-phoneme conversion (GPC) also referred to as phonological re-coding. Phonemes are a fundamentally auditory expression of language, with both a sensory and an articulatory component. The sequence of phonemes forms a word the same as a sequence of letters forms a word. Phonemes are sensory in that the heard sequence of specific sounds leads to meaning[36]. Phonemes are articulatory in that they are produced by specific invariant motor sequences. The aspects of these motor sequences, such as tongue backing or lip rounding, are used to categorize phonemes based on the presence or absence of these motor aspects[37].

That the articulatory production of phonemes leads to variation in a phoneme's sound presents challenges for theories of linear, auditory-based phoneme perception[38]. This is because phonemes are not regularly heard in isolation, but as part of an articulatory stream which affects the perception of the sounds. For instance, the exact same tone, in this case the middle portion of a phoneme, can be heard concurrently in each ear but the participant will experience a phoneme in the ear also receiving the surrounding sounds and report an isolated tone in the other ear if the surrounding sounds are not present[39]. In another manipulation, a cough or an incorrect tone that replaces a small part of a speech sound will be incorrectly heard as the replaced phoneme sound; however, if only the cough or incorrect tone is played it will be correctly identified[40]. Additionally, visual presentation of the articulatory lips can affect the phonemic experience of identical sensory stimuli. If lips are perceived to be mouthing a ‘D’ or a ‘G’ will bias the hearer to encode the same auditory stimulus as the phoneme matching the visual articulatory movement[41]. Thus it is clear that phonemes are vocalized and heard as fundamentally auditory units, but their encoding and representation in the brain fuses some aspects of articulatory, auditory sensory, and visual sensory aspects.

The auditory phonological system may be related to the development of reading, leading to the possibility that phonemes as such are both an auditory and visual language phenomenon. During the development of these internally stored letter representations, reading ability is correlated with other linguistic abilities such as the ability to identify phonemes[42]. Further, problems with language in the auditory modality are often correlated with difficulties in reading[43]. This is taken by some to provide evidence for a shared approach and potentially shared pathways for decoding visual and auditory language.

Words: Ordered Graphemes & Phonemes lead to Word Identity & Word Meaning

Ordering graphemes into words into previously learned arrangements is the gateway to a rich set of meanings and contexts. Further, conscious language processing is geared for word processing above letter processing, i.e. the lexical above the sub-lexical. Letters are recognized more quickly when they are part of words[44], words can be recognized even when letters have been deleted[45], and words which are more frequently encountered in daily life are more easily identified[46]. The importance of the word level of processing has made it the major landmark in thinking about reading cognitive operations, splitting these operations into ‘pre-lexical’ & ‘post-lexical’.

There are two aspects to understanding a word, aspects which are not well delineated: identity and meaning. The accessing of word identity is commonly called ‘lexical access’. The theorized ‘store of words’ in the brain is often referred to as the ‘mental lexicon’, a term first introduced in 1961[47]. This ‘mental dictionary’ was theorized based on evidence from patients with lesions who were unable to understand spoken words but could talk, read, and write[48]. This separation of the ‘lexicon’ of word identity as distinct from other language operations has received supporting evidence from reversible brain stimulation which renders difficultly in identifying specific word identity even though the concept is understood[49]. This has led to a general theory that meaning and word identity have some level of neural separability. However, this view not accepted by all[50].

The idea that codes for individual words exists is described as the localized theory of the mental lexicon. The firs theories of localized lexical entries assumed word identity to be accessed as part of a serial search of the internal neural word list until the correct match of graphemes/phonemes was found[51]. A more modern view is of interactive models in which word entries are interconnected in competition and all receive feed-forward grapheme information simultaneously while suppressing their rival entries[52]. The interactive model does not posit that grapheme-word matching produce an exact match, only that a sufficient ratio between target entry activation and surrounding non-target entries is achieved. In both of these operations lexical access necessarily begins with smaller, impoverished pieces of information which are solidified with additional processing until the word is recognized[14]. This may also involve an early, familiarity-based judgement that is a ‘best guess’ based on previous language experience and the limited information available in quick lexical judgements[53].

The alternative to localist theories are distributed theories. The main argument between localized and distributed theories of reading is whether words are localized, discrete entities as described above[52] or distributed representations[54]. In distributed theories there is not a lexicon with individual word entries but rather a set of connections between phoneme/grapheme sequences and semantic meaning, with an ambiguous place for lexical access. Put simply the disagreement is whether the word stage is characterized by incoming graphemes being assessed first for similarity to a pre-learned set of words (localized theory) or are the graphemes connected directly to meaning by a set of learned weighted neural connections (distributed theory). Answering this question has been difficult as human neuroimaging currently lacks the spatial and temporal precision with which to arbitrate between these two theories. What is of importance for the relationship of visual and auditory language is where and when these representations of word identity and meaning, be there local or distributed, are accessed. Three viewpoints pre-dominate: First, word identity is believed to be represented primarily by the auditory system through phonological codes[14] which would suggest that word-level findings would predominate in the auditory cortex. Second, lexical entities are accessed by a modality-independent code[55] which would suggest that word-level findings are in neither the visual nor the auditory cortex, but the associative regions in between. Third, there exist independent mental lexicons for both the visual and auditory language (it is not clear how meaningful pictures interact with words in this viewpoint)[47].

Speech Production: From Input to Output

The idea that words produced vocally have a separable neural locus from the representation of encoded words dates back to the earliest cognitive models of language[56]. This was originally conceived as having both auditory and motor representations of the words. Further, the process of counting while performing a reading task, which should interfere with any task dependent on the speech production system, produces results consistent with separable neural loci for different reading tasks[57]. Behaviorally, a large contributor to the understanding of word reading and its relationship to auditory language has been the process of reading aloud. This presents some difficulty, as it is unclear whether auditory language effects in reading out loud are located in the reading system itself, or whether they occur during the transition from visual script to motor output.

As mentioned in the phoneme section, it is also unclear how the articulatory system relates to phonemic representations. Motor theories of speech perception posit that a motor system which co-evolved with the auditory system in developing language is necessary to encode phonemes[37]. Based on a strong relationship between each phoneme's speech motor movements and the produced sound, a system which decodes the intended motor movements from sound through covert mimicry would have strong access to phoneme identity. The problem the motor theory would solve is how co-articulation affects the produced sound; Phonemic sounds overlap and the resulting sound if influenced by multiple neighboring phonemes simultaneously[58,59]. However, this account is disputed by numerous auditory-centric phoneme decoding theories[60,61].

Cortical Representations: Columns or Patches?

The idea of a single group of neurons collectively representing neutrally a single concept has had a strong influence on thinking about neural processing and neural organization. In the cat somatosensory cortex it was found that all cells recorded in a vertical column responded to the same stimulus (e.g. either a deep or superficial stimulation of the skin). These columns were assumed to be ~500um and were intermingled in a mosaic pattern[62]. This dove-tailed with contemporary research that vertical synaptic relationships were more predominant than horizontal relationships[63]. These findings were soon extended to visual cortex where it was found that vertical neighbors always shared receptive fields. Here were found two types of columns. Smaller micro-columns ~50um in width had a shared receptive field preference. Larger columns ~500um in width were made up of micro-columns for one eye[64]. This columnar organization has found support in studies of cortical formation, where radial glia act as vertical scaffolds for cells to proliferate outward from the cerebral ventricles, setting the cortical column as the organizational unit when building cortex[65]. Taken together, this has led to suggestions of the mini-column representing a neural correlate as the basic unit of the cortex which are grouped in larger functional macro-columns.

However, decades of further study of the concept of a cortical column representing a single neural correlate have found only mixed success. Critically, evidence for cortical columns outside of sensory-motor cortex, such as in association cortex is scant[20,66]. But while a discrete functional unit such as a cortical column may not strictly exist, there is evidence for connected cortical patches at scales matching supposed macro-columns. Tracer injections in the visual cortex label a cloud of connection spanning ~500um[67]. Expanding on this, another study found that within ~500um of labeled neurons connections are less functionally specific but outside of this area horizontal connections are more functionally specific[68]. Additional research on cortical areas in an attempt to locate sharp minicolumns in the cat somatosensory cortex (e.g. the original evidence for columnar functional organization) have only found transitions that are ~350-600um wide[69]. Taken together, this provides evidence that cortical patches about the size of the originally posited cortical column play a role in the functional organization of cortex, but the sharper functional organization posited by the columnar theory may be nothing more than an epiphenomenon of cortical development. However, the concept and size of columns are still very much up for debate[70], with putative macro columns with widths of about 400um down to widths of about 50um for 'micro-columns'.

These cortical columns may underlie the fundamental cortical circuits which process stimuli in a feed-forward/feed-back interactive manner. Cortex contains multiple layers which have predictable connectivity patterns. The current work cannot make direct contributions to the question of patches versus columns, it will report methods developments which will allow for deeper study of this area. Of importance to the current language work however, is the question of reproducibility across subjects of the cortical patches involved in language representation in the brain. The neuroimaging upon which most theories of language representation in the brain are based on averaging over many subjects, which presents problems of interpretation given the variability in brain structure, within constraints, from person-to-person. For example, an iEEG study into early visual processing in humans reliably found areas specific to faces, orthographic stimuli, and numbers. While these regions were reliably present in a broad area their exact location varied across each subject[71]. A study of language critical cortex similarly found that necessary language regions were reliably located in general areas but did not have a reliable location within these regions[72].

Computational Models of Reading

Computational models of reading have settled on architecture based on a two route theory and the progression of sensory to orthographic and phonological units to words to semantics with variations on this basic sequence. The first route is an orthographic route based on visual letters accessing word identity and a parallel phonological route based on converting visual letters into their phonological representations then accessing word identity. They are built with a macro-map organization, e.g. one level decodes letters, another level decodes whole words, and often represented visually with a box-plot and arrow model. This approach has been popular in cognitive modeling of language since at least 1885[56], though the complexity of the modeling process has increased substantially with the advent of computers. With increased computational power, each macro-map 'box' can now easily include meso- and micro-map units which represent and calculate the relevant 'representation' of their level (e.g. calculating 'WOOD' at the word level from letters 'W' 'O' 'O' 'D' which are passed on from the letter level). Information thus passed along to the next representation level is termed "feed-forward" and information passed backwards to the previous representational level is termed "feed-back".

The original 'macro-map' modeling practice arose from the neuro-psychological observation that damage to specific brain structures reproducibly removed specific language functions[73]. This can be seen even in patients with intact brains undergoing neurosurgery that show specific and reversible deficits in language task performance when specific brain regions are 'knocked out' by electrical stimulation. That these critical brain regions are circumscribed, sometimes less than 1 cm in diameter, provides additional support to the neuro-psychological evidence that specific cortical patches undertake specific critical calculations for language[72,74].

Cognitive neuroscience is largely engaged in establishing what are the specific calculations carried out by different neural populations within the brain that underlie cognitive abilities, such as language[16]. This goal is made concrete by cognitive modelers such are being described below who posit specific architectures and specific calculations which generate hypotheses for testing. A major goal of the present work is to provide biological constraints for computational models of reading.

The basic dual-route architecture shared by every modern model comes from a variety of sources, but is most easily illustrated by two putative forms of dyslexia. Dyslexics were exposed to two different types of stimuli and asked to read them aloud: pronounceable pseudowords (‘LEXA’) and words with irregular grapheme-phoneme correspondence (‘PINT’). Some dyslexics could pronounce pseudowords but could not correctly pronounce irregular words. This suggested they could translate graphemes to phonemes but did not have a visual store of words in case the grapheme/phoneme correspondence was problematic. In contrast, other dyxlexics cannot read pseudowords aloud but can correctly pronounce irregular words suggesting a non-functioning ability to translate graphemes into phonemes, but an intact store of the pronunciations of previously encountered words[43].

Below we will examine the dominant models of the last 15 years.

Dual-Route Cascaded Model (DRC)

The model contains multiple layers of representation for each of the orthographic and phonological routes. For the orthographic route it contains a visual feature level, a letter level, and an orthographic word level. For the phonological route it contains a (shared) visual feature level, a (shared) letter level, an output phoneme level, and a phonological word level. The interaction between the two routes is restricted to the interaction between the orthographic and phonological word levels.

The first major theoretical assumption the DRC uses is a ‘cascaded’ processing which means that information that flows into the system is immediately ‘fed-forward’ to higher levels of processing. This means that incomplete information will cascade throughout the system, potentially causing conflict. While pronouncing the pseudoword ‘COFF, not only will the phonemic representations of ‘C’, ‘O’, & ‘F’ become active but these letters will also activate word entries it resembles orthographically such as ‘COIF’ but not activate the orthographic representation of ‘COUGH’ while simultaneously the phonological lexicon will activate ‘COUGH’ and also similar entries like ‘COT’ and ‘CAUGHT’. These conflicts between orthography and phonology lead to the participant to decide ‘COFF’ is not a word slower than if the letters matched no phonological word[75].

Another consequence of feed-forward cascaded processing combined with feed-back processing is that interactions occur not just at the same representational level, such as at the word level between the orthographic and auditory lexicons as described above, but that different levels in the hierarchy can interact. For an example of PR interacting with semantics, it has been found that the pseudoword ‘LOUCH’ will be pronounced like ‘COUCH’ if preceded by ‘SOFA’ but will be pronounced like ‘TOUCH’ if preceded by ‘FEEL’[76]. For an example of PR interacting with the lexicon, a study in Italian found that pseudowords with a grapheme which could be converted into two different phonemes, ambiguous phonology depending on context, were named slower when the pseudoword conflicted with an existing word in Italian that the pseudoword resembled[77].

The second major theoretical decision the DRC makes is to pre-specify the architecture of the model instead of engaging in ‘learning’. They rely on pre-specified representational levels, pre-specified connections between levels, and pre-specified rules. The DRC model begins with the visual features of the letters, which flow uni-directionally into letters. These letters next feed into both the orthographic and the phonological routes. The relative weighting of the two routes, i.e. both the strength of their activations and their speed in contributing information to the overall task decision, was determined by contrasting pseudoword/irregular word pairs till the system could pronounce both correctly. The two routes operate independently, connecting only at the beginning with letter identification and at the end with the phonological and orthographic lexicons.

The phonological route relies on single representations of phonemes, computed based on strict rules from each letter combination which activate single phoneme representations, though there is context sensitivity for letter combinations like ‘SH’. The grapheme-phoneme rules were based on the dominant grapheme/phoneme relationships in English. The GPC operates one letter at a time, from left to right. This flow of information from letter to phoneme is uni-directional, but from phoneme to auditory lexicon is bi-directional. It is important to note that the phonemes used in the DRC are output phonemes; i.e. the phonemes used to pronounce words are the same phonemes used to access the phonological lexicon. There are no encoding phonemes. This is the chief contrast with the BIAM model discussed below.

The orthographic system flows simultaneously from letters to the orthographic lexicon. Each letter sends excitement to each word which matches its letter and position whereas the letter inhibits each word it does not share its letter/position combination. Word frequency is modeled by a faster increase in activation for high-frequency words. Activation of an orthographic word immediately cascades to the auditory representation of this word (which then cascades backwards in the phonemes that make up this word).

Bimodal Interactive Activation Model (BIAM)

The BIAM is very similar to the DRC in both architecture and calculations. The model has two layers for each of the orthographic and phonological routes, the pre-lexicon (single letters & graphemes/phonemes) and the lexicon (single words for each modality).The main difference between the BIAM & DRC lies in the phonological route[78]. The DRC cannot well-model a phenomenon called masked phonological priming (‘CHERCH’ primes ‘CHURCH’ but ‘CHORCH’ does not prime ‘CHURCH’). The DRC needs to speed up its left-to-right letter/phoneme conversion to account for this priming, which removes its ability to name exception words (such as pronouncing ‘PINT’ differently than ‘TINT’). Another way to account for these effects was to assume the output lexicon is the phonological lexicon rather than making decisions based on the orthographic lexicon.

The BIAM solves this problem with fast mapping between letters and phoneme representations. This mapping is instantiated with a two-layer associative network which is separate from but feeds into the output phonemes used to read words aloud. The conversion is handled by converting letters into graphemes; Each grapheme is connected directly to all input phonemes. Critically, grapheme/phoneme conversion occurs in parallel in contrast to the DRC, though they do not provide reasoning for this change. It is possible that since letters are assumed to feed into the orthographic lexicon in parallel, they considered it likely that letters were fed into the grapheme buffer, and therefore into the phonological route, in parallel as well.

Division of Labor Model (DOL)

Though the DRC and BIAM both share many overlapping assumptions, the DOL family of models takes a different approach[79]. First, it denies a specific moment of 'lexical access'. Second, it denies pre-setting the model architectures, as this is supposed to allow for adding additional components in response to any modelling problems in an ad hoc manner (similar to how the BIAM adds an input phoneme level to account for problems in the DRC). These models instead rely primarily on a connectionist framework with three levels: spelling, sound, and meaning[54]. These connectionist models are based on patterns of activity, instantiated as weights between active nodes, to differentiate between possible representations. There is not a specific node that when its activation gets high enough leads to 'CAT' but rather when the pattern of activity amongst all units approaches the learned weighted activity of 'CAT', the model responds. Critically, these models learn all the weights between nodes, meaning that while all the models can perform the same tasks they all have unique though similarly constructed representations underlying this performance. This learning protects them from some issues associated with hand-wiring (like the DRC & BIAM), such as overfitting existing empirical studies. Since learning is such a critical aspect of the reading system, these models present opportunities for prediction not afforded by hard-wired models.

Orthographic Dual Route (ODR)

Though not a fully realized computational model, the ODR provides an alternative account of the dual route with two routes prior to GPC[80]. They highlight that all the previously mentioned models assume the neural representation of orthography is at the single letter level. The ODR proposes that the reading of a letters must account for the left-to-right position relationship of the letters above the simple idea of knowing what position a letter is in a word (e.g. the only knowledge a reader has is the that ‘L’ is position second in ‘BLADE’). First, the retinotopic fixation words during reading is such that words are often fixated only once and at variable locations in the retina. The brain must therefore convert variable retina locations to invariant locations within the word. Since letters are seen in parallel, identification of a letter must take advantage of multiple routes in orthography: One which is concerned with relative letter positions (‘L’ is to the left of ‘T’ in ‘LEFT’ and in ‘DELETE’) and one which is concerned with exact letter positions (‘L’ is position 1st position in ‘LEFT’ and 3rd position in ‘DELETE’).

Orthographic versus Phonological Theorists: Feedback versus Feedforward

Also not a fully developed computational model, almost all developed computational models, and certainly all in this overview, posit a weak phonological theory[81], theories of strong phonological theorists believe that phonology is the dominant form of accessing word identity[14,81–83]. To explain pseudohomophone (‘BRANE’/’BRAIN’) and homophone (‘REEL’/’REAL’) effects, they posit a secondary spelling check on the phonological lexicon[81]. Strong and weak phonologists do both agree that phonology is calculated sub-lexically and automatically. This is despite evidence that phonological effects in behavior are variable based on task and (see behavioral section). Phonological theorists are in conflict with orthographic-emphasizing feed-forward theorists. The feed-forward view rejects that feedback from higher-order areas or alternative sources of information, such as phonology, are necessary or desirable to explain a variety of behavioral effects[84]. The primary way feed-forward theorists explain effects from phonological sources of information is that the feedforward process proceeds until an orthographic word representation is recognized at which point the alternative sources are accessed as well[85].

Empirical Studies: Stimulus Types

The models discussed above have introduced important questions regarding the cognitive representations and operations which underlie reading in the brain. To explain why these disagreements would exist and to understand how they might be answered requires an understanding of the empirical evidence of reading. This evidence takes the form primarily of an intermixing of neuropsychology, behavior, and/or neuroimaging which will be discussed in the following sections. Experiments on reading using these methodologies have focused on two main manipulations: paradigms and stimulus types. Paradigms will be discussed extensively in the behavioral section; Here we explain in some detail the types of stimuli and their theorized effect on the reading system. In addition to the different types of visually spelled and auditorily pronounced words we encounter on a daily basis, there are a variety of types of sensory and linguistic controls.

False Fonts

False fonts are a sensory control which mimics many of the critical features, i.e. the sensory experience, of letters.

Consonant Strings

Consonant strings use letter combinations that are unpronounceable, such as ‘TSLK’. A critical question for consonant strings is whether these orthographically and phonologically unnatural stimuli engage the cognitive operations as words. These stimuli are discriminated as non-words faster than pseudowords[86] (such as ‘DEXA’) and reduce the facilitatory effects of semantic relatedness by their presence in a stimulus list[87]. This suggests both that pronounceability is used in word identity and in word meaning. A non-stimulus driven explanation for these effects it that participants engage in a strategic modulation to favor the orthographic route when they realize a portion of the stimuli are consonant strings. That word/consonant-strings tasks fail to engage semantic representations is further reinforced by a study which found that typically occurring effects for low imageability words in a lexical decision task, slower RT and more errors, disappears if lists include words and consonant strings[88]. Despite the lack of evidence for lexicosemantic processing of consonant strings, there are suggestions that in some orthographic systems consonant strings may engage phonological processes. Studies in Japanese report that consonant strings are ‘filled in’ with an auditory illusion of having perceived a pronounceable pseudoword[89]. However, in French, however, a more similar orthographic system to English, this effect is absent.

In neuroimaging, differences between consonant strings and words can be found in posterior visual areas[90] suggesting early discriminability between legal and non-legal orthography. Another study found a more posterior ‘letter-form area’ in the fusiform gyrus which responded equally to consonant strings and words, with increases to words relative to consonant strings found at 225ms[31]. The N400 waveform, commonly thought to index lexicosemantic processing, is absent for consonant strings in a priming task[91]. Another study using backward masked priming found that at ~200ms differences emerged in processing pseudowords versus consonant strings, and a lack of priming from illegal strings, suggesting a greatly diminished processing of illegal clusters at an early temporal point[92]. However, the N400 waveform is still present for illegal consonant strings when a sentence is read which has been taken as evidence that semantic access is still attempted for consonant strings in normal reading[93]. Additionally, consonant strings can be learned to have semantic meaning in the context of acronyms such as ‘HDTV’.

Taken together, evidence suggests an early discrimination between consonant strings and both words and pseudowords. The processing and representations of orthographically illegal consonant strings appears to occupy a low-level stage of the language hierarchy, prelexicosemantic access and possibly pre-phonological recoding. Whether they activate any sort of lexicosemantic processing on their own is unlikely. There is less evidence for phonological processing of consonant strings, but the little evidence there is suggests that in orthographies such as English at least, it does not occur.

Pseudowords

These are pronounceable non-words, such as ‘DEXA’, which follow all pronunciation and spelling rules but have not been encountered before. Therefore they cannot access meaning or lexical identity, except for faint access through neighboring words (e.g. ‘HAKE’ might cause some lexico-semantic activity for words such as ‘RAKE’, ‘CAKE’, etc.). These words have traditionally been assumed to rely on the phonological route for processing, particularly in pronunciation experiments, since they cannot have been encountered previously and therefore have no representation in the visual lexicon. This theory received an early rebuke in a review of neuroimaging experiments found no brain areas where the response to words was always greater than pseudowords[10]. While it is not clear how lexical identity and semantic meaning are impacted by pseudowords, the networks underlying each representation are consistent[94].

Homophones & Pseudohomophones

Homophones are words that have the same sound but are spelled differently such as ‘DO’ and ‘DUE’. Pseudohomophones are pseudowords which are phonologically a word, such as ‘KAYK’ which is phonologically identical to ‘CAKE’. Both these stimuli are primarily used to examine the phonological route, due to the conflicts they can cause when a these linguistic stimuli are phonologically identical to words which are orthographically distinct, homophones, or non-existent, pseudohomophones.

Orthographic Statistics

Words and letters have statistics having to do with their frequency of occurrence, their orthographic and phonological similarity to other words, and their semantic meaning similarity to other words.

Repeated Words

Repetition priming uses the same stimuli multiple times to investigate the encoding of various levels of the language hierarchy. Repeating a stimulus leads to two main empirical regularities: 1) Improved behavioral performance in the form of faster response times and increased accuracy and 2) decreased neuronal activity in task engaged cortical regions[95]. The neuronal activity decreases are observed both in humans with fMRI[96] and in single-cell recordings in animals[97]. These facilitation effects can be observed at long time intervals, such as decreased cortical activity following one stimulus presentation after 3 days[96], faster picture naming remaining after 48 weeks[98], increased picture identification remaining after 17 years[99]. These effects are also automatic, persisting in amnesiac patients who showed increased priming effects in pictures naming after 7 days[100]. Animals under anesthesia still show repetition effects of decreased neuronal firing[101]. The increase in response speed is also independent of direct attention to the stimulus[102]. Thus repetition priming has robust behavioral and neuronal effects that are stable over long time periods and appear to occur automatically without conscious effort.

Several different theories have attempted to explain how decreased neuronal activity could lead to better behavioral performance. The first is that the activity curve is faster, mirroring increased behavioral speed, which leads to a decrease of overall activity despite a similar magnitude peak. However, this is not found in studies of human brain activity to repeated stimuli[103]. A second theory is that only the most relevant cells continue firing after repetition priming and the loss of irrelevant cells leads to the appearance of an overall neuronal response decrease. However, the decrease is firing rate is observed across all measured cells in a population[104]. A third theory takes the feed-forward/feed-back nature of the cortex to propose that feed-back predictions decrease feed-forward activity. In support of this theory, evidence has been found that when frequent repetition are expected repetition effects are stronger[105]. A complementary theory to how the feed-forward/feed-back connections interact is that repeated stimuli engender increased neural synchrony between regions. This has been found in monkeys, finding decreased neuronal firing after repetition priming in addition to but the remaining spikes were more synchronized to local LFP[106]. Therefore it is likely to be a combination of both oscillatory activity and feed-forward/feed-back interaction which suppresses activity in repetition priming.

Behavioral Studies

Behavioral experiments rely on two main measures of brain function: response accuracy and response time. Differences in either of these measures between experimental conditions are taken to be informative about cognitive operations in the brain.

Behavioral Studies: Naming

One of the main sources of behavioral evidence in reading is the naming task which has participants vocalize a string of letters. It's use with in clinical settings with lesion patients reading either exception or pseudowords was one of the main pieces of evidence used to ground the dual-route theory reading. It has been found that reading words is faster than pseudowords and high-frequency words are read faster than low-frequency words[107]. Additionally, Naming of pseudohomophones is faster than pseudowords[108]. Taken together, both orthographic and phonological familiarity with a letter-string leads to faster naming.

Behavioral Studies: Lexical Decision

The second major task family, lexical decision task presents a series of pseudowords and words (ROYM, ROOM, etc.) and asks the participant to make judgements about the lexical identity of the stimuli. Early lexical decision studies compared lexical decision and naming response times to search for whether the same processes underlay both tasks. In English, varying the phonological complexity of a word did not affect lexical decision response measures[107,109,110]. English letters and phonemes are not tightly coupled, and pronunciation for two very similarly spelled words can differ. For example, the same word stem 'INT' has two different sounds depending on whether it in the word 'PINT' or 'MINT','TINT',GLINT', etc.

Studies in English fail to find a response time difference based on the ambiguity of a words phonological representation. These studies found that regularity of a word affected the naming latency, presumably due to the ambiguity encountered by the phonological route, but that lexical decision latencies were unaffected[111,112]. Another study replicated that irregular sound-spelling correspondence only affect naming but not lexical decision response times and further found that this delay due to irregular correspondence was only present for low-frequency words[109]. Further evidence was found in Hebrew where the lexical decision task response times were unaffected by phonological complexity but naming was slower for phonologically complex words[113]. These studies were interpreted as evidence that phonological effects were only present in naming, which emphasizes the phonological route, but were absent in lexical decision presumably because it relied mainly on the orthographic route.

Phonological effects and semantic effects interact in that pronounceability affects semantic influences in the lexical decision task. When consonant strings are used as foils, the semantic relatedness effect decreases[87]. Another study found that semantic aspects of a word affected lexical decision response times, but only in the presence of pseudowords but not consonant strings[114]. Finally, words with multiple meanings had faster reaction times than words with a single meaning and this effect is increased when pseudohomophones are included as foils[115].

However, several difficulties exist in the use of the lexical decision task to probe the phonemic representations of words. The behavioral approach cannot fully rule out a role for phonological access as even though the orthographic route may be used in decision criterion, the phonological route may still be active. Second, the lexical judgement task may not require full access to a word's identity and semantic meanings, but rather reflect a familiarity judgement[53]. This drawback can be minimized by requiring a judgement based on semantic meaning of a word (i.e. 'is this an animal'?) to ensure full access to a word's identity and meaning.

Behavioral Studies: Semantic Decision Task

A semantic decision task asks the participant to decide whether a word is a member of a category, such as whether 'TRUCK' is an 'automobile' or whether 'TREE' is an 'automobile'. It can also include a component that asks the participants to make a decision regarding an attribute of the word, such as what size the word the object represented by the word is (e.g. is 'TRUCK' larger than a 'shoebox'). Both of these manipulations ensure the participant is engaging in the full representation of the word and not just performing a familiarity judgement.

Phonological effects have been found in semantic decision studies. Participants produce more mistakes when a word is homophonic to a category, e.g. mistaking 'ROWS' for a 'flower' or 'SUTE' for 'clothing'[116,117], though patients were often able to avoid these mistakes. It is important to note that a pseudoword such as SUTE has no direct lexical access, signaling that the phonological route has the ability to make contact with a word's meaning independent of the orthographic route. Some of the semantic error findings were clarified by a study which found these errors were mostly restricted to either low-frequency words or small semantic categories[118]. However, another follow-up study found that the majority of homophonic errors could be explained by orthographic factors, e.g. many of the supposedly 'phonological' mistakes involved swapping 'EE'/'EA' like replacing 'TEACH with TEECH', and that the overall magnitude of the effect was dependent on orthographic similarity between pairs[119]. Taken together, these results point to phonology having potential access to meaning but do not convince that this is a dominant form of the system.

Behavioral Studies: Masked Priming

Priming involves displaying another stimulus before the target stimulus in order probe how the prime and target interact. Priming experiments can use any of the naming, lexical decision, or semantic decision paradigms. Various aspects of priming can be manipulated, including whether the priming stimulus is consciously perceived. This is referred to ask 'masked priming', such as when a word is presented shortly (15-60ms), masked with a visual pattern, and then the target word is presented. The participant will only consciously perceive the target word, but reaction times to the target can vary based off the properties of the prime. Phonological effects can be demonstrated by priming with can be phonologically similar stimulus (MAYD->XXXX->MADE) or graphemically similar stimulus (MARD->XXXX->MADE)[120–122]. These experiments found that both graphemic and phonological masks decreased response latency, with phonemic primes being more effective than graphemic primes[122]. These experiments have been used to argue that phonemic activation occurs early and is an automatic part of visual word reading due to participant behavior being modulated by unconsciously perceived stimuli. A meta-analysis of all of these effects finds that the behavioral effect of masked priming is reliable, but very small (~10ms)[81], but it cannot be ruled out that non-findings by groups the authors were unfamiliar with may erase that small effect.

To examine the timing of these manipulations follow-up studies varied the timing at which the prime and target are presented relative to each other. For example, a study which found increased response speed in a naming task when priming a target with a semantic homophone ('FROG' primed by both 'TOAD' and 'TODE') when the prime was exposed for 50ms but only the correctly spelled prime was effective when the prime was exposed for 250ms[123]. This result counterintuitively demonstrates that a longer visualization time is necessary for the orthographic system to correct the phonological system's error. Another study found that phonological priming with homophones ('TOWED' primes 'TOAD') and pseudohomophones ('TODE' primes 'TOAD') occurs at stimulus-onset asynchronies of 30 & 60ms as well as the longer 250ms[83]. Combining both these studies together, this result appear to show that sublexical phonology is calculated quickly and does not rely on lexical orthography but that lexical orthography will correct pseudo homophone errors if given enough time. However, both these studies used naming which is guaranteed to activate the phonological system so it is not possible to fully rule out that silent reading would not show these effects.

An important consideration with priming experiments is to make sure the visual processing of the stimuli is well understood. For example, increasing the luminance of a prime can triple the priming effect size when holding the duration of a prime constant[124].

Behavioral Studies: Transposed Letter Effects

These studies attempt to answer the question about how the brain codes letter position. When pseudowords are created by switching two letters ('JUGDE') they are more difficult to reject as non-words than other pseudowords[125]. In priming, 'JUGDE' will prime 'JUDGE' to a greater degree than replacing two letters like in 'JUNPE'. Further this effect is more pronounced when the letters are in central locations ('JUGDE' versus 'JUDEG')[126]. Another study replicated this transpose priming effect and further found that deleting a letter also provided priming ('MIRCLE' primes 'MIRACLE')[127]. Beyond just activating the word which resembles the transpose-pseudoword in form, these priming studies show that the meaning of the word receives some activation from the transpose pseudoword as well. For example, 'JUGDE' will prime 'COURT' very similarly to the real word but 'JUDPE' will not[128].

Additional studies have demonstrated that this effect was not only restricted to neighboring letters, but extend to a range of positions. When transposed letters are consonants, they can be switched across multiple spaces and still produce priming effects ('CANISO' primes 'CASINO') but not vowels ('ANAMIL' does not prime 'ANIMAL')[129]. Having a subset of the letters present provides priming as long as the relative position of the letters remains solid (e.g. 'ARICT' primes 'APRICOT' but 'ACIRT' does not)[130] however deleting too many letters removes priming[131]. In the opposite direction adding letters to words still primes (e.g. 'JUASTICE' primes 'JUSTICE')[131]. The effect of adding letters appears to be linear, with the more letters added the worse the performance[132]. Altogether, this has been taken as evidence of fast, relative letter position processing in the orthographic route as opposed to the slower, precise letter position processing in the phonological route.

Behavioral Studies: Consistency

Given strict GPC rules, a word can be either regular ('TINT','GLINT','MINT') or irregular ('PINT'). However, a second way to conceptualize regular/irregular is the consistency of a word; A word can be graded on a continuum from consistent to inconsistent. At the simplest definition, consistency means proportionally more neighbors of the word are pronounced similarly and inconsistent words have the opposite proportion. Words that are inconsistent are named slower[133]. The effect is largest when the neighboring consistent words are low-frequency and the neighboring inconsistent words are high-frequency. This is modeled by neighbors cascaded activation in the phonological system either being facilitatory, many consistent neighbors activating similar phonemes, or inhibitory, many inconsistent neighbors activations dissimilar phonemes[47].

Behavioral Studies: Repetition Priming

The number of intervening items decreases the facilitation of repetition priming for known words down to a stable floor after 3 intervening non-prime stimuli but after only 1 intervening unknown pseudoword[134]. Both time between repetition and number of intervening items have been theorized to make independent contributions to the decay of repetition facilitation.

Behavioral Studies: Articulatory Suppression

This task involves having participants perform a paradigm while repeating to themselves some meaningless stimulus, such as counting or saying some word repeatedly. This will occupy the articulatory motor and planning muscles. In a paradigm where participants attempt to recall stimuli viewed under normal circumstances participants remember less words if they are phonologically similar, such as homophones, or is the words have more syllables. Under articulatory suppression these phonological effects disappear. The interpretation of these results is that occupying the articulatory mechanisms blocks visual words from being phonological re-coded and creating memory conflicts[57].

In a task asking participants to make either semantic judgements (‘MOURN’ is like ‘GRIEVE’), visual judgements (‘HEARD’ is like ‘BEARD’) or phonological judgements (‘TICKLE’ is like ‘PICKLE’), an early paper showed that counting delayed the phonological judgement by an additional 150ms beyond the delay to the semantic or visual task[135]. Another task with children and adults asked them to make semantic judgements or phonological judgements about word-picture pairs. Articulatory suppression affected the rhyme judgements but not the semantic judgements in both groups[136]. Another study on phonological judgements for both pictures and words was found to be disrupted by articulatory suppression, but not by repetitive chewing or listening to other speech[137].

However, the interpreting these findings implications for phonology are made more difficult by another line of research using articulatory suppression along with whole-word phonological representations. When comparing whole-string letter sounds (such as deciding if ‘PALLIS’ sounds like a word), no effect of articulatory suppression was found on response time, though an increase in errors was found. Another interesting result is that deciding if non-words were homophones showed no response time increase when articulating, but deciding if words were homophones led to an increase in response time to non-word levels[8]. A study in children showed a pseudo-homophone effect error effect that was consistent across articulatory suppression but was removed for poor readers when articulating[138]. Finally, a study in which lists containing phonological confusability were remembered less well across words, pseudo-homophones, and pseudo-words, all of which showed no effect when articulating. Interestingly, pseudo-homophones were remembered better than pseudo-words both when articulating and not[139]. When comparing information read versus information heard, phonological similarity effects were present for heard but not for read stimuli when articulating[140].

Taken together, these studies offer a strong demonstration of the disrupting effects of competing use of the phonological output system on phonological re-coding under some, memory and phonological judgements, but not all, lexical access for pseudo-homophones, task conditions. Results from this manipulation could be interpreted as reading has access to both articulatory and receptive phonological representations.

Behavioral Studies: Stroop Task

Besides questions about the timing of phonological recoding in the hierarchy of lexico-semantic access, there is a question regarding the automaticity of phonological control. A process which would result in an error can be conceived of as a race between a stop signal and the process itself running to completion[141]. An early behavioral task, the Stroop task, shows that visual word reading completes before it can be shut down and in time to adversely affect color recognition. Participants identify the color of letter-strings, but are slower to identify a color when the word formed by the letter string contradicts the color it is printed in[142]. The 75% increase in response time reported in this story despite the participant knowing that each word was a mismatch displays the automaticity and speed of visual word reading. An interesting note is that despite claims of the evidence for automaticity of visual reading presented by Stroop interference stronger interference is actually associated with worse reading skills[143]. Paradoxically, this finding provides even stronger support for the automaticity and speed of visual word reading, because slower readers are assumed to have greater interference because the visual word is accessed concurrently with color name instead of before as in skilled readers[144].

The question is whether this automatic access can proceed down both the orthographic and phonological routes, or whether it is restricted. The orthographic route, that is a visual-based route, is shown to be capable of automatic lexico-semantic access by replicating the Stroop effect of orthographic languages in logographic symbol-based languages[145]. Indeed, the interference effect was larger in a logographic language, Chinese, than an orthographic language, English[146], which suggests that the less involved phonology is in reading the greater the interference effect. Teaching participants novel symbols also leads to a Stroop interference effect[147].

For the phonological route, pseudohomophones (‘BLOO’ instead of ‘BLUE’) have been reported to cause a Stroop interference effect[148]. Another study replicated the interference effect for pseudohomophones similar to words, but found a faciliatory effect for only visual words and not pseudohomophones[149]. This suggests that pseudohomophone lexical access is delayed relative to visual word lexical access, as the faciliatory effect would necessitate access before color access based on the computational model noted above. A study in English-Hebrew bilinguals found that pseudowords which were transliterations of Hebrew color names (i.e. ‘KAHOL’ sounded out is ‘BLUE’ in Hebrew, but is not visually blue in English) also reliably cause Stroop interference effects[150]. Teasing apart the lexical and semantic access aspects of phonology, a study had both color words (‘BLOO’) and semantically related to color nouns (‘SKIGH’), which demonstrated similar Stroop effects to visual word versions of the same manipulations[151]. Taken together, both the orthographic and phonological routes appear to have automatic access to lexico-semantic color concepts. However, it is suggested by the lack of faciliatory effects with pseudohomophones that the phonological route access is slower.

Behavioral Studies: Strategic Control

The variety of behavioral findings, and their sometimes questionable reproducibility, has led some researchers to suppose that the visual reading system will dynamically alter its behavior based on task and stimulus. For an example of task factors, a double lexical decision is faster when a word is paired with a word that sounds the same (‘GROAN’ and ‘GROWN’ presented) but if the participant is aware that pseudohomophones are included in the stimulus list (‘BRAIN’ and ‘BRANE’ presented) the homophone effect disappears[152,153]. The interpretation is that the brain is aware of the high rate of errors induced by the pseudohomophones phonological route capture and downregulates the use of this route. However, the evidence is equivocal as others have not been able to replicate these findings[154]. A further complication is where in the processing stages these task-dependent differences manifest. The previous two studies above suggest that the phonological route is cut off at the sub-lexical stage whereas another study suggests that the sub-lexical stage of both the phonological and orthographic route are automatic and task differences manifest in response criterion applied to lexical stage of the decision making process[155]. A final example comes from Italian in which lexical influences were found in GPC when words and non-words were mixed, but these effects disappeared and overall response times decreased when only non-word were included. This suggests that the phonological route was the only route used when non-words were present, but both routes were used, increasing response times and orthographic influences, when both non-words and words were present[77]. Another study found that the facilitatory effects of high-frequency words were strongest and reaction times slowest in the presence of pseudo-homophone trials as well as quicker reaction times for pseudowords than consonant strings. This suggests increases in difficulty with the more phonologically word-like a stimulus is[156].

For an example of stimulus factors word frequency it has been found that certain effects of spelling-sound ambiguity, such as slower naming times for irregularly spelled words, are only true for low-frequency (unfamiliar) words and are not observed for high-frequency (familiar) words[109].

Taken overall, strategic control is thought to operate at the level of weighting the parameters of the system instead of dynamically altering the architecture of the system. Put another way, the overall phonological and orthographic routes are static but somewhere within these routes the brain is able to alter the speed, weighting, or decision criterion to maximize performance. An additional example to the ones reported above is that the presence in a stimuli list of first position irregular grapheme/phoneme affects (‘CHEF) the speed of naming for regular words and non-words relative to naming speeds when the list includes later position of irregular grapheme/phoneme correspondence (‘COOK’)[157]. Model simulation with a slowed phonological route, to avoid first position mistakes, accurately modeled this data. These data show that during the task, depending on the filler stimuli present, the participant will generally shift their response criterion in performing the task which will affect performance for all stimuli, even those that are separate from the experimental manipulation. However, an fMRI study of lexical decision in the presence of different foils showed increases across the inferior frontal gyrus for increased phonological difficultly, suggesting that the phonological route is not down-regulated but instead involves more processing in the presence of conflicting information[158].

Behavioral Studies: Eye Fixation

Although not relevant to interpreting the results from the present studies, due to single word presentation being used, some discussion of naturalistic reading will follow. Eye fixation studies show that the average fixation on a word while reading is 250-300ms, with overt vocalization fixating ~50ms longer than silent reading, placing constraints on the expected time course of word reading[159]. Because oculomotor calculations take time, the literature on eye movements assumes lexical access is underway by ~150ms in order to calculate the next movement. Most information necessary to read is available in the first 50ms of fixation[160]. Coincidently, this 50ms time is the amount of time it takes for the visual information to move from the eye to V1[161]. The saccade distance is ~8 letters in length and the length of the saccade is about 30ms, which is a smaller distance than during scene inspection[162]. However, the preparation for making a saccade is ~150-170ms as evidenced by the delay between instruction and execution of a saccade[163]. During this period, saccadic suppression occurs during which new visual input is suppressed[164]. This is most impressively shown by a study completely replacing the text during the 20ms of saccade which had no effect, in contrast replacing the text for the 20ms immediately after the saccade disrupted reading[165]. However, linguistic processing of the information is not suppressed during this movement as evidenced by a lack of difference in response times and accuracy between longer and shorter saccades[166].

Where to saccade to during reading is based partially upon necessity of information. For instance, content words are fixated >80% of the time whereas function words are fixated <40% of the time[167]. This can be potentially explained by longer words being fixated much more frequently[168]. Another feature is regressions, with eye movements back toward previous parts of the text. Though usually quite smaller (2-3 letter spaces) sometimes they can be large skips back to a part of the text which was not understood. Poor readers engage in more backtracking than skilled readers[169].

Because during reading there is more information available than during single word, or serially presented word, experiments it is important to note that a key part of naturalistic reading is missing from the present work. First, it appears that no information is gained from text lines above or below the currently attended line[170]. Typically, a number of letters to the left of the current fixation and a greater number of letters to the right are available for processing. To the left, typically the end of the presently fixated word is the stopping point of processing (3-4 letters)[171]. To the right is typically 14 letters available, with letters but not words providing the best description of what is encoded to the right. Further, 3-4 letters presented to the right had about as much influence on reading the next word as presenting the whole word suggesting the most informative information is present in the closest 3-4 letters to the right[172]. When texts are hard to understand, such as giving elementary school readers a college text, the perceptual span shortens[173].

How the information to the right, i.e. those 3-4 most informative letters, is used has been investigated in overt articulatory reading. A study was conducted in which a parafoveal word was changed during fixation, which the eye can't detect, and the participant was asked to read the new, fixated word. If the old word and the new word shared an initial 2-3 letters naming time was facilitated[159]. This same effect is obtained when the eye remains fixed, but the parafoveal word is moved into the foveated area (simulating a saccade)[174]. A clue that this integration of information from pre- and post-saccade is not visual comes from a study which alternated case every time the eye moved ('ChAnGe' turned to 'cHaNgE') which did not differ from a condition in which not case changing occurred[175]. Further centering the linguistically informative level on the letter representation, a study comparing orthographically similar and semantically similar words found a facilitative effect of orthography but not of semantically related information[176]. A phonological preview benefit is also found in hearing skilled readers but not in deaf readers[177].

Because some information is available parafoveally, and because online processing is a constant process, there are a number of orthographic, phonological, and semantic factors which influence processing. Readers fixate longer on low frequency words (a 20ms effect) and low-frequency exception words were fixation longer still (30ms effect) but no effect for regularity on high-frequency words[178]. The effect of word frequency on fixation time is not present in non-reading contexts such as visual search[179]. While reading for meaningful words, participants made more errors to pseudo-homophones than pseudowords and fixated for a shorter period of time indicating that phonological regularity is taken into account when calculating eye movements[180]. But participants also fixate on homophones longer than pseudowords suggesting that while phonological information has an influence on fixation it is not the primary determinant[181].

There are priming effects as well. If semantically related terms are present in the same clause, fixation times decrease[182] and the second time a text is read fixation times decrease[183]. The familiarity effect of decreased fixation is more pronounced for low- relative to high-frequency words[184]. These findings all point to eye fixation being a proxy for difficultly in integration into a semantic context. For example, the likelihood of a word being lower (‘assaulted her with his knife’ being lower probability ending than ‘stabbed her with his knife’) leads to longer fixation times[185].

One model[186] of reading suggests that and early familiarity check triggers calculation of the next saccade whereas a complete ‘lexical access’ is required to trigger movement. In this model, actual ‘attention’ begins to shift to the right before the actual eye movement which explains the parafoveal information gathered. The high-spatial (foveal) information is used for lexical processing and the low-frequency information (word boundaries) is used for saccade targeting. Backwards saccades are triggered by failure to integrate into the larger semantic context.

Behavioral Studies: Miscellaneous

Another examination is speech detection, where a noise-vocoded stimulus is presented with corresponding visual text and the participant is expected to detect targets in the auditory stimuli. When the visual text phonologically matched the sounds participants were more likely to hear a human voice in the noise, even if one was not present[187,188]. This effect disappears if when print preceded speech, as opposed to simultaneous presentation, suggesting that the effect is transient and fast.

The letter search task is another demonstration of phonological influence, where the task is explicitly orthographic in that participants must say whether a target letter is present. For example, they are presented with 'BRANE' and asked whether the letter 'I' is present. Participants are more likely to make a mistake when the phonological form of the word includes the target letter (BRANE -> BRAIN), which is called a pseudohomophone or make times longer when the pseudohomophone did not include the latter (GAIM->GAME)[189,190].

A stroop study found that pseudohomophones and words caused equal delays when incongruent compared to pseudowords. However, when color and word were congruent, they were faster than when color and pseudohomophone were congruent. This suggests phonological recoding is a slower process than lexical access[149]. Using the stroop in bilingual cross-script homophones, i.e. a word in one language which sounds like a color in the other language,

Extracranial Electrophysiology: The Time-course of Reading

Lesion and neuroimaging data implicate wide areas of the cortex as being involved in encoding of words. However, despite the implicit hierarchical assumptions about language as it is commonly thought about, both models[47] and neuroanatomical data[191] suggest simultaneous activity across hierarchical levels and involved neural regions. Further it is not clear if different hierarchical levels are sepearated cortically; It is possible that the same area may process information at multiple levels. Attempting a more precise localization is difficult but can reveal important information regarding how meaning is extracted from sensory processes.

The extracranial study of electrophysiology has proceeded upon the same model basis as the rest of the field, largely examining putative pre-lexical and post-lexical component processes. However, with the added component of time, which behavior, lesion, and neuroimaging are blind to, they can inform in ways that the aforementioned data cannot. The time course of modeling is very important for resolving disputes between models, such as the speed of the phonological route, and for making sure models are neuroanatomically grounded. Additionally, the processing of visual and auditory information differs in temporal terms. Visual processing is much stronger on simultaneous representation of space whereas auditory processing is much stronger on temporal coding, which should inform theories on how these two different systems interact[192]. This has led to hypotheses about a coarse-grained visual parser for the orthographic route based on spatial relationships and a fine-grained parser for the phonological route based on sequence[80].

There are two main types of electrophysiology below, both generated by the same fluctuating electrical currents in the brain but with very different spatial properties[193]. The first is electrophysiology (EEG)… The second is magnetoencephalography (MEG). MEG measures the neuromagnetic field produced by the electrical activity in the brain, aided by magnetic shielding and by measuring the magnetic gradient instead of the field itself. The MEG is only sensitive to tangential electrical sources, often associated with sulci, whereas EEG is most sensitive to radial sources, often associated with gyri, though it does measure tangential sources as well. MEG produces tighter spatial measurements because it is not smeared by the skull but this leads to only minor increases in spatial specificity[194,195]. However, modeling the inverse solution greatly advances the ability to spatially localize both EEG and MEG[196].

Electrophysiology Studies: The N400

The N400 refers to a cognitive component beginning ~250ms and peaking around ~400ms which reflects a widespread period of accessing word meaning and integrating this meaning into the larger cognitive context[191]. It was first reported when sentence ending words did not match the context of the sentence ('He spread the warm bread with socks')[197]. Loosely defined, the N400 refers to potentially many stimulus-related cognitive operations active between ~200-600ms with widespread neural populations. From this viewpoint the N400 complex is defined broadly by sensitivity to the match of stimulus meaning and the current cognitive context rather than specific neural populations and specific cognitive operations[198]. The sensitivity appears mainly attached to meaning integration with the ongoing context; Having a semantically incongruous word produces an N400 no matter where in the sentence it occurs. Grammatically unexpected errors did not produce an N400[199].The amplitude of the N400 is modulated by manipulating the ease of integrating a word into a context. N400 amplitude linearly increases with how expected a word is even if all the words are legal endings to the sentence[200]. Further, the N400 decreases in amplitude as a sentence develops and constrains expected words[201]. These effects exist outside the sentential, to a larger discourse context. For example, sentences in which two endings were equally valid in the single sentence but only one ending was valid in the context of a paragraph of information elicited an N400 in the paragraph but not when the surrounding information was absent[202].

The context did not necessarily have to be associated with a sentence-level processing; If five words were presented and a fifth word in a list did not match the semantic category of the previous four an N400 was generated[203]. Indeed, the context overrides truthfulness in generating an N400; The sentence 'A ROBIN IS NOT A BIRD' produces no N400 but 'A ROBIN IS A TRUCK' does produce an N400[204]. The N400 is evoked to pronounceable pseudowords but not to unpronounceable consonant strings[205] and overall being of larger amplitude for pseudowords than real words[206] suggesting an attempt is still made at integration if a stimulus if judged to be potentially meaningful.

There is an ‘access’ versus ‘integration’ debate, regarding whether the N400 reflects accessing long-term representations such as words or if the N400 reflects processes following this supposed access (i.e. the integration). An early study suggested that the N400 was not affected by masked repetition priming, suggesting that the N400 was a conscious process (integration) instead of an automatic process (access) since it was disrupted by masking the prime[207] (However, see the ‘Masked Priming’ section below for many counter studies). Other studies argue for extremely early lexical access such that later activity reflects other processes. Some studies report word-frequency effects occurring at ~130ms preceded by 10s of ms by lexicality effects[178]. Another study found word length effects emerging ~100ms and word-frequency effects emerging ~150ms[208]. A study using a regression analysis for multiple orthographic characteristics found a lexicality effect emerging ~160ms, with letter n-gram frequency and word length ~90ms, and lexical frequency ~110ms[209]. While these early effects are impressive, it is unclear that using lexical frequency to index ‘lexical access’ is a valid approach.

In the ‘access’ corner of the debate are a variety of studies showing that a variety of factors which appear to ease lexical access also decrease N400 amplitude. For instance, low-frequency words (assumed to be more difficult for lexical access) show a greater N400 amplitude than high-frequency words (though only in early sentence positions)[201]. Full repetition also decreases N400 amplitude[210]. Pseudowords also evoke a larger N400, taken to demonstrate a frustrated attempt at lexical access.

The N400 does appear to be an active integration process in more than just language. After participants learned the spatial locations of objects in a virtual-reality simulation, if the object was switched to another location this would generate an N400[211]. But when two different contexts are combined, such as having a sentence end with an abstract picture instead, the N400 is not present suggesting the brain is unable to even attempt to integrate the meaning[212].

Despite its generic nature, N400 effects can tell us a great deal about how language is processed. For example the N400 to single-word priming and words in sentences are qualitatively identical[213]. This places lexico-semantic access as part of a broader, larger set of processes than a simple mental lexicon view would suggest. Indeed when comparing the effects of high-level versus low-level factors interactions can be found in the N400 timing. However, when comparing single-word priming and sentence-level processing there are separations of processing pointing to a semantic integration context for the N400 rather than a general violation of any set of rules. Hemispheric differences were found when selectively presenting visual language to one visual field or another[214]. This is part of a larger body of work which points to a later component, the P600, as being primarily concerned with syntax-specific violations rather than meaning-specific violations[215].

Examination of N400 effects in the presence of violations of either an orthographic, phonological, or semantic nature showed the timecourse of how the brain detects violations in a sentential context. An N270 was revealed whenever orthographic violations were detected. The N400 effect was detected to both pseudowords and semantic violations, but not to pseudohomophones suggesting the brain failed to detect the violation by 400ms[216].

One interesting finding about sentence violations is that the earliest differences may result from slight deviations from expectations versus larger expectations. One study compared differences of sentence-ending pseudowords (‘CEKE’ versus ‘CAKE’) which showed positive differences emerging at ~130ms. The earliest effect reported for consonant strings was a negative deflection ~170ms [217].

Electrophysiology Studies: Lexical Decision

Comparing waveforms from pseudohomophones with carefully matched orthographic controls (e.g. 'ROZE' versus 'ROFE') reveals differences as early as ~150ms based on phonological lexicality[218].

Electrophysiology Studies: Semantic Priming

Semantic priming in electrophysiology is used to examine the effect of a word's meaning on the processing of a following word (i.e. 'CAR' primes 'TRUCK'). This contrasts with form-level priming which could rely on a lower-level of processing. It was found that semantically related words decreased the negative deflection peaking at ~400ms with effects beginning ~225ms[219,220]. This has been interpreted as the first word priming the semantic meaning system for processing the following word which follows, leading to decreased activity. Follow-up studies have attempted to determine the time course of this semantic priming.

The speed of possible semantic priming effects, some as fast as ~170ms[221], has led to questions about how quickly semantic processing begins in visual word reading. One way to investigate timing of semantic priming is with masked priming, which indexes priming effects very quickly after presenting the prime, not giving much time for the priming to develop. Semantic priming has been reported with primes as short as 50ms, which are not modulated by stimulus list relatedness manipulations[222]. The N400 has also been reported to be modulated by primes of 67ms backward masked and unperceived[223].

Another set of papers have disputed the early effects of semantic priming, instead suggesting repetition priming is quick while semantic priming is more delayed. Priming below conscious perception (40ms) led to repetition priming effects in the N400 while priming above conscious perception led to both repetition and semantic priming, both with a SOA of 500ms[224]. A follow-up study with priming at 70ms found repetition priming beginning at ~250ms but failed to find semantic priming for related words[225]. Comparing semantically, phonologically, and orthographically related words, only phonological similarity caused priming effects at ~200ms and increased reaction time while effects ~400ms was affected by all 3 manipulations[226].

The disconnect between repetition and semantic priming leads to questions about letterform, word identity, and meaning contributions to priming effects not easily answered. Another approach is to use bilinguals to see if priming across languages shows a similar time-course to semantic priming within a language. In French-English bilinguals, robust repetition priming of words by the other language was found across multiple tasks and brief prime exposures[227]. These effects began ~250ms and continued through the N400 in the subjects second language[228].

Electrophysiology Studies: Masked Priming

This task primes a target word with a rapidly presented letter string, which can be either full repetition, partial repetition, or unrelated to the target. The earliest effect occurs at ~150ms with a more positive deflection as posterior electrodes on the right side to full repetition words than unrelated words, with a graded effect for partial overlap[229]. Interestingly, this early component timing has been replicated in single-letter studies which found effects of letter-case which would suggest sensitivity to visual features instead of orthographic representations. Visual similarity started ~120ms with case-independent letter identity, i.e. invariant representations, not emerging till ~220ms[230]. Another study manipulated both size and font, finding that only font affected the priming component, localizing the invariant representations somewhat farther along than basic sensory processing such as size[231]. This component is also sensitive to overlap with letter positions between prime and target: if the prime and target are offset by one place either forward or backward this priming effect is decreased, although components later than 150ms were unaffected by this manipulation[232].

At ~250ms, a negative deflection with a more widespread scalp distribution is sensitive to priming. This sensitivity is present to both words and, to a lesser extent, pseudowords. Further, there is no N250 to auditory targets in a cross-modal priming paradigm[233]. Another study found this N250 was present for both full and partial repetitions[229]. This effect is not sensitive to visual sensory manipulations locating this effect as orthographic instead of sensory in nature[232]. In addition to being orthographic, the N250 is sensitive to phonology as well showing a priming effect for pseudo-homophones relative to orthographic controls ('BAKON' primes 'BACON' but 'BAFON' does not). Transposed-letter primes also show an effect at the N250 ('BARIN' primes 'BRAIN' but 'BOSIN' does not). The phonology manipulation shows a later and more anterior distribution than the orthographic manipulation[234].

Two later components, the at ~325ms and ~400ms were thought to index the lexico-semantic processing. The ~325ms and ~400ms effect is sensitive to differences between words and pseudowords but not between pseudowords and non-repeated stimuli[229]. The effect at ~325ms holds true even when the prime is a pseudohomophone of the word[234]. At the ~400ms timing, masked primes modulated activity if they were identity ('CAR' primes 'CAR') or semantically related ('CAP' primes 'HAT')[224]. Interestingly, while the sub-lexical (~150ms & ~250ms) and lexical (~325ms & ~400ms) effects are present at shorter SOA's, only the lexical effects are present at longer SOA's. Interestingly, only the longer prime durations led to both a sub-lexical and lexical effect while shorter prime durations led to only a sub-lexical effect[235].

Electrophysiology Studies: Cross-modal Studies

There are two ways to investigate the cross-modal language. The first is to compare processing of auditory and visual language. At ~400ms, the effect of visual-visual and visual-auditory repetition priming was the same at 67ms of priming but stronger for the visual-visual priming at the 50ms timing. Interestingly, the repetition occurred only at the lexical stage of processing and not before[233]. Comparing visual-auditory and auditory-visual repetition priming, it was found that visual-auditory effects were earlier and stronger than auditory-visual effects[236].

When comparing the N400 for both auditory and visual processing and the N400 complex tends in general to be qualitatively similar for both auditory and visual language processing[198]. It has been found in lexical decision tasks that having a prime leads to an earlier

N400, also larger and longer lasting, for auditory words than for visual words[91]. Taking co-articulation into account may lead to the N400 being delayed to the same latency range as visual words[237]. This received further evidence when comparing the earlier N400 generated by natural speech sentences compared to the smaller N400 from sentences with words spaced by 750ms[238]. It is also possible that the visual lexico-semantic access is quicker than auditory. When priming auditory words with visual words N400 priming effects were present even when presentation of the two modalities was simultaneous. But when priming a visual word with an auditory stimulus, even though behavioral priming effects were evident at simultaneous presentation N400 effects were present only at 200ms delay of the visual word[239].

The second way to compare is to ask patients to do fundamentally auditory tasks, such as rhyme judgements, or fundamentally orthographic tasks, such as letter judgements. An early study comparing meaning and phonology found a semantic-incongruity effect at 350ms, a classical N400 effect, and a qualitatively similar but statistically non-significant effect at the same latency for rhyme-incongruity[240]. Another study confirmed this finding with that rhyme judgements caused a difference of rhyming/non-rhyming stimuli from 300-600ms which was not present for a letter-matching task[241]. A follow-up study confirmed this timing of rhyme effects and found a decreased effect when the word pairs included an irregular word, perhaps reflecting a diminution of the phonological route when irregular words are included in the task[242]. Perhaps most interestingly, this rhyme-incongruity effect latency is the same when the rhyme/non-rhyming stimuli are pictures instead of words[243]. A study comparing rhyme (‘MAKE’/’ACHE’) and visual stem similarity (‘SAID’/’PAID’) found reaction times were faster when comparing visual stems than rhyming, and that judging whether a word rhymes when it is visually similar causes increases in response time and increases in errors; These errors are increased with shorter ISI. The P300 latency matched the results of the behavioral latencies, with latency effects noted >500ms (earlier effects were not discussed)[244]. Taken together, these studies are suggestive of late phonological effects in a rhyming paradigm, at least ~50-100ms later than the times reported in masked priming studies.

During a rhyming judgement task a deflection ~320ms at temporal sites was present for pronounceable but not non-pronounceable stimuli. During a lexical decision task, differences emerged at a ~350ms deflection between words and pseudowords. Differences between semantic classes emerged at ~450 suggesting a cascade of processes from orthographic to phonological to lexical identity to semantic[245].

The ~300ms timing off the rhyming effects was used as the basis of a theory that placed the N400 semantic effects in the context of a phonological mechanism, lending credence to the strong phonological theory. However, the N400 complex is observed in congenitally deaf adults who show the same N400 complex to incongruous sentence endings in American Sign Language which produced a similar waveform between visual written language, auditory language, and visual sign language[246]. Given this data, it appears that the intuition that the N400 reflects a multitude of distributed processes that are simultaneously active appears to account for different effects being localized to the same window.

Electrophysiology Studies: Miscellaneous

Comparing non-target oddball responses differing at the visual, phonological, lexical, and semantic levels revealed a cascaded time course. At ~170ms a negative deflection at posterior sites was larger for orthographic than non-orthographic stimuli.

Electrophysiology Studies: Anatomically-constrained Electrophysiology

Finding the anatomical location of the electrophysiological components described in this study is notoriously difficult. For example, motor movement ERPs can be larger over the ipsilateral hemisphere which is the opposite of the location of the neural generators for that movement[247]. Similarly with visual patterns, the amplitude is highest over the ipsilateral hemisphere which is again contralateral to where the neural generators the signal come from[248]. However, making some assumptions can improve the ability of extracranial electrophysiology to be able to be localized. For early sensory responses, assuming a small number of generators may be appropriate[249]. However, for more distributed processing such as reading where widespread generators have been located, a novel approach is necessary to effectively localize neural generators. Because it is known how neural anatomy effects measured electrophysiology, e.g. generally that it is generated in grey matter perpendicular to the scalp[250], using anatomical knowledge from a subjects MRI can localize electrophysiology with some confidence[251].

Using this anatomically constrained approach allows for investigation of electrophysiological sources during reading, in complement to intracranial studies. A single word study of novel and repeated words found differences emerging around ~250ms increasing to ~385ms in the posterior and anterior ventral occipito-temporal cortex, lateral occipitotemporal cortex, orbitofrontal and IFG cortex, and precentral sulcus with weaker effects in the superior temporal gyrus, intraparietal sulcus[196]. A second study found bilateral occipital activation beginning at ~170ms in ventral occipitotemporal cortex, ~230ms in the STS and ITG, ~350ms in the anterior temporal and orbitofrontal cortices. Auditory stimuli began activation began at ~55ms in STG, ~100ms perisylvian activity, and ~250ms anterior temporal & IFG activity. The visual activity was more left-lateralized while auditory activity was bilateral. Auditory repetition effects emerged in superior temporal plane and anterior temporal areas at ~225ms while visual words merged ITG & IFG at ~225ms. Later effects were more overlapping in left anterior temporal region and IFG emerging at ~400ms. Effects were overall much weaker in the visual condition[252]. A study of silent word stem completion found posterior visual activity in posterior visual cortex ~100ms, spreading to lateral temporal cortex ~210ms, and IFG ~ 370ms. Repetition differences emerged at the ventral temporal cortex at ~200ms, lateral temporal ~250ms lateral temporal cortex, and IFG ~325ms[253].

A study of sentences found an onset of incongruity effects in Wernicke's area ~250ms and anterior temporal areas ~270ms, Broca's area ~300ms, and dorsolateral frontal cortex by

~320ms. Incongruity effects were found most strongly ~300ms in anterior temporal and IFG areas, which were left lateralized. Word position differences were also found, much smaller, in similar areas but also included ventral temporal areas. Word frequency effects were restricted to left anterior temporal areas. Content/Function word differences emerged in ventral temporal areas as early as ~105ms[254].

A number of anatomically constrained studies have examined the latency of IFG involvement in reading. A study of masked priming localized phonological priming as greater than orthographic priming in the precentral gyrus and pars opercularis at ~100ms in a priming paradigm[255]. Another study found VWFA activity beginning ~200ms which was co-activated with areas in the IFG and middle-temporal gyrus[256]. A less convincing study focusing on the beta frequency range and found that the pars opercularis showed response beginning ~130ms which was about the same time as middle fusiform responses[257]. A study using dipoles attempted to demonstrate posterior ventral occipito-temporal areas received top-down information from the IFG to the ventral area within ~200ms[258].

Extracranial EEG can be localized with some very rough estimation. One such study found greater deflections for phonological detection task than a semantic categorization task in the STG starting at ~160ms. Starting at ~240ms the semantic decision task showed a greater deflection in the anterior temporal lobe, mostly driven by increased connectivity with the posterior inferior temporal lobe. The frontal lobe showed early deflections and increased feedback connectivity with both the putative phonological and semantic focused regions[259].

Electrophysiology Studies: Lesions

In patients with a split brain, regardless of whether the sentences were presented in the right or left visual fields the patients were able to process whether the word made sense. All patients displayed typical N400 to anomalous sentence endings for right-field stimuli, but only patients with an overt speech capability in the right hemisphere showed an N400 to left visual field stimuli[260]. The initial negative waveform found in left posterior electrodes when words are presented is a negativity ~180ms. This negativity does not occur for patients with callosal lesions when stimuli are presented in the left visual field. However, when non-word stimuli were presented, deflections were observed ~150ms in each hemisphere[261].

Lesions: Studies of Critical Language Anatomy

Acute Lesions

The initial studies of language focused on patients with lesions to areas which disrupted their ability to understand and produce speech. The relationship between auditory and visual language was implicated in patients that failed to both understand language in either modality despite both vision and hearing being undisturbed[73]. This suggests that language may have an overlapping 'hub' somewhere downstream from the early sensory areas. Similarly, patients that experienced difficulty in producing coherent spoken sentences, though no trouble in producing words, faced similar difficulties in producing coherent written sentences though they had no difficultly in producing written letters[73]. Here again, though the motor areas are distinct, overlapping difficulties suggest the existence of an overlapping hub somewhere downstream from motor production.

However, despite the evidence for a central hub both the sensory and motor areas of visual and auditory language are separate. Damage to auditory sensory areas that spares putative language areas leaves the ability to read and write intact though the patient has no ability to understand auditory language. Conversely, damage to the occipital regions underlying vision leaves auditory language intact[1]. The suggestion from all these lesion studies is an overlapping language system, differentiated in modality only by the sensory regions and motor regions used in their perception and production.

However, other lesion studies with a different locus of damage suggest the possibility of a separation of language faculties. There are reports of patients with 'word meaning deafness' in auditory language but not written language. Several patients have been described who could hear and repeat or write down words auditorily but not report its meaning (likely just using their phonological system to store and repeat the phonemes or transfer the phonemes to graphemes for writing). However, these patients could read words and report their meaning[262,263]. This could either be explained by a very specific point of damage between the phonological and common lexicon or in the destruction of an auditory lexicon but a spared visual lexicon.

Damage to primary visual sensory areas can lead to the inability to understand written words, even though they can be copied and written perfectly[1]. This suggests a separation of the visual processing of lines and curves downstream of the language processing regions. This has been localized to the left side of the brain[1,264,265] due to the absence of damage to the corpus callosum allowing the right side to send visual information to the left hemisphere. It has been reported that 96% of aphasics have damage to the left side of the brain[266].

Progressive Aphasia: Semantic Dementia

Most lesions studies on reading have focused on patients with sudden cortical disruption which is supposed to remove a key element of the reading network. However, progressive deterioration of cortical areas also informs our knowledge of the reading network as well. The deterioration of the anterior temporal lobe, most predominant in the dominant language hemisphere, leads to a syndrome named ‘semantic dementia’. Patients diagnosed with semantic dementia show grey matter reduction in the anterior temporal pole but also middle and inferior temporal gyri as well as the fusiform gyri[267]. A study using PET found that hypo-activation was spread beyond grey matter damage in the anterior temporal lobe to also include orbitofrontal areas[268].

The most striking feature is loss of specific semantic knowledge; Patients were able to sort items into ‘non-living’ and ‘living’ but failed to sort at a more specific level such as ‘kitchen item’ versus ‘non-kitchen’ item. Speech production grammar and syntax as well as repetition is not impaired but frequent word finding difficulties are observed. A frequency effect is observed across language conditions, where higher-frequency words produced fewer errors[269]. In addition to the frequency effect, difficulties with words with low imageability are more pronounced in semantic dementia.

In reading, though visual perception is preserved patients with this syndrome exhibit surface dyslexia, the inability to read incongruent words and regularization errors but a preserved ability to read pseudowords[270]. In a meta-study of 51 cases of semantic dementia, a composite score of semantic performance accounted for ~50%-to-~87% of the variance of exception word performance, strongly tying progressive loss of semantic knowledge with loss of phonological knowledge of exception words[271,272]. These exception word vocalization difficulties are also present in spelling[273]. However, there are also reports of patients with preserved irregular word pronunciation even in the face of impaired semantics performance in semantic dementia[274,275] and Alzheimer's[276]. A study found two patients with semantic dementia, one who committed regularization errors of irregular words but intact pseudohomophone performance and another patient with the opposite pattern, which suggests different localizations of progressive deterioration[277]. Taken together, this evidence points that progressive semantic dementia proceeds in a variety of ways, which defies easy interpretations about the contribution of the anterior temporal lobe and the abstract concept of 'semanticss to lexical knowledge and phonological recoding. There is a strong need for anatomical localization of damage for theoretical interpretation.

When comparing semantic dementia to patients developing Alzheimer's, patients with semantic dementia show preserved recognition memory of a previously seen object but impaired naming of the object. In reading, only the semantic dementia group, again in contrast to the Alzheimer's patients, showed increased reading latencies for low-frequency words and word length[278]. Overall, semantic dementia and Alzheimer's show overlapping damage to the anterior hippocampus, but spared posterior hippocampus in semantic dementia[279]. Comparing overall cortical damage, semantic dementia is much more anterior, focused on the temporal and ventral frontal areas and overall is very separate from Alzheimer's damage which includes more posterior and parietal regions[280]. Comparing semantic dementia to patients with pure alexia, who typically have posterior occipito-temporal damage, reveals pure alexia patients to suffer from letter-based errors, early visual processing, in contrast to semantic dementia patients suffering from regularization of inconsistent words[281].

Neuroimaging: Anatomical Organization of Reading

The two route theory of reading dominates thinking in interpreting 30 years of language functional Magnetic Resonance (fMRI) and Positron Emission Topography (PET) neuroimaging[10–12]. Early lesion studies motivated the development of the dual route model of reading and studies using PET and fMRI have attempted to flesh out the story by allowing investigations of normal functioning readers. Both fMRI and PET measure changes in blood-related parameters such as blood flow, blood oxygenation, and glucose metabolism. Therefore, they rely on hemodynamic changes to understand how the brain functions. Tying these blood changes to either electrophysiological data or neuronal spikes is difficult and a matter of some debate. For instance, study in the rat somatosensory cortex found a non-linear relationship between BOLD signal and neuronal spiking and BOLD level increases even after neuronal spiking has peaked[282].

BOLD neuroimaging during language tasks has led to several common findings include left occipito-temporal (l-OT) activation, inferior and ventral temporal areas (vT), middle and superior temporal areas (mT & sT), the supramarginal/angular gyrus (SM), the pars opercularis (PO), and the pars triangularis (PT). These are commonly split into the orthographic route (l-OT, vT, mT, PT) and phonological route (sT, SM, PO).

Because neuroimaging relies on contrasts, the sections below will be grouped based on the type of contrast. Broadly, contrasts used in reading research typically involve one of several such contrasts. First are stimulus differences. Since different letter strings have different properties (‘SPECY’ a pseudoword versus ‘SPECK’ a word or ‘RUN’ a verb versus ‘TEN’ a number), these contrasts are assumed to be treated differently by the brain. Within the same set of stimuli, there are different statistical characteristics that have been useful in investigating activation, such as frequency of occurrence in the language. There are also multicultural contrasts where speakers of languages with different characteristics are assumed to privilege one way of processing over another in informative ways. The second set of contrasts involve paradigm differences. These can try to activate one purported route more than another, such as rhyme tasks versus semantic decision tasks. The third type of contrast involves information available to the participant. These include priming, where you enter information into the system ahead of the target stimulus or conflict where you put in conflicting information to see where the conflicts cause changes. There are also tasks which withhold information, like leaving out letters or mixing up letters to see how the various systems compensate for the missing information.

Different anatomical reviews take different different approaches to classifying activation patterns, animated by their particular interpretations of the dual route theory. Jobard et al.[10] looked at a number of contrasts, such as word versus pseudoword, and assumed one set of stimuli would be more likely to activate the orthographic route while the other would be more likely to activate the phonological route. For instance, words would be more likely to activate the orthographic route since they have an orthographic representation while pseudowords would be more likely to activate the phonological route as they have no orthographic representation. Using this approach they found that every area was a mix of activations.

Ventral Occipito-Temporal (vOT)

The L-vOT area has been dubbed the ‘Visual Word Form Area’ due to its preference for orthographic stimuli over other object classes such as faces or houses[283]. An initial examination found the L-vOT activated by words, but not when patients with a callosal lesion saw words in the left visual field[261]. Follow-up studies attempted to define the tuning of this area and determine how specialized it was for orthographic stimuli. A study found the L-vOT activation can discriminate words from consonant strings, but is equally activated by both pseudowords and words[90] and another study found that pseudowords activated this area more than words[284].

Early reports were that auditory words do not activate this region and it is not sensitive to semantic category leading early theories that it was a pre-lexical stage of visual word processing[285,286]. However, another study did find overlapping activation to listening and reading words near the putative VWFA[287] and in naming objects and words found multiple sub regions that were specific or overlapping to either words or objects relative to meaningless controls[288]. A study in the blind found that when learning ‘soundscapes’, which are auditory representations of a visual scene, the vOT was selectively active to letter soundscapes compared to texture soundscapes. Anterior to the putative VWFA was an overlapping region for orthographic stimuli and an auditory rhyming task[289]. A study of auditory selective attention found that vOT areas were suppressed, except when attending to linguistic stimuli which did not suppress the area associated with the VWFA[290]. This suggests a connection to auditory processing areas and bolsters claims regarding a preference for linguistic stimuli[291]. Activation in this area increases as participants progressively recognize an object[292].

The role of the L-vOT has been attributed to being a critical part of the orthographic route. Irregular words, reliant on the orthographic route, activate this area more than pseudowords during word vocalization[293]. A study going from false-font strings to progressively more frequent letter combinations to words found a feed-forward oriented gradient of selectivity[294]. Evidence for this location as a store of orthographic representations comes from the invariant responsiveness of the L-vOT. Stimulus differences such as letter-case or physical location in space do not affect activity here[295,296]. Although studies have not found semantic differences in the L-OT, they have found habituation to both faces and letters, suggesting the ability to discriminate a variety of identities if not meanings[297]. A study found that repetition effects in the vOT were at the lexical and not the sublexical level[298].

Both stimulation and lesion cases demonstrate the importance of the dominant basal temporal lobe for reading. Stimulation of the dominant lobe fusiform gyrus leads to speech arrest during reading aloud independent of mouth motor movement which was spared[299]. A patient undergoing resection of part of the L-vOT for clinical purposes was studied before and after resection. Though they had intact object naming, facial recognition, oral language, and letter identification the patient developed slower and more error-filled visual word identification. fMRI before and after the resection showed the disappearance of the word specific activation loci despite intact regions specific for faces, houses and tools. However, whole words still showed activations relative to consonant strings, with consonant string activity falling near 0, suggesting that early orthographic processing was most affected[300].

Pure alexia is a condition after damage to the left Occipito-temporal regions. A common finding is that patients read letter by letter, with each additional letter adding time to word identification not seen in intact reading[301]. In general, accumulating evidence points to alexia, also called word blindness, being associated with damage directly to the vOT rather than being simply a matter of disconnecting the vOT from language areas[302]. The heavy lateralization of vOT for words is demonstrated by a patient displaying alexia only for words displayed in the right visual field after damage to the splenium[261]. Alexia without agraphia, cases where reading is impaired but writing is not, are often connected to damage to the splenium which connects right and left occipito-temporal regions[303–305]. In a neurosurgery case allowing fine discrimination of brain damage leading to alexia without agraphia, it was found the damage limited entirely to white matter and spared occipito-temporal cortex[306]. Another study found that after neurosurgery a patient with medial lobe removal but intact lateral occipitotemporal cortex and white matter connections recovered reading whereas a patient with lateral removal did not recover[307].

Of importance is the relationship between the dominant language vOT, usually on the left, and the non-dominant vOT on the right. Lesion cases point to the importance of an intact right-left OT connection for reading. Typically, both the left and right vOT are activated by letter stimuli, but only the left vOT shows selectivity for those letter stimuli. Behavioral studies have found that parallel processing of letters appears to occur for words presented exclusively in the right visual field but letter-by-letter processing as evidenced by word length effects appears when words are presented to the left visual field[308]. This has been generalized into a theory that the left hemisphere visual system processes in an invariant, abstract level of identity whereas the right hemisphere is more involved in variant, location specific levels of identity[309]. Visual information in the right hemisphere is transferred to the left for language processing through the splenium of the corpus callosum. Disruption of this splenium leads to lack of activation in the vOT by visual words presented to the left visual field[310]. Finally, the right hemisphere is theorized to be able to identify letters in a serial fashion when can lead to slow but somewhat preserved reading in patients with damage to the left vOT[311]. Further evidence comes from transcranial magnetic stimulation transiently knocking out letter-by-letter reading in a lesion patient with alexia[312].

Beyond bilateral vOT connections, these occipito-temporal regions have extensive connections with the rest of the brain. Highlighting the importance of vOT connections to perisylvian areas are findings that lateralization of activity in vOT correlates with lateralization of spoken language, specifically the IFG when generating words[313,314]. During reading, white matter changes are observed along the inferior longitudinal fasiculus, which connects the temporal and occipital lobes, and the arcuate fasiculus which connects the temporal and inferior parietal cortex to the frontal lobef[315]. Lesions to the vOT in the region of the VWFA lead to decreases in white matter chiefly along the inferior longitudinal fasiculus[316]. A systematic study of vOT connections found that caudal areas were predominantly linked with other caudal visual areas as well as the ventral frontal regions. More anteriorly, vOT was linked to superior temporal and more superior frontal areas. When comparing connectivity from VWFA to FFA, Rolandic regions were implicated as well[317].

More anterior vOT areas take on lexico-semantic processing in theories of reading. For instance, it responds to words greater than letter strings when the input is visual, word reading in sighted participants, when the input is tactile, braille reading in both late-blind and congenitally blind participants[318]. In patients with surface dyslexia the midfusiform did not show activation relative to control subjects[319]. Transfer from the right vOT, of visual words presented to the left visual field, to the left anterior vOT preserves the ability to elaborate upon the meaning of a word but not its identity if the anterior collosum is intact but the meaning approximation disappears if it is entirely severed[320].

Moving more anteriorly, the anterio-medial temporal pole is reliably activated by semantic tasks across both PET and fMRI modalities in areas that include lateral aspects of the anterior lobe as well[321].

Posterior Temporo-Parietal

The posterior temporo-parietal regions are traditionally assigned to the phonological, dorsal route for reading. This is chiefly associated with phonological recoding, but may also be part of auditory lexico-semantic access.

Angular Gyrus/Supramarginal Gyrus (SMG)

Left SMG was the original site proposed by Dejerine as containing the representations of visual images of letter due to various patterns of functional loss due to lesions in this area[1]. He posited this area as a hub of visual-to-auditory conversion. This localization gained support from other lesion studies in the same era[322]. However, modern interpretations have moved the semantic hub from the angular gyrus to the pMTG region just inferior to this region, which could have also been damaged. Instead a number of studies have implicated the SMG as part of the phonological route. An fMRI study found greater activity in the bilateral SMG when making judgements about the number of syllables than during judgements of living/non-living[323]. A study found that the angular gyrus was more activated for words, both regular and irregular, relative to non-words[324]. This region was more active for rhyming judgement tasks than for semantic judgement tasks[325]. A study comparing activity in spelling judgements versus rhyming judgements found more activity in this area to rhyming judgements[286].

However, an alternative explanation for these differences exists. Examining angular activation for words versus consonant strings it was found that increased activation for words versus consonant strings was explained by suppression of activity for consonant strings with words being no greater than fixation[326]. In the auditory modality, a similar finding was evidenced by decreased activation to an auditory perceptual task but during a semantic retrieval task it was the same as baseline[327]. This evidence calls into question whether activity in the angular gyrus in involved in in lexico-semantic processes, with positive lesion findings reflecting damage to the nearby posterior MTG and fMRI findings reflecting a lack of suppression rather than an increase in activity.

Middle Temporal Gyrus

The posterior left MTG has been associated with lexico-semantic processing. An early PET study found that activity in this area was increased for words relative to false fonts and interpreted this increase with accessing word meaning, which would be impossible for false fonts[328] or pseudowords[329,330]. Another study found greater activation when deciding living/nonliving versus deciding the number of syllables[323]. A study comparing semantic category decision task activated the bilateral MTG to a greater extent than a rhyme judgement or letter judgement task[331].

As the division between lexical identity and lexical meaning is unclear, it is also unclear if this region's activity is associated with the visual lexicon or with word meaning in general. Further, since this area has also been reported in a number of auditory language studies and has shown overlapping activity for visual and auditory tasks[287], it has been theorized that activity here is more related to a-modal processing rather than visual specific processing.

Superior Temporal Gyrus

This gyrus is most often associated with phonological processing[332] and there has been one report of neurons in the STG with correlated responding to letters and the phonemes that respond to them[333]. A study found that naming time for pseudowords was correlated with activity in the STG[330]. More phonological route activity was found here, however this was only during pronunciation tasks[334]. Interestingly, this area is more activated for semantic judgements than rhyming judgements in both English[325,335] and Chinese. When comparing visual to auditory processing, this area has more activity for auditory processing, though when comparing spelling to rhyming judgements in visual processing this area has more activation[286].

Both the left STG and fusiform were not activated in semantic-dementia patients with surface dyslexia who made regularization pronunciation errors[319].

Parietal Regions

Patients with surface dyslexia with fMRI and MRI of damaged areas, the intraparietal sulcus was implicated as important to phonological conversion, due to greater activation during pronunciation regularization errors for surface dyslexics[319]. This region often blends with the supramarginal gyrus such as when both the parietal lobe and supramarginal gyrus were implicated in being more active during rhyming judgements than semantic judgements[325]. This has been replicated in Chinese[335].

Inferior Temporal Gyrus

Pars Opercularis

An early review classifying results as either the orthographic or the phonological route classified the PO as part of the phonological route[10]. Other reviews have classified this as a hub engaged in both phonological and semantic processing[336], which would be consistent with a presumed role for phonological in lexicosemantic access. Further evidence is found that functional connectivity between PO and ventral occipital and temporal cortex for words, pseudowords, consonant-strings but not for false fonts[337].

L-PO was found to be more activated for non-words relative to low-frequency exception words, suggesting contributions to the phonological route[319]. This area has also been associated with greater activation to both pseudowords and low-frequency words relative to high-frequency words, contrasts assumed to give greater weight to the phonological route[329]. A study requiring the learning of a made up script found that when letter-sound correspondence was included, more activity was found in the PO than when the script had no letter-sound correspondence. However, this was true only for relatively unknown 'words', equivalent to low-frequency words, but activity was equivalent when words were well known, the equivalent of high-frequency words[338]. This region and the neighboring pre-motor regions were more active in rhyming judgement tasks than semantic judgement tasks[325]. This has been replicated in Chinese[335].

In attempting to articulate what the PO takes part in, it has been suggested that it is involved in verbal working memory. An early neuroimaging paper found that PO was involved across tasks involving a sub-vocal maintenance of linguistic pieces, such as short term memory for letters and rhyming judgements[339]. Another study found greater activation in this area for rhyme judgements relative to semantic judgements[331]. A study found overlapping activity for a rhyme judgement as well as increasing activity in a lexical decision task which increased in phonologically difficulty[158]. was also found to have increased activation while silently maintaining linguistic stimuli but not numbers[340]. Another found greater activity for both pseudowords and exception words relative to words[341]. A study comparing words, irregular words, and pseudowords found that the PO increased in activity with difficulty in naming (pseudowords > irregular words > words)[324]. Damage to this area has been reported to decrease rhyming ability, pseudoword manipulation, and remove the ability to articulate speech but leave auditory and visual comprehension of words intact (though this was the right PO of a right-handed woman)[342].

L-PO shows an increase for pseudowords over words during a phonological and a lexical decision task[343].

Pars Triangularis

L-PT was found to be activated for low-frequency exception words relative to regular low-frequency words suggesting more involvement in the orthographic route[319] or only activated for low-frequency words at all[329]. A study comparing semantic decision with phonological decision tasks found the anterior portion of the IFG associated with the pars triangularis was active in the semantic but not the syllable counting condition[336].The fact that damage to the frontal lobe does not affect meaning retrieval, but affects meaning selection from alternatives, shows that L-PT could be involved in lexicosemantic selection, especially when there are many competing meanings[344]. Functional connectivity is only found between this area and occipital and temporal areas for words but not for pseudowords and consonant strings[337]. Furthering this research, another study found an increase in connectivity for exception words, reliant on the orthographic route, between the PT and the anterior fusiform[341]. A study contrasting semantic and phonological relatedness decisions found semantic activity greater than phonological activity here[325].

L-PT showed an effect of pseudowords over words in a lexical decision but not a phonological decision task[345]. Direct causal modeling implicated a posterior temporal L-PT connection during lexical decision tasks not present during phonological decision tasks which drove this effect[343].

The Precentral Gyrus: An Ignored Contributor to Reading

Across the three major reviews noted in the last section, the precentral gyrus is not given a role in learning how to read. Jobard et al. notes that “Even though they will not be discussed [in this review], it must be kept in mind however that other regions such as…precentral gyrus, have been reliably found as activated in reading…”[10]. Reviews that did include the pre-central gyrus relegated it to part of the phonological output system necessary for vocalizing printed language[9,11]. However, the view that the phonemic codes used in reading are articulatory instead of receptive is part of the most well-known computational model of reading[47] and has been an established psychological hypothesis since at least 1979[7]. As noted in the articulatory suppression literature, using the articulatory apparatus during reading appears to interfere strongly with some phonological aspects of reading[57]. Below we examine additional data to support the role of motor areas in reading.

A study found greater activity in the precentral gyrus when making number of syllable judgements versus living/non-living judgements[323]. Further, masked presentation of word stimuli activates the left precentral gyrus even though the words are not consciously perceived[295]. Motor cortex shows differential activation based on the spelling-sound consistency of a word, implicating it in processes beyond simple output phoneme representation[346]. Rolandic areas also, along with the PO, showed increasing activation with increasing difficultly of GPC (pseudowords > irregular words > regular words)[324]. A study comparing lexical decision with reading aloud found increased activation in the precentral gyrus when reading aloud compared to silent reading. However, the post-central gyrus was more active during lexical decision. The difference in activation was greater for pseudowords than words in the precentral gyrus, moreso during speech production than lexical decision[347]. A study correlating resting state connectivity and reading ability found that the precentral gyrus having a stronger connection with surrounding motor areas. Additionally, connectivity between fusiform cortex and Broca's was found to be a hallmark of skilled but not learning readers[348].

Areas just anterior to the primary motor cortex, but outside of the well-studied IFG regions, have also been involved in reading. A study found increased coupling between the dorsal premotor areas and the posterior fusiform area during pseudoword vocalization but not for exception or normal words[341]. Showing that these effects are not only vocalization-based, areas that have been associated with language vocalization, such as the supplementary motor area, have been found to be active during both silent reading and vocalized reading[284].

Damage to the Rolandic area, of which the precentral gyrus is a part, reduced a patients ability to make phonological recoding judgements about words, such as phonological similarity and syllabic stress judgements[349]. A second patient was found to have damage to both the left Rolandic area and the R-PO who showed retained comprehension of visual words but the inability to make rhyming judgements or manipulate pseudowords[342]. The reader will notice in both cases of Rolandic damage, the deficits were limited to tasks involving explicit phonological judgements (rhyming tasks or phonological similarity) but they retained the ability to read. A study of a woman who showed bilateral destruction of the rolandic fissure gives more evidence that this area is not necessary for all forms of reading though[350].

The motor area involved with handwriting, Brodmann area 6 which overlaps with the precentral gyrus, is also active when viewing letter passively. This was only true for learned letters but not for sensory control pseudoletters[351]. This overlapping writing and perceiving area is also hand dependent: it is located on the left for right-handers and on the left for right-handers[352]. Cortical stimulation of the area identified in fMRI showed handwriting deficit areas which were typically just anterior to pure hand motor movement areas. The pure agraphic responses to stimulation did not overlap with oral language tasks[353]. These areas are collectively located near the superior frontal gyri. All ‘writing’ cortical areas identified overlap with drawing related areas, however the previously identified frontal area becomes left lateralized during writing but remains bilateral during drawing[354].

Additional evidence comes from children with Rolandic epilepsy. This syndrome is called ‘Benign Epilepsy with Centrotemporal Spikes and is associated with infrequent seizures generated in Rolandic areas which typically resolve as the child grows up[355]. These seizures are typically associated with lower face seizures [356]. Typically this syndrome has not been associated with any significant overall cognitive impairments[357], hence the ‘benign’ moniker but a variety of specific deficits have been located suggesting different seizure loci lead to different deficits[358]. However, reading[359,360], phonological awareness[361], and lexico-semantic but not morpho-syntactic knowledge[362] have been reported. Specific deficits include decreased performance on lexical decision tasks and longer response times to pseudowords[363]. A meta-analysis found that the phonological effect size was moderate while the single-word reading effect size was large, and both were homogenous across groups of varying selection criteria[364].

The onset of these articulatory, visual language, and memory problems occurs before the age of 7[365] with increased chance of developing a learning disability the earlier the onset of seizures[366]. Analysis on what regions were most connected during seizures found the Rolandic regions and IFG as well as supramarginal become more correlated during seizures[367]. Connectivity analyses found decreased connectivity between left sensory-motor Rolandic cortex which correlated with decreased language behavioral performance and the IFG[368]. The seizures in Examining the reduction in white matter connectivity in Rolandic epilepsy found left-hemisphere centered reductions in white matter to the pars opercularis and suprmarginal gyrus.

Intracranial Electrophysiology: The Spatiotemporal-course of Reading

Recordings directly from the brain are possible in patients undergoing mapping for epilepsy. The local field potentials (LFP) recorded from the brain surface are analogous to extracranial EEG, but with greater spatial specificity. Additional information is available in the form of high-gamma power (HGP).

Orthographic Route Visual Processing in Ventral Occipito-Temporal Regions

Several studies have compared striate and extrastriate cortical responses to a variety of stimuli including orthographic words and letter strings. Activity in the primary visual cortex beings at ~75ms and begins in occipito-temporal cortex ~110ms. By ~150ms the activity has spread to parietal, lateral temporal, and medial temporal cortices[370]. The first study found discrete face and orthographic selective areas, compared to control stimuli, throughout the fusiform and ITG bilaterally at ~200ms. Also reported was some overlap and some separation between numbers and letters in the same regions and time. However, the orthographic selective cortex recorded from here failed to find differences between words, pseudowords, and consonant strings[71]. A follow-up study found a bilateral distribution of these ~200ms orthographic specific responses which included a later ~700ms component as well[371].

A patient undergoing surgical resection in the L-vOT developed slower and more error filled reading. This study was able to examine electrodes surrounding the L-vOT identified word-sensitive area from fMRI. Contrasting masked and unmasked words, words greater than a blank screen was found for unmasked words at both 220ms & 500ms but only at 220ms for masked words. These effects were bilateral, but lateralized toward the left. A word frequency effect was found late ~460ms in only a single electrode[300]. A second study of masked and masked word presentation found that at ~800ms, the amygdala is sensitive to the emotional valence of a word. This effect occurs much earlier, ~400ms, for unmasked words. This suggests that even words that do not elicit a late potential in the L-vOT are still processed extensively by the lexicosemantic processes, though less extensively than unmasked words[372].

A study directly compared the posterior (L-vOT) and anterior fusiform gyrus to examine the proposed feed-forward stream of the orthographic route near its posited beginning and ends. Posterior fusiform (L-OT) activity was sensitive to linguistic stimuli but not checkerboards, but failed to distinguish meaningful from non-meaningful words. More anterior areas dissociated expected from unexpected nouns suggesting a hierarchicial flow along the ventral temporal areas from smaller (letters) to larger (words, sentences) units of meaning. Additionally, face responses were found in neighboring but not the same electrodes[373]. This anterior fusiform component is not present to illegal pseudowords, to be diminished by semantic priming, and to be larger to content versus function words[374].

Another area of interest in the anterior temporal lobe is the medial temporal areas including the amygdala, hippocampus, and para-hippocampal gyrus. This area has chiefly been studied in the context of lesions which creates a severe amnesia for recent events[375,376]. In word recognition, this area responds differentially to repeated and novel words peaking ~450ms but beginning ~200ms earlier and putatively located predominantly in the left para-hippocampal cortex. This component was also present in explicitly language tasks such as lexical decision and naming[377].

A study using linear micro-electrodes probed the feed-forward/feed-back nature of vOT processing in anterior vOT. Theses micro-electrodes can localize transmembrane activity to specific cortical Feed-forward activity being localized to lower cortical layers and feed-back activity being localized to higher layers[378]; This allows principled inferences about the nature of the measured neural activity. In inferior temporal and perirhinal cortex activity begins ~120ms in lower cortical layers with sustained activity for 100ms, followed by a slightly higher layer activity till ~500ms, and higher layer activity >600ms. This pattern is lessened for previously seen stimuli in which activity rapidly fluctuates between upper and lower cortical layers. In contrast between perirhinal and inferotemporal decreases to repeated stimuli, entorhinal cortex showed increases to repeated stimuli, suggesting a memory-oriented process[379]. In these same areas repetition effects and semantic differences between animals and objects emerge temporally very close, in some areas as early as ~220ms. A single subject displayed evidence that animal/object differences can be extracted during the first pass of information sweep ~120ms[380]. In the hippocampus proper, units were found in the anterior hippocampus which responded selectively to 1 out of 10 repeated words, though this was not word specific but rather tuned to a specific word out of a repeated set. The units were mixed in whether they responded only to repeated words or had non-specific activation to non-repeated words as well. Despite overall repetition suppression evident in electrical activity to these stimuli the units responding themselves were not diminished. The responses started ~300ms and were sustained for 200-500ms. However, these hippocampal units did not appear especially sensitive to words versus non-words, but instead were specific to specific target stimuli relevant to the task across different task types[381,382].

Lateral Temporal Structures

An intracranial study identified auditory responses which were voice-selective in the lateral temporal cortex. These same patients also performed a visual text task where words were either attended or ignored. They found that ventral temporal areas showed a response. Lateral voice-selective areas showed activation deviate from baseline at ~250ms and attend/ignore differences emerge ~500ms with increases only to attend words. Grainger causality revealed a significant time of significance between 350ms and 550ms[383].

The Development of the Reading Network

Reading is a recent cultural invention, not selected for by evolutionary constraints and optional (i.e. without concentrated learning a human will go through life illiterate). This has led to competing theories regarding the underlying neural architecture of reading: the advent of domain-general cortex[384] or neuron recycling[17]. Domain-generality suggests that the large expansion in cortex in primates allowed us to adapt to whatever environmental challenge presented itself. This is in contrast to the view of neuron recycling which that we have hardwired neurobiological architectures developed in response to our ancestors environmental challenges which constrain our adaptation potential. This view is consonant with the evolutionary principle of extaptation, wherein mechanisms evolved historically for a different environmental challenge are used by the modern organism to meet current, and unforeseen, challenges in the present[385]. Recycling is assumed to reflect the strong anatomical and connectional constraints present from birth and to require 'invasion' of older circuits for new function. This would also predict that these new representations and operations would be reliably distributed across cultures and individuals, which is broadly supported (see "Multicultural Contexts" section). Which theory is adopted has huge ramifications for understanding how to model reading at the computational level.

One point of agreement between domain-generality and the recycling hypothesis is that auditory language system is assumed to always precede the development of a visual language system. Therefore, even is a domain-general view is adopted visual language is learned within the constrained context of an already established language system. During the development of reading, difficulties in the phonological system are mirrored in difficulties in learning to read[386]. Neuroimaging of participants with dyslexia suggests an early predominance for the more lateral, dorsal route assumed to underlie the phonological route and later development of a ventral occipito-temporal route associated with the orthographic system[387]. Therefore, at a base level, whether the brain is modality-general or recycling the visual language system develops in the context of an already developed language system, specialized for a different sensory modality.

There is evidence that learning to read does rewire the visual system at a very basic level. Using insights gained from eye-tracking, a study investigated Hebrew (read in one direction) and Roman (read in the opposite direction) and found that readers performance on a letter identification task was modulated by where the letter was in relation to normal parafoveal location for the script[388].

The question is once skill in reading has been acquired, what is the relationship between the direct and phonological routes. Studies of children show that as reading develops, the mistakes attributable to phonological problems decrease[389]. This web of evidence suggests that skilled readers rely very little on the phonological route. However, a strong role for the phonological system could still exist if we assume that it is not just the development of the orthographic route that increases reading ability but it is also the improvement of the phonological route[14].

Behavioral Studies: Phonology and Learning how to read

The self-learning hypothesis is based on evidence that pronouncing words aloud contributes to orthographic learning. Each novel, pronounceable word encountered provides an item-based opportunity for developing a print-to-meaning connection. This theory acknowledges the primary place of phonological knowledge in word learning it posits an increasing autonomy of the orthographic lexicon from phonological knowledge[390]. As beginning readers encounter 10,000 new words a year[391] and these encounters come at varying frequencies with some estimates placing ~100 words as making up ~50% of all visual words encountered in school[392]. For the lower-frequency and novel words, some form of rule-based knowledge is necessary to link, a role which phonology fills to a much greater degree than orthography. For example, in Dutch children, children are reported to differentiate words and pseudohomophones, i.e.

knowing that similar sounding letter strings are not equally words, within 6 months of beginning to learn how to read[393]. While spelling-sound correspondences vary across the reading abilities, from letter-sound to letters-syllable to letter-word, simple phonological rules provide a strong starting point for each encountered novel word[394].

The phonemic nature of learning to read is demonstrated by the large share of variance in reading skill accounted for by pseudoword reading speed[395]. When comparing children's reading across ages 6 and 7, it was found that phonological skill at age 6 predicted orthographic skill at age 7 but not vice versa[396]… Delayed readers can large differences in pseudoword reading speed[397], demonstrating that deficiency in phonological recoding have dire implications for learning to read visually. For example, 13 year olds with delayed reading showed pseudoword reading skills at a 7 year old level[398].

Investigating the potential motor nature of this self-learning hypothesis has used articulatory suppression. Reading pseudowords aloud leads to improved orthographic knowledge of pseudowords compared to a condition of articulatory suppression on visual identification and improved spelling[399]. Having students read stories aloud with pseudowords embedded in the story replicated this effect, finding that the pseudowords read aloud in the study on target naming and spelling. This improvement was limited to pseudowords read aloud ('YAIT') versus homophonic pseudowords ('YATE')[400]. This was further replicated in Hebrew[401].

Examining abnormal readers finds further evidence for the involvement in articulatory areas for learning how to read.

Behavioral Studies: Dyslexia and Learning how to read

Studies have often tried to replicate the double dissociations of the early lesion studies with children learning how to read, using one set of stimuli to index development of the phonological route and another set of stimuli to index the orthographic route. For example, a study used pseudowords to index the phonological route and irregularly spelled words to index the orthographic route over the course of 4 years in children. They found that Grade 1 pseudoword reading predicted variance of Grade 4 pseudoword and irregular word reading but irregular word reading did not help to predict Grade 4 pseudoword reading. This suggests that phonological skills early in reading contribute to development of both the phonological and orthographic routes, but that orthographic development does not enhance the phonological route[402].

Behavioral Studies: Artificial Script Learning

Studies which teach participants an arbitrary orthographic script provide some insight into the learning mechanisms of unskilled readers, though it is somewhat strange given that they have already learned one orthographic script for English. In one study, they explicitly taught participants letter-sound correspondences while learning or did not include stimuli with letter-sound correspondences. Participants who learned letter-sound correspondences performed more accurately, though with slower response times, and retained long-term learning better than those that did not learn letter-sound relationships[403]. A previous study also found that participants were not able to implicitly learn letter-sound correspondences during orthographic learning of an arbitrary script[404].

Neuroimaging Studies: Neural Changes during Learning how to Read

Early studies focused on just visual language and found a decrease of the effect of context on visual language[405]. This is suggestive of an increasingly competent bottom-up process of visual word recognition. In general, ERP components tend to decrease in amplitude and latency with age, suggesting overall faster and less effortful processing interpreted as better bottom-up processing. Overall, N400 amplitudes decreased with age, which was interpreted as the bottom-up language processes improving with more experience and therefore being less reliant on context for lexico-semantic access. That this pattern was present in both the auditory and visual modalities is problematic for reading-centric views of learning[406].

That differences in neural responses exist between illiterate and literate individuals is not surprising. An ERP component which shows a larger negative deflection in response to word-like stimuli at ~170ms developed over the course of 2-years of learning how to read, from kindergarten to 2nd grade but remained smaller than for skilled adult readers[407]. The development of this early ERP sensitivity to print was replicated and localized to classical vOT areas with fMRI[408]. Activity in the posterior ventral occipito-temporal regions is selective to words, but only in the language in which the subject is literate[409]. Additionally, brain structure changes have been documented in developing literacy. Learning to read late in life, after childhood maturation, leads to increased grey matter in the bilateral angular gyri, middle temporal, left supramarginal, and superior temporal gyri as well as a white matter increase in the splenium of the corpus callosum when compared to illiterate brains[410].

An in depth fMRI study examined the neuron recycling hypothesis in depth with regards to reading[4]. Comparing the reading responses of early-literates, low-SES early-literates, late-literates, and illiterates they found difference brain activity across canonical reading areas such as the L-vOT, R-O, L-STG, L&R-premotor areas, & L-IFG. Temporal areas preferred auditor to visual stimuli and vOT areas preferred visual stimuli. Frontal areas were about equal visually and auditorily but only for literate readers. Most importantly for the neuron recycling hypothesis, illiterates showed increased activity to non-letter stimuli such as faces and literates showed a reduced area of cortex responding to faces. The face-response was much stronger on the right (non-linguistic side) in literates, suggesting a re-organization of the visual system with increasing literacy. This received additional support from a behavioral study finding differences in holistic versus analytic approach to houses and faces in illiterates compared to literates[411]. Overall visual responses in vOT areas were higher for literates, suggesting a positive effect of practice with letter stimuli. Finally, the pattern of results suggested that this re-organization is only pronounced for early- and not late-literates which would restrict the effect of re-organization to childhood when the brain is presumably more malleable and plastic.

Non-normative Reading Contexts

Interpretations of what non-normative reading means for the dual route models of reading vary based on the assumptions of the researcher and the methodology they use to characterize differences in processing. For example, in dyslexia many researchers relied on a naming task to identify disruptions of normal processing. However, problems identified in naming could happen at a number of different stages in the hierarchy of encoding, and perhaps the problem comes after the word has been successfully encoded and the breakdown occurs in the vocalization of the word. These considerations will play into the interpretation of the evidence laid out below.

Dyslexia

Dyslexia can either be studied in a lesion context or in a developmental context. In the lesion literature, there are multiple types of dyslexia, presumably from alterations to one or the other of the direct and phonological routes of reading. Surface dyslexia appears to create difficulties for the orthographic route while phonological dyslexia leads to problems with the phonological route[412]. Surface dyslexia is characterized by the inability to profit from word frequency and have difficulty with words which violate rules of GPC. Phonological dyslexia on the other hand are able to achieve both of these feats, but have great difficulty reading novel words and non-words. These dissociable types of dyslexia provide great support for the dual route theory of reading. Studies of surface dyslexia have tied regularization errors to damage to the posterior middle-temporal gyrus.

Attempting to locate surface and phonological dyslexia in developing readers has been an inconclusive endeavor.

A third type of dyslexia, deep dyslexia shares the problems with non-word reading of phonological dyslexia but also show a pattern of deficit in semantic mistakes in which words that are phonologically and orthographically unrelated to the target word are produced (i.e. PEBBLE leads to STONE)[413]. Interpretations differ on where the problems of deep dyslexia occur, critically because lexico-semantic errors cannot be localized in time from behavioral measures. Another wrinkle is that deep dyslexic readers find difficultly in vocalizing words leading to a possibility that deep dyslexia effects occur at a later lexical or output stage of processing, leaving the sub-lexical stage of the phonological route intact. An example is a study which found that that when a deep dyslexic unable to vocalize non-words or vocalize the sounds of letters performed a lexical decision task they displayed normal spelling-sound regularity and pseudohomophone effects[414].

Because of the contrasting data on deep dyslexia, localizing this deficit neuroanatomically is difficult and the damage could very well occur at an a-modal step in lexico-semantic processing even though the early stages of both the orthographic and phonological routes are functioning correctly. An alternative account is that deep dyslexia are not profitable to study from a reading perspective because these patients have developed an abnormal reading system. For example, a patient who had her left hemisphere removed but the right hemisphere intact developed deep dysxlexic-like symptoms[415]. Another patient with a callosal lesion showed normal reading when words were presented to the left hemisphere, but deep dyslexic like symptoms when words were presented to the right hemisphere[416]. Finally, in neuroimaging it was found that a deep dyslexic patient showed more right hemisphere activation than controls or a phonological dyslexic[417].

Researchers have attempted to localize dyslexia to either the language system itself or ancillary systems. A study in MEG found that early visual potentials at ~100ms in occipital regions to degraded versus non-degraded symbols were similar to both dyslexic and normal readers but differences emerged later at ~150ms to letter string stimuli[418]. A study comparing dyslexic and regular readers with fMRI, findings areas of hypoactivation in posterior ventral temporal and posterior temporo-parietal areas. Reading skill was positively correlated with ventral temporal activity. There was also a bilateral increase in IFG activity for older dyslexic children[419].

Deaf

People born without hearing present a case study into the development of reading without the phonological system, or at the very least a profoundly altered phonological system. The deaf as a population read at a lower level than their hearing classmates[420]. But though the deaf phonological system is profoundly altered, it still affects reading for deaf individuals. A study found that rhyming visual words facilitated lexical decision judgements the same as hearing individuals[421]. Though deaf individuals cannot hear, they can still lip read and speak both of which are proposed to develop the phonological system[422]. Findings done in deaf individuals raised in hearing households suggest that pre-lingual deaf individuals have impoverished but still existent phonological systems[423]. When their reading is test, deaf individuals raised with oral communication show phonological recoding effects but individuals raised with sign language do not show these effects[424].

Multicultural Reading Contexts

The overwhelming majority of cultures have developed written language, called orthography which is a description of how the written symbols are connected to the language[425]. A cross-study of 100 languages found that the construction of letters across 100 languages all had similar construction, e.g. ~3 strokes per character[426]. However, there exist important differences in written scripts between different cultures. The most obvious difference is between orthographic systems (such as English) and pictographic systems (such as Hieroglyphs). It has been argued that pictographs are not effective[427]. fMRI studies of Chinese, more pictographic, versus English, more orthographic, reading reveal English has greater activity in the superior temporal gyrus[428,429], an area strongly associated with phonemic processing as would be expected for an orthographic processing based visual language system. Pictographic symbols are not used in the orthographic system of interest in the present work (English), so they are not considered further. The relevant, and unanswered, question about phonemic orthographies such as English is to what degree difference in orthography are reflected in differences in the neural networks and calculations needed to perceive and understand them.

At the surface, phonemic orthographies, such as English, come in different unit sizes such as syllables or individual phonemic sounds. For example, Japanese contains a small number of syllables (113) whereas English contains a great deal more (8000) leading to differently constructed writing systems. Evidence that reading systems can differ is demonstrated in a study performed in Japanese which includes both a syllabic (orthographic-route focused) and phonological (phonological-route specialized) script. Words are typically read in one visual context or another, i.e. presented only in the syllabic or phonological context. In this study words were named slower when shown in the opposite context than normal[430] which suggests differences in processing related to differences in writing.

The main difference between phonemic orthographies is the consistency of the relationship between the written graphemes and the auditory phonemes these graphemes represent. This is referred to as “deep orthography”, in which the relationship is less consistent, and ‘shallow orthography’ in which the relationship is more consistent. English is considered a deep orthography due to the loose rules and many violations present within its spelling-to-sound correspondences. For example, HEAL & HEALTH are pronounced differently despite sharing a stem. However, because DEAL/DEALT, STEAL/STEALTH share a similar disconnect, it is possible coherent rules exist but are ‘deeper’ than a simple letter-sound correspondence[431]. Further, the problem is not necessarily the orthographies fault; HEAL & HEALTH are semantically very similar but phonologically distinct independently of the orthography. The ‘deep orthographic hypothesis’ is that shallow orthographies rely more on the phonological route whereas deep orthographies rely more on the orthographic route in lexical access[431].

To test this hypothesis, studies assume that the depth of the orthography affects the relationship between the two visual language routes. For example, in a shallow orthography reading words aloud should rely less on access the visual stored word (the orthographic route) and more on the phonological route when compared to deeper orthographies, which has been shown[432,433]. The speed of naming may also be affected, an in shallower Italian being read faster than deeper English[434], presumably because GPC relationships are more consistent. In another study subjects compared simultaneously displayed auditory and visual words for match/mismatch judgement. In this study it was shown that a deep orthography suffered far more from degradation of the auditory stimuli than a shallow orthography; The most likely explanation being that the strict grapheme/phoneme correspondence made it easier for the shallower orthography to activate the phonological route and compensate for the obscured phonemes[435]. Finally when comparing shallow and deep orthographies in the context of naming with non-words, which should increase the reliance on the phonological route, it is found that deeper orthographies are primed semantically (presumably through orthographic route activation of the visual lexicon) but shallow orthographies are not primed semantically (presumably because they rely more on the phonological route and thus activate the visual lexicon less strongly)[436]. In the other direction, the introduction of non-words in a naming task, which should recruit the phonological route more strongly, had no effect in a shallow orthographic naming task (presumably because it is already using the phonological route) but did show differences in deeper orthographic naming latency (presumably because the phonological route which is used less by default is more strongly recruited)[432].

That orthography differs in deepness, and therefore may differ in processing, presents challenges of interpretation for visual language study. As noted previously, writing developed independently at least 3 times in human history. However, convergent development of similar phonemic orthographies does not necessarily guarantee that the brain adaption is the same in each case. It is not clear that the brain is different between orthographies, but there are measurable differences of varying deepness. Knowing whether results are generalizable to the ‘human brain’ versus constrained to the ‘English-speaking human brain’ is critical for interpretation; especially given that many controversies in visual language study are driven by differences across cultures.

For instance, in the ‘lexical decision task’ section above, studies in English are noted because they are relevant to the population studied in the present work. However, subtle differences are observed in the lexical decision task when it is given to individuals from shallower orthographies than English. For example, a study in Serbo-Croatian, a language with two alphabets which share overlapping letters, it was found that letter-strings that were ambiguous (i.e. a valid word in both languages) were responded too slower than unambiguous words[437]. Another study in this language found that decision latencies increased with the number of ambiguous letters in the word[438]. Studies in Serbo-Croatian thus point to a phonological route dependence in lexical decision due to these words being orthographically unambiguous but affected by ambiguity of the word phonology. This stands in contrast to the non-findings of phonological ambiguity in the studies using English as reported earlier. However, other studies have replicated tasks across shallow and deep orthographies[439].

Neuroimaging helps to clarify some questions of similarity based on deepness. In Italian, which is shallower and words are name faster, PET imaging revealed increased superior temporal activations for Italian (phonological route) and greater activations in the posterior inferior temporal gyrus for English (orthographic route)[434]. In Hindi, a shallow orthography, participants showed more activation of the left inferior parietal lobe but the left inferior frontal gyrus for English, but only if they learned both languages simultaneously. If they learned Hindi first, the left parietal lobe was more active in both languages[440].

In modeling, French (a shallower orthography than English) could be modeled by the DRC, but the parameters of the phonological route had to be changed. When the speed of the

DRC phonological route was increased it was able to simulate naming in French[441].

Having reviewed the evidence it is clear that though readers in different orthographies may use subtly different strategies, the system is constructed in a similar manner across orthographic systems. Learning to read in shallow orthographies may be easier than learning to read in deep orthographies[442]. But being aware of phonology is important in reading education across all cultural levels of orthographic depth, with its importance more pronounced in deeper language like English[443], suggesting that even in the deepest orthographies there still exist both reading routes. Therefore the results of the present work are directly applicable to shallower (or deeper) orthographies than English, but it must be taken into account that the relative weighting and interplay of the two systems used in reading visual print may be slightly different.

The Relationship of Visual and Auditory Language: Key Questions

Overarching Questions

It is not generally questioned today whether there are two distinct routes the reading of visual words[14,444]. Here we seek to refine models of visual language by contributing to three critical questions:

1) Where: Can phonological processing be located and can this location contribute to theories about how is phonology derived from the orthographic structure?
2) When: Does phonological processing in reading occur in time to contribute to lexico-semantic access?
3) How interrelated are the auditory and visual language networks?

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PART 1: The relationship of Visual and Auditory Language

CHAPTER 1: The Contribution of the Precentral Gyrus to Silent Reading: An Intracranial EEG Study of Fast Semantic Decisions.

Abstract

Neuroanatomical models of silent reading do not typically include a place for the precentral gyrus. These models typically split into the ventral visual route in the occipito-temporal lobe and a dorsal route typically centered in lateral temporo-parietal cortex. However, evidence from behavioral, neuroimaging, and lesion studies all implicate the precentral gyrus, perhaps in the form of articulatory phonemic representations, as involved in the process of silent reading. Here we record electrophysiology directly from the cortical surface during a speeded semantic decision task from 22 patients with grids in the perisylvian region including the precentral gyrus. We report that the precentral gyrus showed a significantly higher proportion of electrodes responsive to linguistic stimuli than posterior temporo-parietal regions including the STG and parietal regions. Phase-locking value revealed significant phase-locking between the fusiform gyrus and the precentral gyrus starting at ~220ms. Using the large number of patients performing this task, we also perform exploratory analyses of regions typically involved to better characterize the cortical spatiotemporal relationships during silent reading.

Introduction

The study of reading has been of interest since the advent of modern cognitive neuroscience in the late 1800s with lesion studies[1]. Original theories posited a visual letter identification system appended through visual-to-auditory conversion onto an already existing, fully-formed perisylvian auditory language network[2]. More recent evidence from lesion[3], neuroimaging[4], developmental[5], and modeling[6] studies has instead demonstrated the existence of a multi-route network for reading with concurrent cognitive operations[6–8] carried out across large portions of the frontal, temporal, and occipital cortices[4,9,10]. This theorized widespread and simultaneous processing matches well with the widespread and simultaneous electrophysiological activity measured across the cortex during visual language processing with intracranial electrophysiology (iEEG) [11].

Broadly, the reading network has traditionally been broken into two streams, one encoding visual linguistic information and a second route encoding the auditory linguistic information. Over 30 years of neuroimaging studies with a wide variety of paradigms and methodologies have attempted to map these two putative streams onto neural circuits providing a neuroanatomical basis to the models of reading. A current view dominates the field: a ventral visual stream centered predominantly on the fusiform gyrus and a dorsal auditory stream centered predominantly on a lateral posterior tempo-parietal network[4,9,10]. In this introduction we motivate the inclusion the precentral gyrus as a largely ignored candidate area in reading.

The Posterior Temporo-Parietal Region: The traditional locus of the dorsal reading network

The initial lesion studies into visual language from the 19th century implicated the angular gyrus, and more broadly Wernicke's area, as the critical link between visual text encoding in the occipital lobe and the wider perisylvian auditory language network[1]. Comparative fMRI studies provided early support for this localization, with phonological tasks displaying greater activation in and around the angular gyrus for words relative to non-words[12] and greater BOLD activity for rhyme judgements than semantic judgements[13] or spelling judgements[14]. However, an alternative explanation for these comparative differences emerged when it was observed that angular activation for words versus consonant strings was explained by suppression of activity for consonant strings rather than an increase to words, with word activation being no greater than fixation[15].

With evidence equivocal evidence for the angular gyrus involvement in the dorsal network, several neighboring areas have also been examined. Posteriorly the intraparietal sulcus [13,16] and anteriorly the superior temporal gyrus (STG) has also been theorized to be involved in phonological processing. Inferiorly, the caudal middle temporal gyrus (MTG) has been implicated in the semantic processing[4,9,10,17].

The Precentral Gyrus: An ignored contributor to reading

An early major review of the neuroanatomy of reading noted "Even though [it] will not be discussed here, it must be kept in mind however that…[the] precentral gyrus, [has] been reliably found as activated in reading by different studies"[9]. Other reviews attributed rolandic activity to articulatory activity during reading aloud but not during reading silently[10,17,18] (but see[4]). However, early psychological theory emphasized articulatory cognitive operations[19] in silent reading, based mainly on behavioral evidence from the articulatory suppression paradigm. In this paradigm, participants repeat a nonsense phrase to occupy the articulatory cognitive operations while performing a reading task, resulting in suppressed phonological behavioral effects[20–22] but not if mouth movements were non-articulatory[22]. Comparing phonological similarity effects for visual and auditory stimuli, articulatory suppression removed the phonological similarity effect for visual but not for auditory words[23] implicating articulatory encoding operations in silent reading.

A variety of BOLD neuroimaging and lesion studies provide additional evidence for the inclusion of Rolandic cortex in reading. In BOLD studies using masked phonological priming, the masked presentation of visual text activated the left precentral gyrus[24]. Studies find greater activity in the precentral gyrus when making phonological versus semantic judgements[25], find differential activation based on the spelling-sound consistency of a word[26], and show increasing activation with increasing difficulty of grapheme-to-phoneme conversion[12]. In addition to phonological effects, there exists a putative 'hand-writing' area just anterior to the hand motor area revealed by BOLD[27] and cortical stimulation[28] which shows increased BOLD activation during passive viewing of orthographic but not false-font stimuli[29]. Lesion damage to the Rolandic area reduced a patient's ability to make phonological judgements about visual words[30].

A second patient with similar lesion damage had an inability to make rhyming judgements or manipulate pseudowords[31].

The current study

Taken together, the literature strongly points to the involvement of the precentral gyrus in reading. The current work attempts to ground the inclusion of Rolandic regions in neuroanatomical models of silent, skilled reading with electrophysiological evoked-activity from intracranial recordings from the pial surface in 22 patients. The electrodes were mainly localized in the peri-sylvian and peri-rolandic areas, placed for clinical purposes, providing excellent spatial coverage to investigate the relative contributions of each region during speeded, silent reading. The findings presented here emphasize that a neuroanatomical model of silent reading must include a place for Rolandic regions in phonological/lexicosemantic cognitive operations.

Methods

Participants and Recordings

Electrocorticographic (ECoG) recordings were obtained from 24 patients (15 females, mean age 36.6 (range 16-53), mean onset age 17 (range 1-42) undergoing intracranial EEG monitoring as part of treatment for pharmacologically resistant epilepsy. All patients were either right-handed or confirmed to be left-hemisphere language by WADA, or both. All procedures were approved by the Institutional Review Board at New York University and written informed consent was obtained from all participants. Electrode placement was determined by clinical criteria to identify seizure activity and eloquent tissue. Each patient was implanted with subdural platinum-iridium electrode arrays embedded in silastic sheets (AdTech Medical Instrument Corp). Data included arrays of grids (8x8 contacts) and strips (1x4 to 1x12 contacts). Contacts had a diameter of 4mm with 2.3mm exposure. Center-to-center spacing between contacts was 10mm for grids. Recordings were acquired using a Nicolet One EEG system sampled at 512 Hz and bandpass filtered between 0.5 and 250 Hz.

Electrode localization

Electrode localization was done through co-registration of pre- and post-implant MRI images, followed by manual and automatic localization of electrodes[32]. Anatomical parcellations were determined using the Desikan-Killiany atlas[33]. Long gyri were split into 3 equal parts, inferior/middle/superior (Pre-central gyrus, post-central gyrus) or caudal/middle/rostral (fusiform, ITG, MTG, STG, Middle-Frontal) using freesurfer. Three-dimensional reconstructions of cortical surfaces in figures were created using FreeSurfer[34]. Localization into a brain region was performed in each subject's native brain. Subject average electrode location, used for display purposes only, were obtained using FreeSurfer surface-to-surface calculations with the fsaverage brain. Figure 1C shows the electrode coverage throughout the cortical parcellations, highlighting our coverage of relevant left-hemisphere perisylvian regions as well as lateral occipital, inferior frontal gyrus, and ventral temporal regions. Regions with <5 electrodes were excluded from analysis.

Task Design

Patients performed a semantic judgment task in which they were instructed to respond by pressing a button in response to rare animal target items (e.g., SHEEP) which were ~5% of the total stimuli. The task used to evoke cortical responses is an animate/inanimate semantic judgement which will ensure completion of lexico-semantic integration, as opposed to the less complete familiarity judgements possible in a lexical decision task[35]. Stimuli used are words (animate and inanimate), consonant strings, and false-fonts. False-fonts, matched to alphabetic letters on a variety of sensory characteristics[36] such as size, line length, and number of strokes, allowed us to discriminate visual sensory processing from orthographic, phonological, and lexico-semantic processing. Consonant strings isolated orthographic from phonological and lexico-semantic operations. Consonant-strings ('BRZ') were chosen over pronounceable pseudowords ('BAZ') because comparing word- and pseudoword-evoked activity presents difficult interpretations. Pseudowords evoke activity across all reading-involved neural regions[37] and often evoke more activity than words[9]. In contrast, consonant strings are discriminated as non-words faster than pseudowords[38] and reduce semantic effects[39–41] suggesting they provide a good control for orthographic versus phonological and lexico-semantic processes. We were unable to find any literature on whether consonant strings are phonologically re-coded, but as they are unpronounceable and cannot be broken down in syllables it is assumed they evoke no more than cursory phonological re-coding. These three stimulus types will allow us to split word processing into sensory, orthographic, and phonological/semantic operations. Also included are words which repeat throughout the task, which will serve as an assay of if and when information regarding word identity begins to affect processing in a region[42].

Stimuli were presented visually as white letters on a black background in Arial font. Stimuli consisted of 400 novel object words that were presented only once (e.g. 'BELT'), 400 repeated object words (20 words repeated 20 times each), 400 unpronounceable consonant letter strings (e.g. HSMBLT), 400 false font stimuli, and 80 target animal words. The false font stimuli were alphabet-like characters that matched a real letter in the English alphabet in size, number of strokes, total line length, and curvature. The repeated word trials were interleaved with normal trials and spaced with an average of 4.2 intervening stimuli between each instance of a repeated words(2520ms), with a range of 1 to 10 (600ms to 6000ms). Individual repeated words were spaced with an average of 42 intervening stimuli (25200 ms), with a range of 29 to 59 (17400 ms to 35400 ms). Figure 1A shows the task design and sample stimuli.

Data were collected using a rapid stimulus onset asynchrony (SOA; 600 ms) and a very large number of trials per condition in order to obtain electrophysiological data with a high signal-to-noise ratio (SNR) in a short time frame. The experimental task was organized into two separate lists, each list taking approximately 10 min to complete. The tasks were programmed using Presentation software (Neurobehavioral Systems, Inc).

Data Processing

Data were preprocessed using MATLAB (MathWorks), the Fieldtrip toolbox[43], and custom scripts. We used an average subtraction reference for each patient to remove global artifacts and noise followed by a bandstop around line-noise and its harmonics (60,120,180Hz). Data was epoched to the onset of stimulus presentation from -400ms-to-1200ms to have enough temporal padding to avoid any epoch-edge artifacts introduced by converting from the time domain to the frequency domain. Additional temporal padding was removed at the end of pre-processing. For high-gamma power, epochs were transformed from the time domain to the time–frequency domain using the complex Morlet wavelet transform from 70-170Hz in 10Hz increments. Constant temporal and frequency resolution across target frequencies were obtained by adjusting the wavelet widths according to the target frequency. The wavelet widths increase linearly from 14 to 38 as frequency increased from 70 to 170Hz, resulting in a constant temporal resolution with a standard deviation of 16ms and frequency resolution of 10 Hz. For each epoch, spectral power was calculated from the wavelet spectra, normalized by the inverse square frequency to adjust for the rapid drop-off in the EEG power spectrum with frequency, and averaged from 70 to 170 Hz, excluding line noise harmonics. This data was smoothed by a moving window exactly matching the temporal characteristics of the wavelet. Each trial epoch was demeaned with a baseline from -75-to-0ms. Trials containing artifacts were identified by amplitude and variance, visually inspected for artifacts and removed from further analysis.

Task Effect Analysis

Behavior: Behavior was characterized with both measures of performance (d’) and speed (response-time). Patients had to respond to trials containing animate nouns with stimuli coming every 600ms, the fast ISI necessary in order to obtain high SNR electrophysiological data in an acceptable total task time for the clinical patients. Because patients had difficultly identifying an animate noun and performing a motor movement within the 600ms trial consistently, correct responses were allowed which occurred either during the target trial or the following trial (i.e. within 1200ms of the target word onset). Responses outside of this time period were counted as false-positives.

Task Responsivity & Language Sensitivity: Electrodes that had significantly increased activity from a baseline of 0 to any of the 4 stimulus conditions between 25-to-600ms (Task-Responsive electrodes) were identified using a timepoint-by-timepoint t-test corrected for temporal false-discovery rate at $p<.05$[44]. Next electrodes were then run through a one-way ANOVA between the 4 stimulus conditions between 25-to-600ms at $p<.01$ temporally corrected using a bootstrapped shuffling of trial identity 1000 times[43]. Only electrodes which were significant in both these tests were included in further analysis (Language-Sensitive electrodes).

Characterizing Language-Sensitive *Electrodes:* To understand which condition differences were driving the significant differences between condition identified by the ANOVA, pairwise one-way ANOVAs were next run to determine if electrodes were Language-Specific (i.e. Words > False-Fonts but Words = Consonant Strings)*,* Word Specific (i.e. Words > False-Fonts & Words > Consonant Strings), or False-Font-Specific (i.e. False-Fonts > Words). ANOVAs were run timepoint-by-timepoint, once again corrected using the bootstrapped shuffling method. The 'Language Sensitive' ANOVA results was used to mask significant time-periods to ensure differences found between conditions were part of the originally identified language-sensitive time period).

Characterizing Sensitivity to Stimulus Characteristics: Two additional determinations of electrode sensitivity were made based on response sensitivity to Repetition and Word Frequency. The repeated words represent priming[45–49], which has been used effectively to measure N400 processes which are conceived of as simultaneous cognitive operations accessing and integrating word identity and meaning[50,51]. The form of priming in this study is full repetition priming, which leads to multiple well-documented empirical regularities, with decreased neuronal activity previously found in task-engaged regions using fMRI[52], unit firing[53], and iEEG[54]. In this particular study, the representational traces relate to linguistic identities. As the method of repetition occurring here is full repetition, these representational traces relate to both sub-lexical and lexico-semantic level representations. Electrodes sensitive to Repetition

(Novel Words > Repeated Words) were identified. Since repetition effects are related to decreased neuronal firing, this is why only one effect direction is accepted.

Word frequency has a rich history in the study of reading. For just some examples, it affects naming speed[55], affects eye fixation time[56], a number of studied effects in reading are only found with low frequency words[57,58], and extracranial EEG reports effects based on word-frequency[59]. For word frequency, the MCWord database[60] was used to obtain orthographic frequency for all novel words. Then a split was performed with the bottom 40% of words labeled 'Low-Frequency' and the top 40% of words labeled 'High-Frequency' (excluding the middle 20% of words from analysis). The same ANOVA procedure, corrected with the shuffled method, was performed to identify if electrodes were sensitive to Orthographic Frequency (Low Frequency > High Frequency).

Regional Comparisons

Comparisons between regions are difficult in iEEG due to sparse coverage that varies between participant due to clinical considerations. However, studies with large numbers of patients note that while locations of interest, such as language, vary according to neuroanatomical landmark they are located in generally similar regions[61]. For this reason, this study will make use of non-parametric statistics to compare both proportion of electrodes and timing of electrodes between regions. For proportion of electrodes, this will be done in two ways: 1) a planned a-priori comparison between the precentral gyrus and the STG, Supramarginal Gyrus, and Parietal Lobe 2) A broader post-hoc comparison between regions of interest.

The planned comparisons center on the precentral gyrus versus the posterior temporo-parietal regions and is driven by theoretical interest in their likely function in silent reading. Both theoretically[19] and empirically[24–26] the most likely function the precentral gyrus would play in reading is in grapheme-to-phoneme conversion. This role in grapheme-to-phoneme convrersion is usually attributed to some region, or combination of regions, within the posterior temporo-parietal cortex[10,17,18]. Therefore, the core question to answer is the responsiveness and timing of activity in these two constellation of regions between phonemic articulatory cortex (precentral gyrus) and candidate phonemic encoding cortex (STG, supramarginal gyrus, and parietal regions). With 3 comparisons, the corrected p-value threshold was *p*<.016.

The second, broader series of comparisons will include more regions in an effort to take full advantage of our extensive number of patients to see if further information regarding the broader reading network function can be gleaned. For this, 7 regions will be compared to the total pool of electrodes from other included regions (minus the region being tested's electrodes) to see if the region is more/less involved or faster/slower than the total pool of responses. These 8 regions tested are typically focused on in neuroanatomical models of reading will be included in the statistical tests: Fusiform, Lateral Occipital, STG, MTG, Supramarginal, Precentral Gyrus, Pars Opercularis, and Pars Triangularis. Therefore the corrected *p*-value is *p*<.006. As this is a stringent threshold, the total number of datapoints (i.e. significant electrodes) for some conditions is low, and we are using non-parametric statistics which have lower power, p-values *p*>.007 but *p*<.05 will be noted as well, but marked as uncorrected.

In addition to the distribution, we will also compare effect onset timings between regions statistically is difficult because of the variable number of effects per region causes differences in power between regions. For example, a critical question is the timing of the precentral gyrus versus the STG, but the STG contained only 9 Language-Specific electrodes compared to 27 for the precentral gyrus. However, despite these difficulties some regularities emerged. These timing analyses will mirror the targeted/exploratory structure of the regional distribution analyses and share their *p*-value corrections. All tests run will be a ranksum non-parametric test.

Stimulation

A subset of 10 of the patients underwent clinical cortical stimulation for functional mapping prior to possible epilepsy surgery. Testing was performed by epilepsy and neuropsychology teams together. A NicoletOne cortical stimulator delivered a constant current output to adjoining electrode pairs, pulse width of 500ms, frequency of 50Hz, and maximum train duration of 5s. Current was manually controlled starting at 1mA and gradually increasing by 1-4mA until either: a maximum of 12mA was reached, a functional response was seen, or epileptiform discharges were seen. Responses were confirmed with repeat stimulation, and testing of adjoining electrodes was performed when responses were ambiguous. The patient was instructed to inform the testing team if any positive (tonic and/or clonic) or negative (drift) motor or sensory phenomena were experienced.

For this task, stimulation results of interest were language testing and motor testing. Language testing included continuous speech production and naming. Baseline was reevaluated during the procedure to ensure patient participation. Speech production was tested by asking the patient to recite a continuous phrase (e.g., the pledge of allegiance, alphabet, or counting). Interruption of speech unrelated to motor function was noted as a positive finding. Naming was tested using a visual naming task (line drawings) and/or an auditory naming task (naming objects after an auditory description). Response initiation that was different from baseline or paraphasic errors were noted as positive. Positive response were noted as "language" responses without noting the specific task involved.

Motor testing revealed articulatory-selective electrodes. Functional responses are described as a percentage of positive responses over the number of electrodes tested for visual, language, motor and sensory phenomena. Motor and sensory responses are described for speech production muscles (face, mouth, tongue, and throat) and non-speech production muscles, such as the hand, separately. For 1 patient, motor movement type was not listed, but most electrodes were in similar regions, i.e. inferior precentral gyrus, as mouth- and face-motor movement electrodes in other patients. We limit analysis to the left hemisphere due to limited cortical stimulation data in the right hemisphere.

Connectivity

To test the putative network identified in individual electrodes with HGP effects, we used Phase-Lag Value (PLV) calculated pairwise between electrodes as decribed in [62] to test whether

functional connectivity could be inferred between electrodes. PLV measures the consistency of the relative phase of LFPs in two locations. High PLV indicates consistent synchronization of the synaptic currents in pyramidal apical dendrites between the cortical locations underlying the intracranial sensors. Significant PLV was determined by creating a distribution of all PLV values from a baseline period (-200-to-0ms) for each subject. Only if the obtained PLV value after stimulus presentation was $p<.001$ based on the subject's own baseline distribution was a pairwise connection judged to be significant.

Results

Behavior: Behavioral data was available for 19 of the 24 patients due to technical issues with 6 of the patients. Figure 1B shows D' and and response time across subjects. Average d' was 2.79 (range: 0.5-to-4.84) and average correct response time was 787ms (range: 560ms-to-1099ms). This demonstrates participants were able to perform the task effectively and the response times were equivalent, if not a bit faster, than for a similar task in a behavioral database[63].

Regional Effects: Table 1 and Figure 2 display the parcellation regions and their 'Language-Sensitive' electrodes as the percentage of total electrodes recorded from. The table also includes the number of patients with a language sensitive electrode out of the total number of patients recorded from for each region. In this section we take advantage of the high number of electrodes to assess the involvement of each region in visual text encoding and lexico-semantic decision making. Following sections will break these 'Language-Selective' electrodes into specific effects for a more fine-grained characterization of each region's contribution to reading. As noted in the methods, all *p*-values reported for regional effect comparisons use Fisher's Exact Test. Also as noted in the methods, analyses will be broken into the critical comparison of the precentral gyrus (corrected *p*-value of .05/3=.016) and a more exploratory analysis involving the proposed 8 putative critical regions in neuroanatomical models (corrected *p*-value of .05/8=.006). Values between .05 and the corrected *p*-values will be reported but noted as ‘fdr uncorrected’.

In addition to the distribution of effects across the cortical reading network, each section will also include effect onset analyses regarding the onset of these effects. Figure 5 displays the timing of Language-selective as well as Orthographic-, Word-, and False-Font—specific effect onsets. Table 3 displays the median and range of effect onset timing for the left hemisphere

Language Sensitive Effects: As expected, Language-Sensitive activity were overall left-lateralized ($p<0.05$). Follow-up tests between hemispheres for the 8 regions of interest revealed left-sided predominance for the precentral gyrus ($p=.035$; fdr uncorrected) and fusiform gyrus ($p=.016$, fdr uncorrected). The only region right lateralized was the lateral occipital region ($p=.003$).

Focusing on the left-hemisphere, the critical test between the precentral gyrus and posterior temporo-parietal regions revealed that the precentral gyrus had a greater proportion of language-sensitive electrodes than any of the temporo-parietal electrodes. The precentral gyral proportion of language-sensitive electrodes (27%) was greater than the STG (8% ; $p<.001$), Supramarginal (8% ; $p<.001$), and parietal region (5%; $p<.001$).

In the left hemisphere, the exploratory 8-region analysis comparing each region to the pool of the other regions revealed a general trend of occipito-temporal and frontal regions having greater proportion of language-sensitive electrodes and temporo-parietal regions having a lesser proportion. Overall, the lateral occipital (37%; $p<.001$), fusiform gyrus (45%; $p<.001$), precentral gyrus (27%; $p =.005$), and pars opercularis (28%, $p=.02$, fdr uncorrected) had a greater proportion of language-selective electrodes than average. In contrast, electrodes in the STG (8%, $p=.002$), MTG (8%; $p<.001$), and supramarginal gyrus (8%; $p=.002$) were significantly less likely to show evidence for visual language encoding.

For the onset timing of Language-sensitive effects, there were no differences in the targeted analysis with the timing of the Precentral Gyrus not significantly different from the STG, Pars Opercularis, or Supramarginal (all *p*>.20). For the exploratory analysis, the fusiform was faster than the pooled onset (*p*<.005) as was the lateral occipital (*p*<.05; fdr-uncorrected). The Pars Opercularis had a significantly later onset than the pooled onsets (*p*=.009, fdr-uncorrected). The rest of the regions had no significant difference from the pooled onsets.

Letter- and Word-Selective Effects: Having established a occipito-temporal and frontal localization of language-sensitive activity, next we sought to characterize the linguistic level of processing occurring in each region. This involved finding the the preferred stimuli (i.e. false-font, letter, or word preferring) of the Language-Sensitive electrodes identified in the previous section. Figure 3 & Table 2 provides the distribution and the number of the Language-Sensitive electrodes which displayed 'Letter Specific' (i.e. word > false-font but not word>consonant string), 'Word Specific' (i.e. both word>false-font and word>consonant string), and 'False-Font Specific' (false-font>word) responses.

Letter-specific electrodes showed no significant differences between hemispheres (*p*=.08). For the targeted precentral/temporo-parietal comparisons, none of the comparisons reached fdr-corrected significance. In total, the precentral gyrus does have a slightly higher proportion (5%) than the STG (1%; *p*=.08), supramarginal (3%; *p*=.22), or parietal (0%, *p*=.03, fdr uncorrected) regions. The exploratory analysis comparing between the 8 regions within the left hemisphere showed that occipito-temporal regions had greater proportions of letter-selective electrodes. The fusiform gyrus (15%; *p*=.002) and lateral occipital (10%; *p*=.01, fdr uncorrected) had greater proportions of letter-specific electrodes than other regions. No other regions were significantly increased relative to the other regions.

Within the left-hemisphere, for letter-specific onset effects the critical precentral/temporo-parietal revealed no differences in timing (all *p*>.05). In the exploratory analysis, letter-specific effects in the fusiform were significantly faster than the pooled effects (250ms; *p*=.006). Letter-specific effects in the pars opercularis were significantly slower than the rest of the regions (520ms; *p*=.002).

Word-specific electrodes showed an overall left hemisphere distribution (*p*<.001). Follow-up tests between hemispheres for the 8 regions of interest revealed left-sided predominance for the precentral gyrus (*p*=.002) and the fusiform gyrus (*p*=.007, fdr uncorrected). For the targeted precentral/temporo-parietal comparison, the precentral gyrus had a significantly greater proportion of word-specific responses than the temporo-parietal regions. The precentral gyrus proportion (17%) was greater than the STG (6%, *p*=.006), supramarginal (4%; *p*=.003), or parietal (4%; *p*=.002) regions. The exploratory analysis comparing the 8 regions demonstrated that the frontal regions were only regions with a greater proportion of word-specific responses than average. The pars opercularis (20%; *p*=.003) and the precentral gyrus (17%, *p*<.001) displayed this trend. The MTG (2%; *p*=.004) had a significantly lower proportion of word-specific responses.

To further demonstrate the general distinction between word-specific responses in the frontal regions (i.e. pars opercularis and precentral gyrus) and the mixed responses in occipito-temporal regions (i.e. lateral occipital and fusiform gyrus) we ran a test between the letter-specific and word-specific proportions in each region. Overall, word-specific responses were a greater proportion than letter-specific responses (*p*<.001). Both the precentral gyrus (*p*=.004) and the pars opercularis (*p*<.001) demonstrated this pattern. Neither the fusiform gyrus (*p*>.2) nor the lateral occipital (*p*>.2) showed a significant difference between letter-specific and word-specific responses.

Within the left-hemisphere, for word-specific onset effects the critical precentral/temporo-parietal revealed no differences in timing (all *p*>.05). In the exploratory analysis, the pars triangularis word-effects were faster than the pooled effects (260ms; *p*<.05, fdr uncorrected). Interestingly, both a frontal region, the pars opercularis, and an occipito-temporal region, the lateral occipital region, were slower than the pooled word-effect onset times. The pars opercularis (520ms; *p*<.05, fdr uncorrected) and lateral occipital (460ms; *p*<.05, fdr uncorrected) were slower than the pooled responses. Overall, letter-onset was before word-onset (*p*<.05).

False-Font—Selective Effects: A surprising aspect of the responses to the different stimuli classes was the large number of electrodes responding preferentially to False-Fonts. The False-Font—selective electrodes presented a counterpoint to the letter- and word-specific electrodes, as they were lateralized to the right (*p*<.001). For the targeted temporo-parietal analysis there was no significant differences regions (all *p*>.10). Due to this unusual lateralization, for these effects we ran the exploratory analyses in both hemispheres. In both the left (15%; *p*<.001) and right (41%; *p*<.001) hemispheres, the lateral occipital region was greater than the average proportion. The fusiform was also greater than the average for the left hemisphere (15%; *p*=.001) and in the right hemisphere (16%; *p*<.05, fdr uncorrected). No other region was greater than the average in either hemisphere.

Within the left-hemisphere, for false-font—specific onset effects the critical precentral/temporo-parietal was not run because there were not enough effects in these regions. For the Overall, the lateral occipital effects (180ms; *p*=.002) were faster than the pooled effects. Due to the right lateralization of these effects, we also ran tests in the right hemisphere. Here, only the lateral occipital (160ms; *p*<.001) was significantly faster than the pooled. Overall, false-font effects were significantly faster than both letter onset (*p*<.001) and word-onset (*p*<.001). Both of these effects were primarily driven by false-font—onset in the lateral occipital being greater than letter-onset (*p*<.001) and word-onset (*p*<.001).

Repetition-Selective Effects: Here we focus on the first of two effects which give insight into whether a region is sensitive to cortical represntations of either phonological or lexico-semantic identity. Figure 4 displays the location and example waveforms for electrodes displaying a lexical frequency and/or a repetition effect. For repetition-effects, there was no significant lateralization trend (but there was a trend toward left-hemisphere lateralization; *p*=.065). In the left hemisphere repetition effects were predominantly overlapping with word-selective electrodes (*p*<.01) but not for letter-specific effects (*p*=1) or false-font (*p*=1). There were no significant associations in the right hemisphere (all *p*>.5). Examining the distribution of

Repetition effects, in the exploratory 8 region analysis the fusiform (17%, *p*=.002) and the lateral occipital (10%; *p*<.05, fdr uncorrected) showed increased repetition effects relative to the pooled regions.[In raw numbers, the greatest concentration of repetition effects were found in the precentral gyrus (8), fusiform (7), STG (6), and also the lateral occipital (6).

Lexical-Frequency—Selective Effects: To finish our characterization of the distribution of effects we examined the distribution of Lexical-Frequency effects. Lexical-frequency effects were left-lateralized (*p*=.02). Strong overlap with repetition effects was found. Out of the 20 left-hemisphere lexical-frequency effects, 16 overlapped with repetition effects (binomial test against expected percentage by chance: *p*<.001). In addition to overlapping with repetition effect electrodes, lexical-frequency effects were predominantly overlapping with word-selective electrodes (*p*<.01) but not for letter-specific effects (*p*>.5) or false-font (*p*>.5) electrodes. There were not enough Lexical-Frequency electrodes found to make statistical claims regarding the distribution of these effects across regions, but lexical-frequency effects tended to cluster in the STG (4), Precentral Gyrus (4), MTG (2), and Fusiform (2).

Within the left-hemisphere, for lexical-frequency—specific onset effects the critical precentral/temporo-parietal and the exploratory analysis were not run because there were not enough effects in any region. Overall, the median effect onset occurred at ~410ms. Lexical-frequency effects were significantly later than letter-onset effects (*p*<.01) but not word-onset effects (*p*>0.15). A test run within the main region of interest, the precentral gyrus, revealed significantly later onsets for lexical-frequency effects compared to both letter- and word-onset effects (both *p*<.05). There was no significant difference between repetition and lexical-frequency onset across the cortex (*p*>.25).

Stimulation Results

There was significantly less overlap between language-arrest stimulations and language-sensitive responses than expected. This is likely because language-arrest electrodes were concentrated in cortical regions that were un-involved in language-sensitive task responses. A total of 91 electrodes with speech arrest across 6 patients were found, spread primarily across the STG (28%), MTG (22%), and supramarginal (12%). Only 1 electrode was found in lateral cortex with an overlapping speech arrest and evoked response to words a Word-Specific response found in the anterior STG. This was out of 28 word-specific and 26 letter-specific electrodes in these stimulated patients. Note that this roughly equal proportion of word-selective and letter-selective electrodes in these 6 subjects is not typical of the whole dataset in which word-selective electrodes were roughly twice as many as letter-selective electrodes.

One subject had stimulation on the ventral occipito-temporal surface of the brain, with complete overlap between 3 electrodes with speech arrest and evoked letter-selective responses (word > false-font but not word > consonant strings).

Similar to language-arrest, motor-movement electrodes showed limited overlap with electrodes showing language-sensitive activity. However, unlike language-arrest electrodes, motor-movement electrodes did cluster in areas in which language-sensitive electrodes were found, suggesting motor-movement and evoked responses occurred in neighboring but not overlapping cortex. A total of 21 electrodes with an elicited motor movement across 5 patients spread primarily across the postcentral gyrus (46%), precentral gyrus (30%), supramarginal (19%), and Pars Opercularis (5%). Three of the subjects had specific motor responses noted, with 6 face motor responses, 6 orofacial (tongue, larynx, etc.), and 2 hand electrodes found. The hand motor movements were most superior and all face/orofacial electrodes and all evoked responses were inferior to the hand responses. In total, 3 electrodes had an overlapping evoked language response and a motor response. A single evoked Word-selective electrode overlapped with a facial muscle movement in the precentral gyrus. In the supramarginal gyrus 1 Word-Selective electrode had overlapping facial motor movement and 1 Orthographic-selective electrode were found overlapping motor movement (specific movement not specified). This was out of 21 noted letter-selective electrodes and 25 noted word-selective electrodes in these 5 subjects.

Connectivity Results

Only 1 subject was found to have word-specific responses in the caudal fusiform, STG, and precentral gyrus which will serve as a case-study subject to add complementary connectivity grounding to the already mentioned evoked responses which strongly motivate the inclusion of the precentral gyrus regions in silent reading. Figure 7B displays the average PLV connections (6-12Hz) between 4 electrodes: a caudal fusiform, a middle fusiform, a STG, and a precentral gyral electrode. Figure 7A displays the HGP responses in these electrodes to give an idea of the underlying time-course of the neural activity at the same time as the PLV results.

The PLV results point toward an early phase-locking between fusiform sites, between fusiform sites and the precentral gyrus, and between the precentral gyrus and STG, but not between the fusiform and the STG. The earliest significant PLV was between the fusiform sites, beginning at ~100ms and lasting till ~225ms. Neither of the fusiform sites had a significant PLV connection with the STG site. However, both fusiform sites did display phase-locking with the precentral gyrus beginning at ~180ms. The middle fusiform site lasted until ~320ms and the caudal fusiform to ~520ms. Finally, there is also prolonged above baseline connectivity between the STG and precentral gyrus from ~220-500ms

Discussion

Many neuroanatomical models of silent reading do not include the precentral gyrus[9,10,17,18]. Here we present evidence from electrophysiology recorded directly from the cortical surface during speeded semantic decision making which calls this exclusion into question. The location, timing, and connectivity of evoked high-gamma power strongly implicates the precentral gyrus as an important node in the silent reading network. This is in contrast to most neuroanatomical models of silent reading which place significant emphasis instead on posterior temporo-parietal regions. Here we found that these posterior temporo-parietal regions in general were significantly less involved during reading, across patients.

This discussion will be organized in the following way. First is the discussion of the exploratory analysis of the 7 regions most typically involved in neuroanatomical models of reading and how our iEEG findings to relate to previous work on this network. This will be followed by a discussion for the potential role of the precentral gyrus in the widespread reading network and discussion of the hypothesis driven comparisons between the precentral gyrus and the posterior temporal-parietal regions.

Occipito-Temporal: Fusiform Gyrus and the Lateral Occipital Region

The ventral temporal lobe is strongly associated with the orthographic processing of visual text[24,36,64,65], in which specialized cortical patches proceed along the ventral surface of the brain in an anterior sweep from sensory to low-level orthographic to lexico-semantic processing[36,66]. The criticality of these occipito-temporal cortical patches for reading is revealed by lesions[67] and by cortical stimulation[68]. The temporal speed of this early orthographic processing beginning at ~160-180ms is confirmed by a MEG study[36] and iEEG evidence[69,70]. A number of iEEG studies place lexico-semantic effects in the more anterior ventral temporal lobe beginning at ~250ms[71–73]. This 250ms onset of lexico-semantic sensitivity is aligned well with the ~250ms onset of the widespread N400 effect which is taken to index lexico-semantic integration across a wide variety of paradigms[50].

Supporting the early orthographic processing the occipito-temporal region, both the fusiform and lateral occipital regions had a higher proportion of language-sensitive electrodes than the pooled regions and the onset of these language sensitive responses was earlier than the pooled onset times. The early onset times were primarily driven by letter-specific responses and false-font—specific responses which were higher in proportion in both the lateral occipital and the fusiform. The lateral occipital had faster false-font—effect onsets than the pooled onset while the fusiform had faster letter-effect onsets. Overall, these occipito-temporal regions had a mix of letter-specific, word-specific, and false-font—specific onsets, with no effect proportion being statistically distinguishable from another in these regions.

However, despite early orthographic-level effects the word-specific responses in the lateral occipital region, anatomically the earliest processing region for visual language, had significantly later word-specific responses than the pooled average (the fusiform was not statistically distinct from the pooled average). This was coupled with both the fusiform and lateral occipital regions having statistically higher proportion of repetition effects than other regions, but in both regions the onset of these repetition-effect onsets were slower than the pooled repetition-effect onset times. As repetition effects in the posterior fusiform using temporally-blind fMRI are often taken as evidence of early lexico-semantic processing, here the late onset times for word-specific and lexico-semantic repetition effects suggests instead that this area is a late contributor to higher-level processing. This later word-specific processing time, particularly for N400 effects, matches well with previous reports from local-field potentials of late repetition effects in the fusiform gyrus[11] and a single report of a lexical frequency effect in the posterior fusiform occurring at ~460ms[67]. Additionally, in fMRI there is found equivocal evidence for sensitivity to lexical identity[74] or semantic category[14,75] in the more posterior occipito-temporal areas. This suggests that lexico-semantic knowledge in the posterior occipito-temporal areas may result from feedback propogation. Instead of quick word-form matching, these regions may be more of an early clearinghouse for lower-level orthography with later sustained processing in conjunction with more anterior ventral and more lateral areas.

Because visual information reaches posterior visual cortex ~60ms[76] and behavioral response time in lexico-semantic tasks is not for another 500-700ms[63,77], there is time for a prolonged period of feedforward/feedback lexico-semantic integration. This is confirmed by measuring activity across cortical layers in the anterior-ventral temporal lobe. Here a ~100ms feedforward period of activity in the deeper layers beginning at ~120ms is observed followed by alternating superficial (feedback) and deeper layer (feedforward) activity with flips every ~200-100ms for many hundreds of milliseconds[78,79]. Therefore, there is a period of hundreds of milliseconds during which coordination likely occurs between ventral visual areas and the lateral peri-sylvian portion of the lexico-semantic network. We explore these candidate areas next.

A final point regarding the occipito-temporal linguistic processing is the surprising prevalence of cortical locations responding more strongly to false-font stimuli than to consonant strings and words. The false-font effect proportion was overall right-lateralized and false-font effect onset was overall quicker than both consonant-strings and words. This right-lateralized preference for a novel, but sensorily familiar, script in a linguistic context may relate to mechanisms of learning new linguistic mappings. For instance, when learning a second language both hearing[80,81] and deaf[82] individuals show novel-language > learned-language in the right hemisphere.

A second possible interpretation on the right lateralized False-font preferences, is that the right hemisphere makes early and critical contributions to reading at a sensory- and letter-level as shown by lesion studies. For instance, the right hemisphere is theorized to be able to identify letters in a serial fashion leading to letter-by-letter reading in patients with damage to the left vOT[83]. The criticality of the right hemisphere to reading is also seen in cases of damage to the splenium which leave the visual writing system intact, suggesting an intact left hemisphere language system, but impairs reading due to disconnection of the right and left occipito-temporal lobes[84–86]. Additionally, when learning to read there is an increase in white matter in the splenium of the corpus callosum when compared to illiterate brains[87].

Lateral Temporo-Parietal: Inferior Parietal Lobe, Superior Temporal Gyrus, and Supramarginal

These regions, a loose collection roughly analogous to historical Wernicke's Area, has been historically highlighted as the entryway for visual text into the wider auditory perisylvian lexico-semantic network by early lesion studies[2]. As noted in the discussion, early fMRI studies focused on the angular gyral region (part of the parietal region in the parcellations used in this study) providing early support for this localization, with phonological tasks displaying greater activation than non-phonological tasks[12–14], but evidence for involvement of this region in performing reading tasks is equivocal[15]. Here in the parietal region, which includes the angular gyrus, only 5 out of 93 electrodes (2 out of 9 subjects) showed sensitivity to any language manipulation. These electrodes did tend to be word-specific (4 out of 5) and several did show N400 repetition effects (2). Statistically, the parietal region was almost never dissociated from the pooled average across regions. Taken together this pattern of results suggests that this area is not devoid of language processing but it is not the major hub of classical theory.

The superior temporal gyrus (STG) is also a potential connecting node between occipito-temporal and lateral temporal as it is a critical processing area for auditory phonemes[88–90], evidence exists for correlated phoneme/grapheme neural firing patterns[91], and putative phonological activity during reading is reported during fMRI tasks[14,92,93]. Additionally, an iEEG study found electrodes selective for the human voice in the STG that also responded during a separate task to visual words starting at ~250ms[94]. Similar to the parietal regions, the STG was not generally involved in language processing with only 9 out of 106 electrodes (for 3 out of 16 patients) displaying sensitivity to language which was significantly lower than the pooled average. However, also similar to the parietal regions, the majority of electrodes were word-selective (6 electrodes) and all word selective electrodes showed N400 effects (6 repetition, 4 lexical-frequency). This is suggestive of a region which is not typically involved in silent reading, but for patients in which it is involved it has the signatures of a word-level contributor. The timing of STG effects were interesting. The repetition effects in the STG were very early (median ~180ms) primarily driven by a single participant (the other 2 participants effects were ~320ms, a more normal time across regions). This suggests that in one patient with a potentially altered reading route, the STG can make early contributions to lexico-semantic processing in visual reading but that this is not normally a feature of the reading network.

The supramarginal gyrus is adjacent to both the angular gyrus and STG, as well as the rolandic areas, so was included as a candidate temporo-parietal area in reading. It appears to be slightly more involved with 8 out of 99 electrodes showing language sensitive activity (6 out of 16 patients). Its effects were more split between letter-specific and word-specific (3 letter-specific, 4 word-specific) and the word-specific electrodes tended to show repetition effects (3 repetition effects), a very similar profile to the STG and parietal regions.

There are two possible alternative interpretations for the mismatch between the purported importance of these regions for reading contrasted with the lack of language-evoked activity in these regions observed during the present study. The first is that our recordings emphasize gyral activity and perhaps the relevant phonological information processing in the parietal lobe takes place in the intraparietal sulcus, an area that has been hypothesized as involved in phonological processing[13,16]. We are unable to comment on activity in this sulcus but future iEEG studies utilizing depth electrodes may have access to the relevant sulci and be able to comment.

The second alternative is that the lack of observed activity is related to participants are down-regulating the involvement of these putative phonological regions during a task which is rapid (600ms decision time) and semantic-based in its response requirements. Many theories of phonological contributions to lexico-semantic processing emphasize that participants are able to modulate their phonological processing if phonology is unimportant or deleterious to task performance[95,96] (though not all agree with this assertion[97,98]). However, the contributions of other putative regions in phonological processing discussed below, the pars opercularis and the precentral gyrus, call this particular interpretation into question.

In contrast to the phonological theories surrounding the temporo-parietal regions discussed above, the MTG is traditionally associated with lexico-semantic integration. Studies have found increased activity for words relative to false fonts[99] and pseudowords[93,100] and greater activation for semantic judgements[25,101]. Here we found that the MTG was involved in linguistic processing statistically less than the pooled average with only 8 out of 106 electrodes involved (3 out of 16 patients). More important for a region suggested to be critical for lexico-semantic processing, it was statistically less involved in word-specific processing as well, with only 2 word-selective electrodes.

A potential reason for this putative lexico-semantic integration area to not show many lexical-level effects might be that the speeded animate/inanimate task performed for this study may be too easy and not require semantic input from the MTG. Patients with semantic dementia who have difficulty with high-level semantic distinctions such as 'kitchen-item' versus 'bedroom-item' can retain lower-level distinctions such as 'animate' and 'inanimate'[102]. However, the MTG's lack of language-sensitive activity in this relatively easy semantic decision task does call into question how critical it is for lexico-semantic processing during everyday speeded reading.

Inferior Frontal Gyrus

IFG contributions to the reading network are roughly split into two parts, the anterior and posterior portions. The posterior aspect of the IFG, roughly analogous with BA44 and e Pars Opercularis (PO), has been traditionally associated with phonological processing[4,9]. PO has demonstrated greater activity stimuli associated with phonology[16,100] and for phonological judgements[13,101,103]. During artificial script learning pars opercularis activity was related to letter-sound correspondence learning[104]. In this study, the pars opercularis had a higher proportion of language sensitive responses than the pooled average with 14 out of 50 electrodes (8 out of 13 patients) but these effects were significantly slower relative to the pooled regions. This appears to be primarily driven by the late onset of letter-specific effects and word-specific effects (both simultaneously at ~520ms). The effects found this region were predominantly word-specific (10 electrodes) with no letter-specific effects. This word-level of processing meshes well with pars opercularis' putative role in phonology. The later onset time, which with a median of ~520ms is near the end of the N400 lexico-semantic integration window, is suggestive of a late 'check' on processing rather than an early contributor. An alternative addressing the intermixing of motor and language functional mapping found in this study in the Pars Opercularis could relate to mirror neuron theory, as behavioral and perceptual overlap is found in the Pars Opercularis[105].

The anterior aspect of the IFG, roughly analogous with BA45 and Pars Triangularis (PT), has also been traditionally associated with lexico-semantic processing[4,9]. PT has been found to be more activated for stimuli associated with lexico-semantic processing[16,106,107] and to be more activated for lexicosemantic judgements[13,108]. Similar to the general lack of involvement other putative lexico-semantic area, the MTG, the pars triangularis displayed language sensitive responses in 4 out of 30 electrodes but only for 2 out of 10 patients (though unlike the MTG the overall proportion was not statistically distinguishable from the pooled responses). All of the effects were word-specific and the pars triangularis was statistically the only region with faster word-specific effect onset than the pooled onset at a median of ~260ms. The interpretation of the pars triangularis general lack of involvement, but a preserved involvement for a subset of patients, is similar to the interpretation for the MTG. Damage to the PT does not disrupt simple meaning retrieval but for more difficult semantic tasks[109] suggesting that the PT is only involved when lexico-semantic processing is difficult. However, for the 2 patients that did show evidence of pars triangularis involvement, it occurred very early reserving some space for the pars triangularis in lexico-semantic processing for speeded semantic-decision tasks. These two patients also showed evidence of involvement of the STG suggesting that the involvement of the anterior IFG and of temporo-parietal regions may occur if the reading is more difficult.

Precentral Gyrus

As mentioned in the introduction rolandic activity is often associated with articulatory activity during reading aloud but is not associated with reading silently[10,17,18] (but see[4]). However, early psychological theory emphasized a place for articulatory phonemes in silent reading[19]. A variety of BOLD neuroimaging[12,24–29] and lesion studies[30,31] provide additional evidence for the inclusion of Rolandic cortex in silent reading.

The central analysis of this manuscript is the comparison between the two peri-sylvian regions putatively involved in phonological processing, the precentral gyrus and the lateral temporo-parietal regions. Compared to temporo-parietal regions, the precentral gyrus had significantly greater proportion of language-sensitive electrodes and a significantly greater proportion of word-specific responses. The lack of significant difference in letter-specific or false-font—specific effects places the differences between the two regions at the word-specific level; Exactly where it would be expected based on the hypothesized phonological contributions of the precentral gyrus to reading. While there were not enough N400 effects, i.e. lexical-frequency and repetition, to make proportion claims between these two regions, the precentral gyrus and STG did collectively have high numbers of electrodes with both lexical-frequency and repetition effects. While there may not have been enough significant electrodes in the temporo-parietal regions to make fine-grained temporal distinctions, there is no evidence that word-specific timing or language-sensitive onset timing between regions suggesting processing in both regions is simultaneous. However, in the onset of repetition-effects the STG precedes precentral gyrus effects suggesting that in lexico-semantic—level processing in the STG may precede the precentral gyrus.

In the exploratory analyses, the precentral gyrus' role at the word-specific level of processing also came through. Overall, the precentral gyrus had a greater proportion of language-sensitive electrodes, greater proportion of word-specific electrodes, and high numbers of N400 effects placing the precentral gyrus squarely in the word-specific specific contributions to silent reading. This activity in the precentral gyrus was left-lateralized, as is expected based on the overall left lateralization of word-specific processing during silent reading.

To try and find evidence for connections between the regions in the reading network we examined the time-course of phase-locking value (PLV)[62]. In one patient who had word-specific effects in both the fusiform, STG, and precentral gyrus allowing us to examine the PLV between these regions. The earliest PLV was between a caudal and middle fusiform site at ~100ms and both fusiform sites showed significant phase-locking with the precentral gyrus starting at ~180ms (the median time of letter-specific onset effects in the fusiform) both of which lasted for several hundred milliseconds. Neither fusiform site displayed significant PLV with the STG site.

However, starting at ~220ms there was significant phase locking between the STG and precentral gyrus which lasted for several hundred milliseconds. This pattern of results, early connectivity between ventral occipito-temporal areas and the precentral gyrus is surprisingly in line with early psychological theories of reading which emphasized articulatory phonemes place in silent reading[19]. The lack of connectivity between STG and fusiform, but the presence of connectivity between precentral gyrus and STG suggests that encoding phonemic representations may play a role in silent reading, but in connection with articulatory phonemic representations instead of in conjunction with letter representations in the fusiform.

As to why the precentral gyrus is involved in silent reading, we theorize it has to do with the role of articulation in early reading development. Articulatory activity is crucial in learning to read, a theory called the 'Self-Learning Hypothesis'[110]. It is well known that a student's phonemic awareness is a key determinant in the ability to learn how to read[111] and readers exhibit a strong reliance upon the phonological route at low reading levels[5]. Articulating words aloud leads to better word knowledge[112] while engaging in articulatory suppression suppresses this improvement[113]. A recent review of neuroimaging of reading learning disorders found that Rolandic cortex is hyper-excitable in disordered reading individuals compared to normal readers, interpreted as a compensatory mechanism[114]. Disruption of the motor cortex during learning to read disrupts this learning. Benign Epilepsy with Centrotemporal Spikes is associated with seizures generated in Rolandic areas, typically associated with lower face motor seizures[115]. Traditionally this syndrome has been associated with no overall cognitive impairments[116] but new evidence has emerged for a variety of specific learning deficits including reading[117,118], phonological awareness[119], and lexico-semantic but not morpho-syntactic knowledge[120]. Earlier onset of these seizures increases the chance of developing a learning disability[121].

However, this focus on articulatory phonemes linking ventral and dorsal reading streams is somewhat complicated by our findings that the language-specific electrodes in the precentral gyrus were in neighboring but not overlapping cortex with motor cortex associated with facial muscle movements. More fine-grained study will be necessary to fully understand the relationship between the reading, the precentral gyrus, and articulatory phonemes, but three ideas may combine to clarify these relationships.

The first idea is that learning to read results in changes to existing cortical function, referred to as ‘cortical recycling’[122]. While this phenomenon has been studied most closely in the ‘recycling’ of the left fusiform face area into an orthographic processing hub, given the widespread nature of cortical involvement in reading it is more than likely that additional cortical areas undergo functional changes as result of learning a novel language modality. The second idea is that the relationships of visual and auditory language evolve as reading proficiency improves[5]. Combining these two ideas, it is quite possible that an initially motor-articulatory contribution to reading matures into neighboring cortex as orthographic proficiency increases. The third idea is that the precentral gyrus may have contributions to reading in addition to articulatory phonemic representations. A series of studies has identified a ‘hand-writing’ area in the brain[27] which is responsive to letters viewed passively[29].

Further studies will be required to elucidate the exact mechanistic contribution of the precentral gyrus to reading. However, the fMRI studies finding greater activation in this region for phonological manipulations[12,24–29] suggest a role in phoneme-to-grapheme conversion.

Chapter 1, in part, is currently being prepared for submission for publication of the material. The dissertation/thesis author was the primary investigator and author of this material. Eric Halgren is senior author. Additional co-author’s include Chad Carlson, Orrin Devinsky, Werner Doyle, and Thomas Thesen.

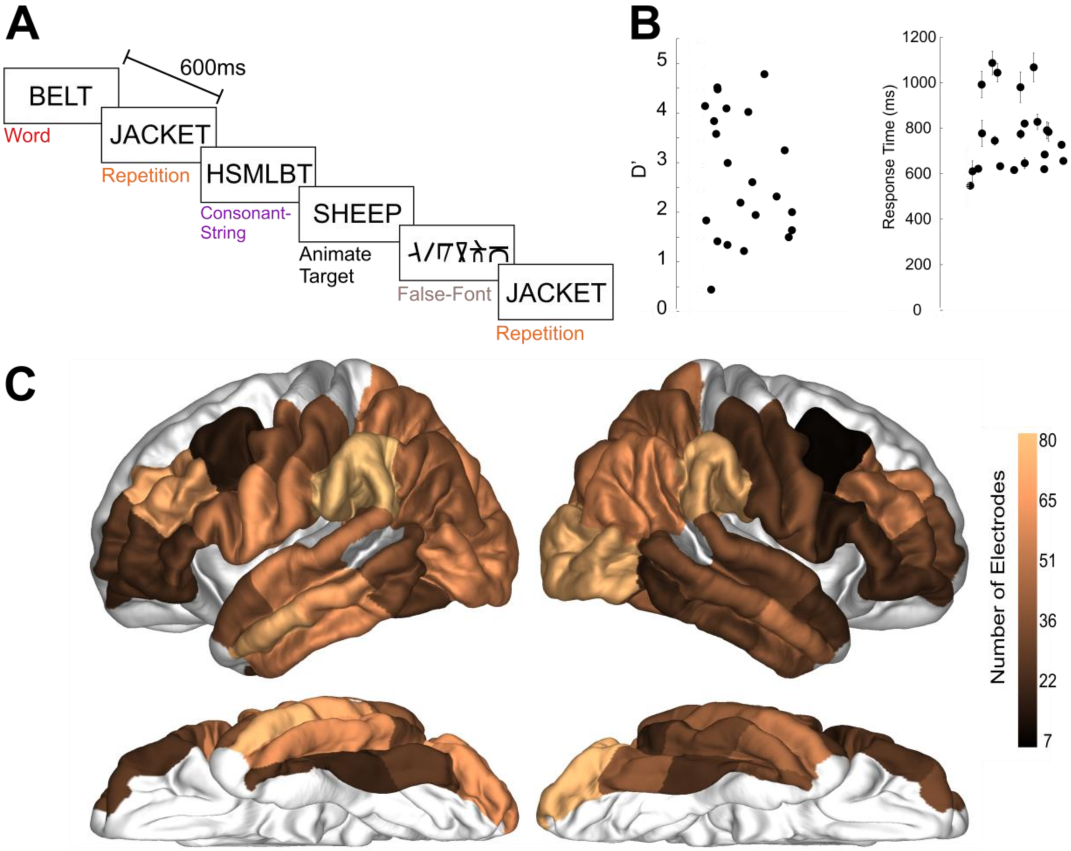


Figure 1.1: Task Design and Electrode Coverage. A) Patients detected animate nouns amid 4 other stimulus types: Words, Consonant-Strings, Repeated Words, and False-Fonts. Stimuli were presented every 600ms. B) Patient performance as expressed by d' and response time. C) Electrode coverage across the included regions.

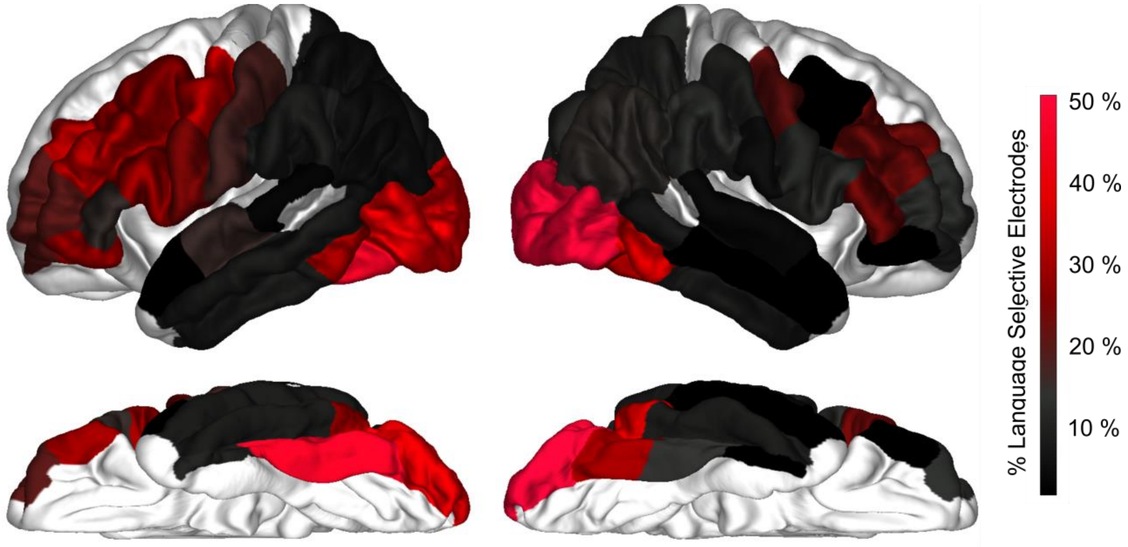


Figure 1.2: Language-Selective Electrode Distribution Across the Cortex. Electrodes were identified which displayed both a significant increase from baseline and a significant difference between conditions for high-gamma power (70-170Hz). Percentages are out of total electrodes in a region. Bilateral occipito-temporal regions and left-lateralized rolandic and frontal regions. Temporal and parietal regions were much less involved.

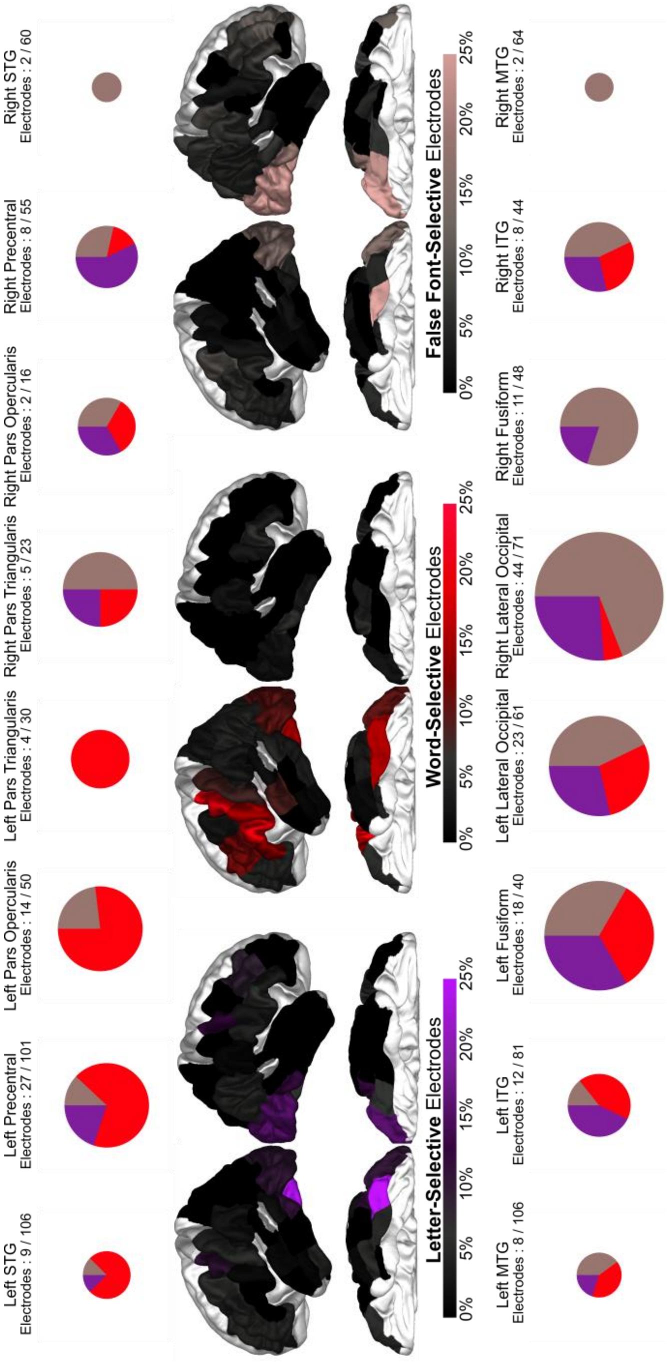


Figure 1.3: Characterizing Language-Sensitive Electrodes. Language sensitive electrodes were characterized as either Letter-Selective (Words > False-Font), Word-Selective (Words > False-Font & Words > Consonant Strings), and False-Font—Selective (False-Font > Words). Surrounding circles display the proportion breakdown in each region between the three effect types for Word-specific (red region), Letter-specific (purple region), and False-font—specific (purple) sections. The relative size of each circle is a representation of the percentages of Language-specific electrodes in each region.

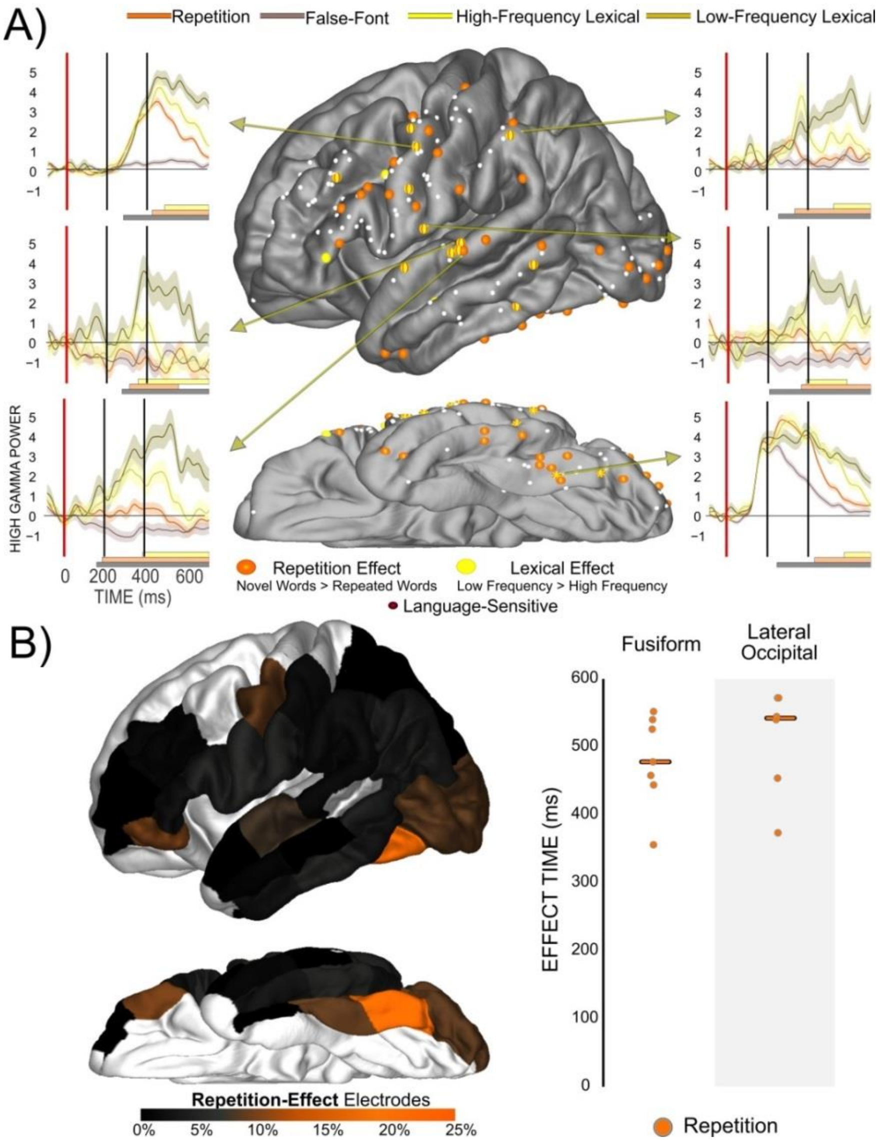


Figure 1.4: The Distribution and Timing of Repetition and Lexical-Frequency Effects. A) Display of electrode location (approximate, morphed to an average brain for display purposes) which demonstrate both a significant effect for orange Repetition (Novel > Repeated) or yellow Lexical-Frequency (Low-Frequency > High-Frequency) from 0-600ms. Arrows from electrodes point to plots of High-Gamma power for Low-Frequency novel words (dark yellow), High-frequency novel words (bright yellow), repeated words (orange), and False-Fonts (grey). The bark bar at the bottom notes periods of significant Word-specific effect, the orange bar notes periods of significant Repetition effects, and the yellow bar notes periods of significant Lexical-Frequency effects. B) On the left is a brain displaying the proportion of Repetition effects, most prevalent in the caudal fusiform. On the right is displayed Repetition effect onset times. Orange circles are onset of a Repetition effect (Novel > Repeated). The line is the median for each effect in the region.

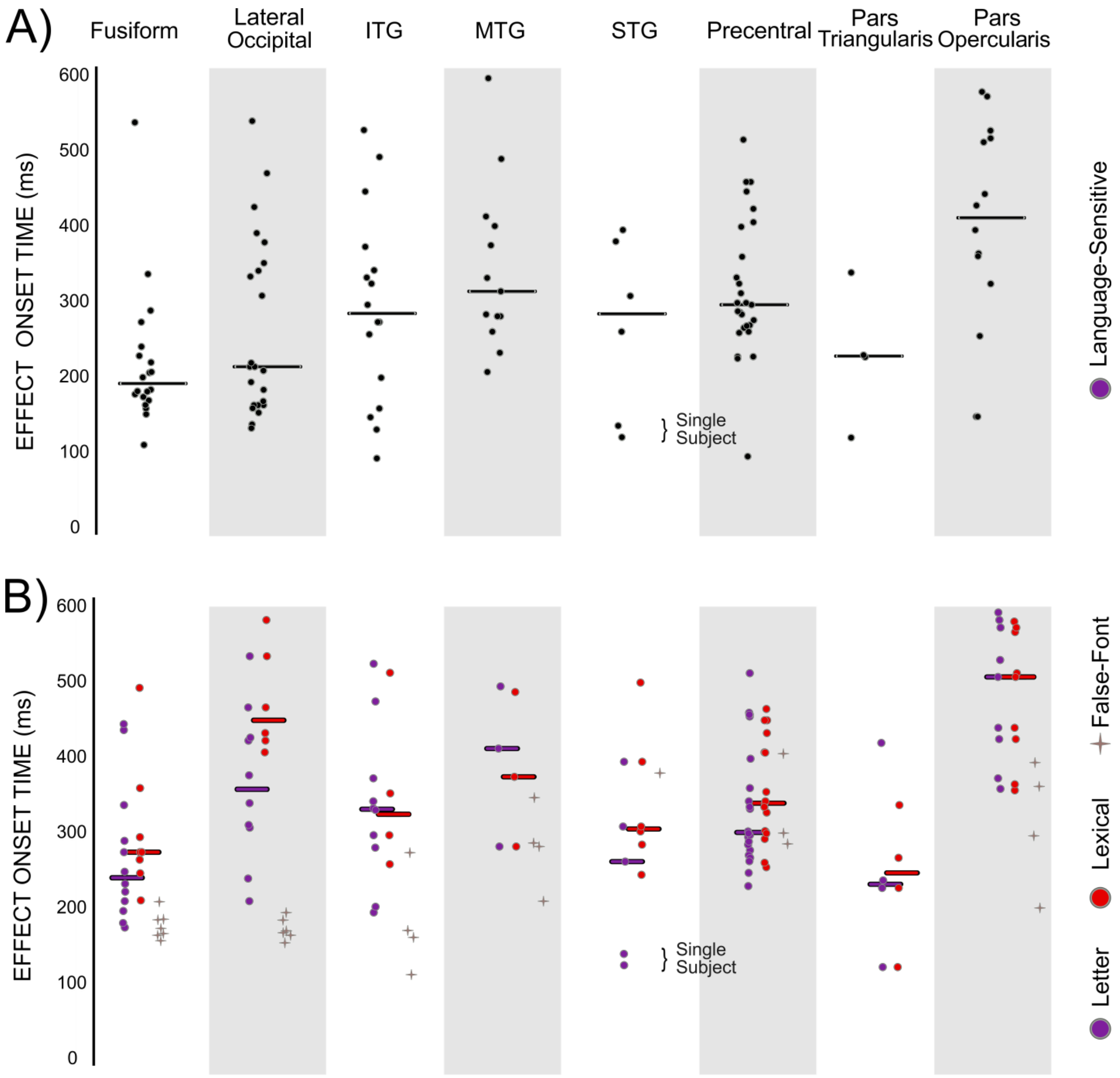


Figure 1.5: Timing of Language-sensitive effect, Letter-specific effect, and Word-specific effect onsets across region. A) Circles are the onset of significant Language-sensitive effects (i.e. ANOVA differences between linguistic stimulus conditions). Dark Purple circles are onset of an effect at each significant electrode while the line is the median for the region. B) Circles are the onset of significant Letter-specific (Word > False-Font) and Word-specific effects (Word > Consonant String). Purple circles are onset of a Letter-specific effect and red circles are the onset of Word-specific effect. The line is the median for each effect in the region. Grey crosses note the occurrence of a False-font—specific effect (False-font > Word). In the STG the early onset of letter-specific responses are noted as a single subject as these early responses were a-typical of the patient cohort.

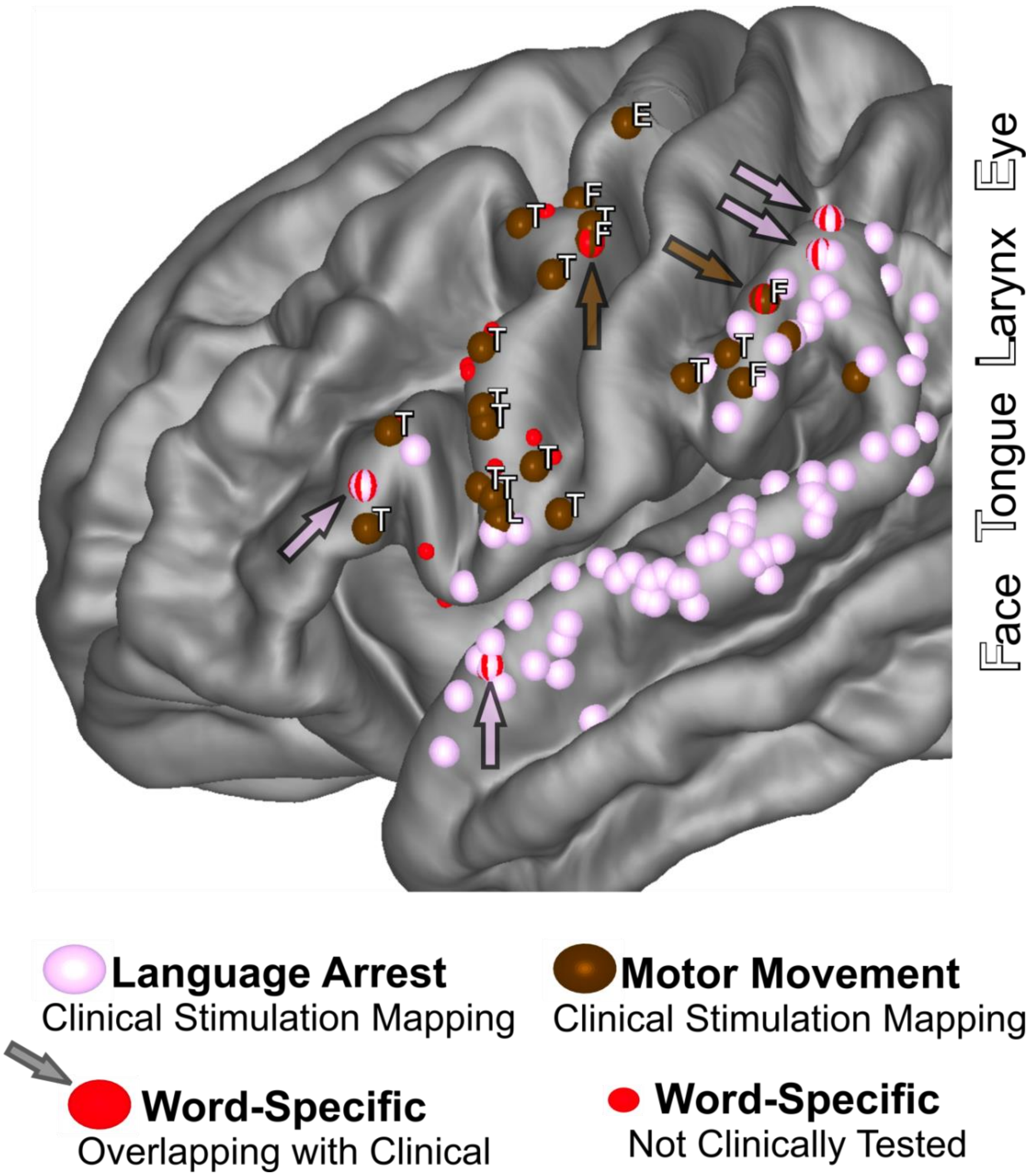


Figure 1.6: Stimulation results reveal partial overlap between word-specific responses and stimulation in language and motor cortex. Pinkish circles represent electrodes identified as critical to speech production by clinical stimulation during a naming task or continuous speech task. Brown circles represent electrodes identified as eliciting motor movement during clinical stimulation. Circles that are a mix of red and either pink or brown are electrodes which also showed word-specific activity during the FW task (performed separately from the clinical stimulation). Small red circles are word-specific responses in electrodes from clinically-tested subjects but for electrodes which were not mappe . Arrows point to electrodes with overlapping effects during the cognitive task and identified functional importance during clinical mapping, color coded by the type of stimulation mapping which the evoked activity overlapped with.

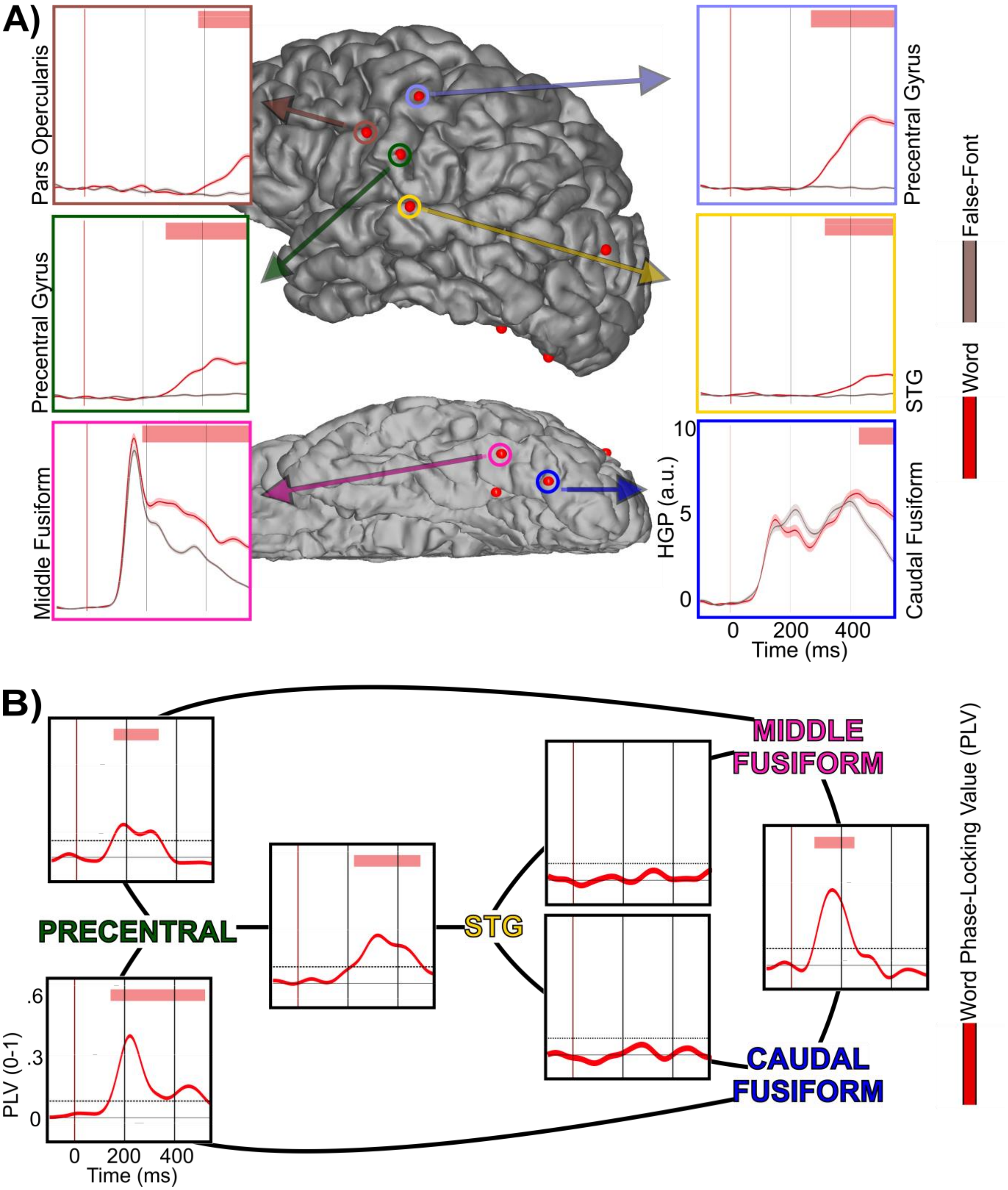
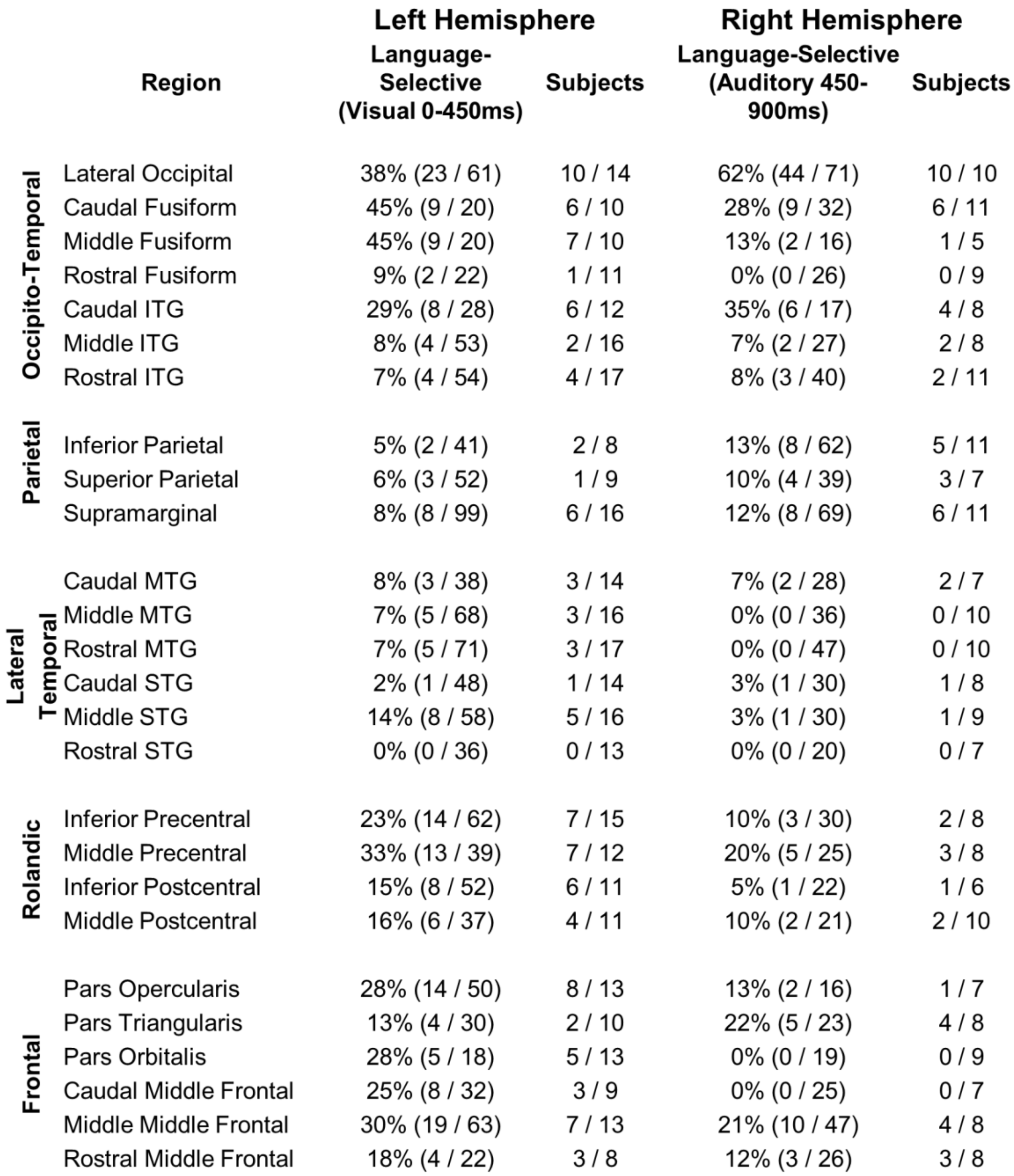


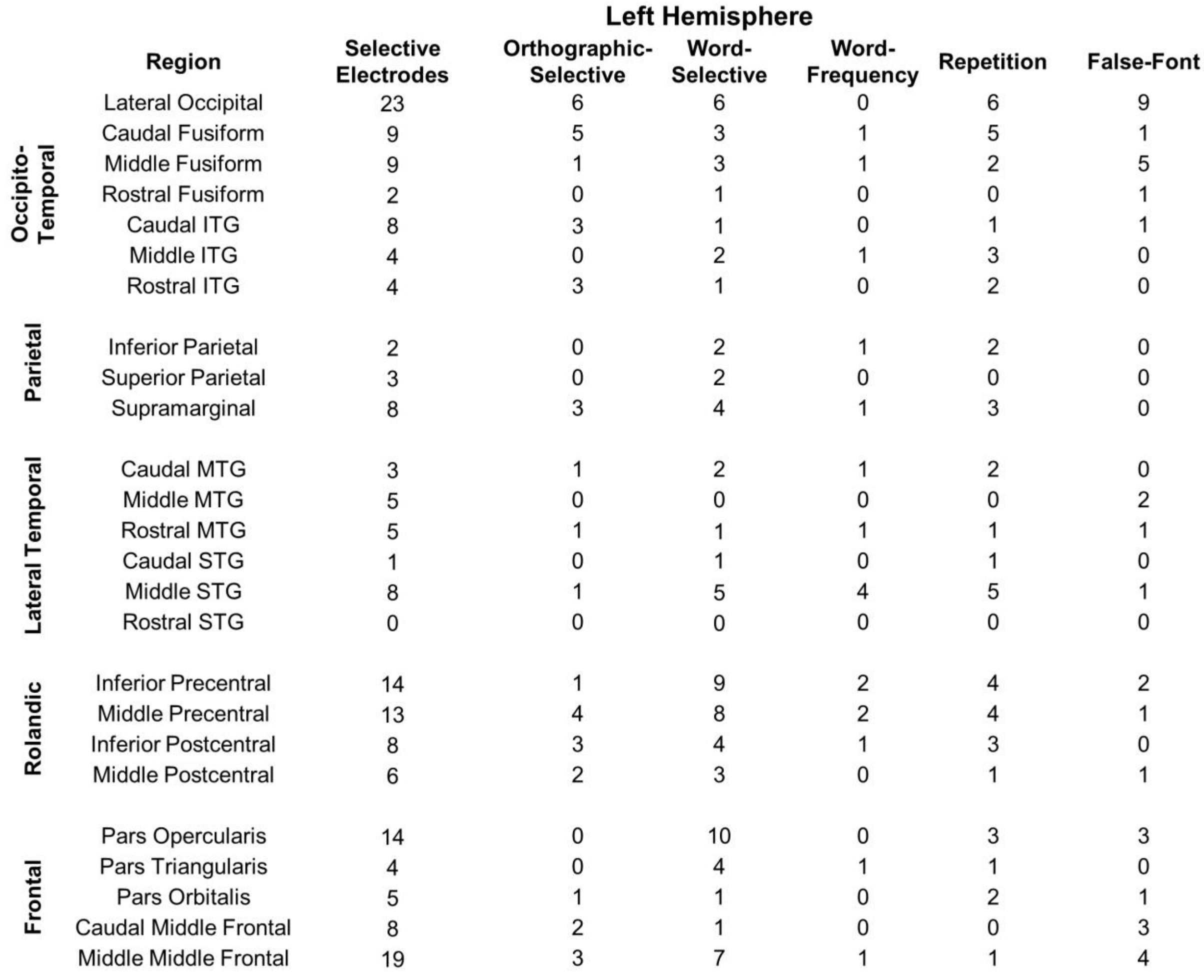
Figure 1.7: Fusiform and precentral gyrus display phase-locking during silent reading. A) HGP responses from the only patient with word-selective electrodes in the fusiform, STG, and precentral gyrus. Red bar at the top displays periods of significant difference between word (red-line) and false-font (reddish-grey line). B) PLV values centered on 4-12 Hz for word trials between the fusiform, STG, and precentral gyrus. Red bar at the top displays periods of PLV which were significantly above chance (*p*<.001).

Table 1.1: Distribution of Language-Selective electrodes, and how many patients were contributed Language-Selective electrodes, in each region



		Left Hemisphere		Right Hemisphere	
	Region	Language-Selective (Visual 0-450ms)	Subjects	Language-Selective (Auditory 450-900ms)	Subjects
Occipito-Temporal	Lateral Occipital	38% (23 / 61)	10 / 14	62% (44 / 71)	10 / 10
	Caudal Fusiform	45% (9 / 20)	6 / 10	28% (9 / 32)	6 / 11
	Middle Fusiform	45% (9 / 20)	7 / 10	13% (2 / 16)	1 / 5
	Rostral Fusiform	9% (2 / 22)	1 / 11	0% (0 / 26)	0 / 9
	Caudal ITG	29% (8 / 28)	6 / 12	35% (6 / 17)	4 / 8
	Middle ITG	8% (4 / 53)	2 / 16	7% (2 / 27)	2 / 8
	Rostral ITG	7% (4 / 54)	4 / 17	8% (3 / 40)	2 / 11
Parietal	Inferior Parietal	5% (2 / 41)	2 / 8	13% (8 / 62)	5 / 11
	Superior Parietal	6% (3 / 52)	1 / 9	10% (4 / 39)	3 / 7
	Supramarginal	8% (8 / 99)	6 / 16	12% (8 / 69)	6 / 11
Lateral Temporal	Caudal MTG	8% (3 / 38)	3 / 14	7% (2 / 28)	2 / 7
	Middle MTG	7% (5 / 68)	3 / 16	0% (0 / 36)	0 / 10
	Rostral MTG	7% (5 / 71)	3 / 17	0% (0 / 47)	0 / 10
	Caudal STG	2% (1 / 48)	1 / 14	3% (1 / 30)	1 / 8
	Middle STG	14% (8 / 58)	5 / 16	3% (1 / 30)	1 / 9
	Rostral STG	0% (0 / 36)	0 / 13	0% (0 / 20)	0 / 7
Rolandic	Inferior Precentral	23% (14 / 62)	7 / 15	10% (3 / 30)	2 / 8
	Middle Precentral	33% (13 / 39)	7 / 12	20% (5 / 25)	3 / 8
	Inferior Postcentral	15% (8 / 52)	6 / 11	5% (1 / 22)	1 / 6
	Middle Postcentral	16% (6 / 37)	4 / 11	10% (2 / 21)	2 / 10
Frontal	Pars Opercularis	28% (14 / 50)	8 / 13	13% (2 / 16)	1 / 7
	Pars Triangularis	13% (4 / 30)	2 / 10	22% (5 / 23)	4 / 8
	Pars Orbitalis	28% (5 / 18)	5 / 13	0% (0 / 19)	0 / 9
	Caudal Middle Frontal	25% (8 / 32)	3 / 9	0% (0 / 25)	0 / 7
	Middle Middle Frontal	30% (19 / 63)	7 / 13	21% (10 / 47)	4 / 8
	Rostral Middle Frontal	18% (4 / 22)	3 / 8	12% (3 / 26)	3 / 8

Table 1.2: Number of electrodes displaying each effect divided in region



Left Hemisphere

	Region	Selective Electrodes	Orthographic-Selective	Word-Selective	Word-Frequency	Repetition	False-Font
Occipito-Temporal	Lateral Occipital	23	6	6	0	6	9
	Caudal Fusiform	9	5	3	1	5	1
	Middle Fusiform	9	1	3	1	2	5
	Rostral Fusiform	2	0	1	0	0	1
	Caudal ITG	8	3	1	0	1	1
	Middle ITG	4	0	2	1	3	0
	Rostral ITG	4	3	1	0	2	0
Parietal	Inferior Parietal	2	0	2	1	2	0
	Superior Parietal	3	0	2	0	0	0
	Supramarginal	8	3	4	1	3	0
Lateral Temporal	Caudal MTG	3	1	2	1	2	0
	Middle MTG	5	0	0	0	0	2
	Rostral MTG	5	1	1	1	1	1
	Caudal STG	1	0	1	0	1	0
	Middle STG	8	1	5	4	5	1
	Rostral STG	0	0	0	0	0	0
Rolandic	Inferior Precentral	14	1	9	2	4	2
	Middle Precentral	13	4	8	2	4	1
	Inferior Postcentral	8	3	4	1	3	0
	Middle Postcentral	6	2	3	0	1	1
Frontal	Pars Opercularis	14	0	10	0	3	3
	Pars Triangularis	4	0	4	1	1	0
	Pars Orbitalis	5	1	1	0	2	1
	Caudal Middle Frontal	8	2	1	0	0	3
	Middle Middle Frontal	19	3	7	1	1	4

Table 1.3: Timing of effect onset divided in each cortical region.

Region	Letter-Selective (ms)	Word-Selective (ms)	Word-Frequency (ms)	Repetition (ms)	False-Font (ms)
Fusiform	250 (180 - 440)	280 (220 - 500)	460 (360 - 560)	460 (340 - 520)	180 (160 - 600)
Lateral Occipital	360 (220 - 540)	460 (420 - 580)		520 (360 - 540)	180 (160 - 200)
ITG	340 (200 - 520)	330 (260 - 520)	280 (280)	350 (240 - 440)	170 (120 - 280)
MTG	420 (280 - 500)	380 (280 - 500)		300 (280 - 320)	280 (220 - 600)
STG	260 (120 - 400)	310 (240 - 500)	360 (340 - 540)	180 (120 - 320)	380 (380)
Precentral	300 (240 - 520)	340 (260 - 460)	490 (400 - 500)	390 (220 - 500)	300 (300 - 400)
Pars Triangularis	240 (120 - 420)	260 (120 - 340)	460 (460)	380 (380)	
Pars Opercularis	520 (360 - 600)	520 (360 - 580)		460 (400 - 520)	330 (200 - 400)

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CHAPTER 2: The Precentral Gyrus Contributions to Early Time-Course of Grapheme-to-Phoneme Conversion

Abstract

The process of reading is influenced by both the visual information and the auditory information present in visual text. However, the process of phonological conversion from an essentially visual code to an essentially auditory code remains poorly understood. Here we record electrophysiology directly from the cortical surface during a bi-modal task where a letter string (‘GUH’) is presented followed by a bi-phoneme and patients are asked to make a match/mismatch decision. We report that the Precentral Gyrus emerged a primary hub, with evidence for cortical representations of both visual letters and auditory phonemes as well as early mismatch effects. The Precentral Gyrus also displayed early phase-locking value connectivity with the caudal fusiform in 2 patients with electrodes in both regions. Finally, in 1 patient who received clinical stimulation, we found overlapping Text-selective and mouth motor electrodes providing evidence that articulatory phonemes may be the link between visual and auditory information during reading. We theorize that the role of articulation in learning to read provides the early link between the visual and auditory reading networks which becomes automatic as reading skill increases.

Introduction

The interaction of an initially auditory-only perisylvian language network and a later developing visual language network has been studied since the advent of modern language neuroscience in the late 1800s[1]. This has led to extensive work in behavioral[2,3], lesion studies[4], neuroimaging[5,6], and modeling[7–9] to understand the division of labor between visual, auditory, and bi-modal cognitive operations when reading. But the most basic question of how a visual stimulus is transduced into an auditory code, known as Phonological Re-coding (PR), remains ambiguous.

The original questions regarding PR were not 'where' and 'when' the conversion from a visual graphemic code to an auditory phonemic code contributed to lexicosemantic processing, but 'if' this conversion took place at all in skilled readers[10–12]. Theories emphasized the overlearned nature of visual word identification, suggesting quick visual lexico-semantic processing with any activity in the auditory perisylvian network occurring post-lexicosemantic access. Decades of intricate behavioral work[2,3] combined with lesion studies[4] led to the development of cognitive models[7,8,13,14] which emphasized both a visual and an auditory flow of information making an interactive contribution to visual lexico-semantic processing. However, the 'when' and 'where' controversies regarding PR remain.

The Posterior Temporo-Parietal Network: The traditional locus of phonological recoding

Initial lesion studies implicated the angular gyrus as a critical link between visual text encoding and the perisylvian auditory language network[1,15]. fMRI studies comparing phonological/semantic or phonological/orthographic decisions provided early support for this localization, with phonological stimuli evoking greater activation than other stimulus types in the angular gyrus[16–18]. Neuroanatomical models of silent word have subsequently incorporated this locus[6,19]. However, an alternative explanation for these fMRI results comes from a study in which differential activity was explained by a suppression of activity for non-phonological stimuli, with evoked activation from visual words being no greater than fixation[20].

A second possible phonological temporo-parietal locus is the superior temporal gyrus (STG), as it is a critical processing area for auditory phonemes[21–23]. Studies from multiple modalities have indicated phonologically related activity in the STG evoked by visual linguistic stimuli. A rare study of single-neurons in the STG found several neurons with correlated firing patterns between auditorily-presented phonemes and their visually-presented letter analogues[24]. In BOLD neuroimaging during vocalization of visual text tasks the STG is reliably activated[25,26] and evoked BOLD to phonological judgements is greater than orthographic judgements[18]. An iEEG study found electrodes selective for the human voice, compared to auditory sensory controls, in the superior temporal lobe and found visual word activity at several of these same electrodes in a separate task[27].

The Precentral Gyrus: An alternate potential locus for phonological re-coding

Perhaps due to early neuroanatomical models of reading focusing on the posterior temporo-parietal lobe, many models of silent reading do not currently include a place for the precentral gyrus. Major reviews have either explicitly ignored precentral activity during reading[28] or emphasized articulatory peri-rolandic activity during reading aloud but not during reading silently[6,19,29](but see[5]). However, several early psychological theories placed PR during silent reading in articulatory cognitive operations[30]. This was based primarily on empirical data from the articulatory suppression paradigm in which participants repeated a nonsense phrase to occupy the articulatory cognitive operations while performing a reading task. Results showed suppressed phonological behavioral effects[31–33] but not if mouth movements are non-articulatory[33]. Further, articulatory suppression blocked the phonological similarity effect for visual but not for auditory words[34].

A variety of BOLD neuroimaging and lesion studies provide additional evidence for the inclusion of precentral gyrus, i.e. a seat of articulatory phonemic representations, in silent reading. BOLD studies using masked phonological priming, the strongest behavioral evidence put forward for early and automatic phonological recoding, evokes activity in the left precentral gyrus even when the words are not consciously perceived[35]. Studies also find greater activity in the precentral gyrus when making phonological judgements for a visual word versus semantic judgements[36], differential activation based on the spelling-sound consistency of a word[37], and increasing activation with increasing difficultly of PR[16].

Lesion damage to the Rolandic area reduced a patient’s ability to make phonological recoding judgements about words, such as phonological similarity and syllabic stress judgements[38]. A patient with a peri-rolandic lesion retained comprehension of visual words but was unable to make rhyming judgements or manipulate pseudowords[39]. In both cases of

Rolandic damage, the deficits were limited to tasks involving explicit phonological judgements (rhyming tasks or phonological similarity) but the patients broadly retained lexico-semantic abilities.

The Present Study

Here we use data from iEEG recordings from the pial surface in 9 patients during a bi-modal match/mismatch task. The electrodes were mainly localized in the peri-sylvian and peri-rolandic areas, placed for clinical purposes, providing excellent coverage to investigate the relative contributions of each region during task performance. Patients will make a silent match/mismatch decision between a three-letter string representing a consonant-vowel (‘GUH’) and a following bi-phoneme. The spatiotemporal precision of iEEG will allow us to identify exactly when the cortical representations of the phonologically re-coded visual letters and the auditorily presented bi-phonemes conflict. The findings presented here emphasize that a neuroanatomical model of phonological re-coding must include a place for the precentral gyrus.

Methods

Participants and Recordings

Electrocorticographic (ECoG) recordings were obtained from 9 patients (4 males, mean age 37 (age range 17-56) undergoing intracranial EEG monitoring as part of treatment for pharmacologically resistant epilepsy. All procedures were approved by the Institutional Review Board at New York University and written informed consent was obtained from all participants. Electrode placement was determined by clinical criteria to identify seizure activity and eloquent tissue. Each patient was implanted with subdural platinum-iridium electrode arrays embedded in silastic sheets (AdTech Medical Instrument Corp). Data included arrays of grids (8x8 contacts) and strips (1x4 to 1x12 contacts). Contacts had a diameter of 4mm with 2.3mm exposure. Center-to-center spacing between contacts was 10mm for grids and 5mm for micro-grids. Recordings were acquired using a Nicolet One EEG system sampled at 512 Hz and bandpass filtered between 0.5 and 250 Hz.

Electrode localization

Electrode localization was done through co-registration of pre- and post-implant MRI images, followed by manual and automatic localization of electrodes[40]. Coordinates were co-registered to a standard MNI template and anatomical parcellations were determined using the Desikan-Killiany atlas[41]. Long gyri were split into 3 parts, either inferior/middle/superior (Pre-central gyrus, post-central gyrus) or caudal/middle/rostral (fusiform, ITG, MTG, STG, Middle-Frontal, Superior-Frontal). Parcellations were excluded if ≤ 5 electrodes had task responsive effects. Three-dimensional reconstructions of cortical surfaces in figures were created using FreeSurfer[42]. Localization into a brain region was performed in each subject's native brain. Subject average electrode location, used for display purposes only, were obtained using FreeSurfer surface-to-surface calculations with the fsaverage brain. Figure 1C shows the electrode coverage throughout the cortical parcellations, highlighting our coverage of relevant left-hemisphere perisyvlian regions as well as lateral occipital, inferior frontal gyrus, and ventral temporal regions. Regions with <5 electrodes were excluded from analysis.

Task Design

Figure 1A displays a schematic of the task. Patients performed a silent match/mismatch decision between a three-letter string ('GUH') and a following bi-phoneme. All stimuli were in consonant-vowel order. Both the letter-string and bi-phoneme were presented for 450m. The visual stimulus was presented first, replacing a 3-symbol fixation (<X>) for 450ms, then immediately returning to the fixation. The Bi-phoneme was played next, with all bi-phonemes length-normalized to 450ms. In total, 4 types of trials were presented each comprising 25% of the total number of trials. This was a silent task with participants responding with their hand, ipsilateral to the hemisphere being recorded from to avoid hand-motor movement activity contaminating the recordings. The vocal silence of the task will ensure that any articulatory activity seen is sub-articulatory and not related to overt motor movement.

The first two trial types were ‘match’ and ‘mismatch’, in which the 3-letter string and the bi-phoneme either matched or did not. The third trial type was a ‘Visual Control’ trial in which a ‘False-Font’ with 3 symbols was displayed in place of the 3-letter string, followed by a normal Bi-Phoneme. This ‘False-Font’ stimuli share the same basic visual features matched to regular letters. For a deeper discussion of these visual orthographic controls see[43]. The fourth trial type was an ‘Auditory Control’, in which a 3-letter string was displayed as in the first two trial types followed by a ‘Noise-Vocoded’ stimulus. The ‘Noise-Vocoded’ stimulus was created by taking the existing Bi-Phoneme stimuli and creating a 6-band stimulus in which white-noise was multiplied by power in each of the bands to create a matched set of unintelligible auditory stimuli with identical time-varying spectral acoustics[23,44–47].

In total, there were 768 trials, with 192 of each of the four trial types. These trials were broken down into 3 runs for 64 of each trial type in each run. These trials were made up of stimuli from crossing 4 consonants and 4 vowels to facilitate balanced presentations of each letter and phoneme. In total there were 48 presentations of each vowel and consonant (and each letter combination analogue). The third run had 4 consonants and 3 vowels (due to running out of legal consonant-vowel combinations), so there were slightly less trials for the 4 consonants presented in the 3rd block (i.e. 36 trials for consonants in the third block).

Data Processing

Data were preprocessed using MATLAB (MathWorks) and the Fieldtrip toolbox[48]. We used an average reference to reduce noise. Data was epoched to the onset of lip movement for visual trials and to the onset of auditory input for auditory and audiovisual trials. Epochs were transformed from the time domain to the time–frequency domain using the complex Morlet wavelet transform. Constant temporal and frequency resolution across target frequencies were obtained by adjusting the wavelet widths according to the target frequency. The wavelet widths increase linearly from 14 to 38 as frequency increased from 70 to 170 Hz (high gamma band activity), resulting in a constant temporal resolution of 16ms and frequency resolution of 10 Hz.

For each epoch, spectral power was calculated from the wavelet spectra, normalized by the inverse square frequency to adjust for the rapid drop-off in the EEG power spectrum with frequency, and averaged from 70 to 170 Hz, excluding line noise harmonics. This data was smoothed by a moving window matching the temporal characteristics of the wavelet. Each trial epoch was demeaned with a baseline from -250 to 0m.Trials containing artifacts were identified b0y amplitude and variance, visually inspected for artifacts and removed from data.

Task Effect Analysis

Behavior: The two critical trial types were match/mismatch, on both of which a response was given. We compared patient performance and response speed on both trial types with a t-test to gauge if differences in trial performance could be attributed to differences in the difficulty of performing each decision (evidence of which would be differences in performance or differences in response time).

Task-Sensitivity: For task effects, our first goal was to assess the pool of how many electrodes were responsive during task performance and were additionally sensitive to our task manipulations. For this we first found electrodes that had significantly increased activity from a baseline of 0 between 0-to-900ms using a timepoint-by-timepoint t-test corrected for temporal false-discovery rate at $p<.05$[49]. Next, electrodes were run a one-way ANOVA between the 4 trial types from 0-to-900ms, temporally corrected using a bootstrapped shuffling of trial identity 1000 times[48]. Only electrodes which were significant in both these tests were included in further analysis (Task-Sensitive electrodes). For analysis we split the Task-Sensitive electrodes into two temporal periods: during the presentation of visual text (0-450ms) and during the presentation of the auditory stimulus (450-900ms). Task sensitivity during the visual text presentation can only be related to visual text processing and preparatory mechanisms while Task-sensitivity during auditory presentation can be related to some or all of ongoing Text processing, Bi-Phoneme processing, and/or decision-making mechanisms.

Language-Selective: Task-Sensitive electrodes were assessed for whether they were responding preferentially to language stimuli as evidenced by an increased response to Text relative to False-Font stimuli (Text-Selective) during Text presentation from 0-450ms or an increased response to Bi-Phonemes relative to Noise-Vocoded stimuli (Phoneme-Selective) from 450-900ms. ANOVAs were run run timepoint-by-timepoint for these two comparisons, once again corrected using the bootstrapped shuffling method. The 'Task Sensitive' ANOVA results was used to mask significant Text-selective and Phoneme-selective time-periods to ensure differences found between stimulus types were part of the originally identified Task-sensitive time period.

Letter & Phoneme Specificity: A key question is the location of the cortical representation of sub-lexical linguistic units for both Letters and Phonemes. An area which houses such representations would be expected to have differential neural responses based on Letter/Phoneme identity. To assess whether the underlying cortical patch being measured by each electrode might have such sub-lexical representations, a 1-way ANOVA was run timepoint-by-timepoint on Task-Sensitive electrodes between consonant identity for either text (Letter-Specific) or voice (Phoneme-Specific), temporally corrected using the bootstrapped shuffling method. The 'Task Sensitive' ANOVA results was used to mask significant time-periods to ensure differences found between conditions were part of the originally identified Task-sensitive time period. Letter-specific responses were restricted to 0-to-450ms while Phoneme-specific responses were restricted to 450-900ms.

Match/Mismatch Specificity: A key test for whether a cortical patch houses both letter-representations and phoneme-representations is whether it is sensitive to multi-modal match/mismatch priming. Mismatch-sensitive electrodes were defined as having a larger response to mismatch trials than to matched trials during presentation of the Bi-phoneme (i.e. from 450-900ms) identified using a 1-way ANOVA temporally corrected using the bootstrapped shuffling method. This increase to mismatch trials may have different neural interpretations, including a priming effect[50]. But all of the interpretations rest upon the underlying neural population being measured containing or receiving information regarding both Text and Phoneme identity.

Control Preference: Due to interest in the relationship between text and degraded speech as another indicator of Text/Phoneme overlap[51,52], we sought to identify cortical patches with preferential responses to noise-vocoded stimuli. The test run was the inverse of the Language preference task. Here, instead of identifying Voice-Selective electrodes from 450-900ms we identified electrodes with greater responses to Noise-Vocoded stimuli, using the same procedure detailed for Voice-Selective electrodes.

Regional Comparisons

Comparisons between regions are difficult in iEEG due to sparse coverage that varies between participant due to clinical considerations. However, studies with large numbers of patients note that while locations of interest, such as language, vary they are located in generally similar regions relative to neuroanatomical landmark [53]. For this reason, this study will make use of non-parametric statistics to compare both proportion of electrodes and timing of electrodes between regions of critical interest when effect numbers provide the power to do so. For proportion of electrodes, this will in a planned a-priori comparison between the precentral gyrus and the STG, Supramarginal Gyrus, and Pars Opercularis.

These particular regions were chosen as comparison regions to the precentral gyrus because they are all candidate regions as the loci of grapheme-to-phoneme conversion representations[6,19,28,29]. The planned comparisons center on the precentral gyrus versus both of the posterior temporo-parietal regions and the pars opercularis is driven by theoretical interest in their likely function in reading. Both theoretically[30] and empirically[35–37] the most likely function the precentral gyrus would play in reading is in grapheme-to-phoneme conversion. However, in neuroanatomical models the role of grapheme-to-phoneme convrersion is usually attributed to some region, or combination of regions, within the posterior temporo-parietal cortex as well as pars opercularis[6,19,29]. Therefore, the core question to answer is the responsiveness and timing of activity in these two regions between phonemic articulatory cortex (precentral gyrus) and candidate phonemic encoding cortex (STG, supramarginal gyrus, and pars opercularis). With 3 comparisons, the corrected p-value threshold will be *p*<.016. {}

In addition to distributions, we will also compare effect onset timings between regions statistically when possible. This is difficult because of the variable number of effects per region causes differences in power between regions. However, despite these difficulties some regularities emerged. These timing analyses will mirror the a priori structure of the regional distribution analyses and share their *p*-value corrections. All tests run will be a ranksum non-parametric test.

Overlap Comparisons

Several of the questions regarding the relationship of Text- and Phonemic representations relate directly to overlapping cortical representations. We sought to assess whether the targeted regions described above could be regarded as having a significant overlap of effects (such as having overlapping Text-selective and Phoneme-selective responses). A binomial test was run for these regions. For example, to asses if the Text-selective effects in a region overlap significantly above chance with the Phoneme-selective effects in the region, we used the following method. We ran the binomial test comparing the number of overlapping Text- and Phoneme-selective effects and the number of overall Phoneme-selective effects, compared to an expected chance level of the proportion of Phoneme-selective effects based on the overall proportion of Text-selective effects.

Stimulation

One of the left-hemisphere patients underwent clinical cortical stimulation for functional mapping prior to possible epilepsy surgery. Testing was performed by epilepsy and neuropsychology teams together. A NicoletOne cortical stimulator delivered a constant current output to adjoining electrode pairs, pulse width of 500ms, frequency of 50Hz, and maximum train duration of 5s. Current was manually controlled starting at 1mA and gradually increasing by 1-4mA until either: a maximum of 12mA was reached, a functional response was seen, or epileptiform discharges were seen. Responses were confirmed with repeat stimulation, and testing of adjoining electrodes was performed when responses were ambiguous. The patient was instructed to inform the testing team if any positive (tonic and/or clonic) or negative (drift) motor or sensory phenomena were experienced. Language testing included three tasks compared to baseline, including speech production, naming, and comprehension tasks. Baseline was reevaluated during the procedure to ensure patient participation. Speech production was tested by asking the patient to recite a continuous phrase (e.g., the pledge of allegiance, alphabet, or counting). Interruption of speech unrelated to motor function was noted as a positive finding. Naming was tested using a visual naming task (line drawings) and/or an auditory naming task (naming objects after an auditory description). Response initiation that was different from baseline or paraphasic errors were noted as positive. Comprehension was tested using simple commands and/or completion of simple phrases. Inability to correctly complete the task was noted as positive. Positive response were noted as “language” responses without noting the specific task involved.

We used cortical stimulation results to evaluate the functional specialization of speech regions. We report functional responses for all speech selective electrodes. Functional responses are described as a percentage of positive responses over the number of electrodes tested for visual, language, motor and sensory phenomena. Motor and sensory responses are described for speech production muscles (face, mouth, tongue, and throat) and non-speech production muscles separately. We limit analysis to the left hemisphere due to limited cortical stimulation data in the right hemisphere.

Connectivity

To test the putative network identified in individual electrodes with HGP effects, we used Phase-Lag Value (PLV) calculated pairwise between electrodes as decribed in [54] to test whether

functional connectivity could be inferred between electrodes. PLV measures the consistency of the relative phase of LFPs in two locations. High PLV indicates consistent synchronization of the synaptic currents in pyramidal apical dendrites between the cortical locations underlying the intracranial sensors. Significant PLV was determined by creating a distribution of all PLV values from a baseline period (-200-to-0ms) for each subject. Only if the obtained PLV value after stimulus presentation was $p<.00005$ based on the subject's own baseline distribution was a pairwise connection judged to be significant.

Results

Behavior: Figure 1B shows the proportion correct and response time for match and mismatch trials. We compared both of these measures to assess evidence for differences in difficulty between these behavioral decisions. Average proportion correct for match (89%) and mismatch (92%) was not significantly different ($p>.20$). Likewise, response time for match (660ms) and mismatch (678ms) was not significantly different ($p>.40$). Therefore, there is no behavioral evidence for neural differences being based on differences in difficultly in performing either judgement.

Task-Sensitivity: Our first goal was to characterize the regions and timing involved in performing the task during both the Text and Bi-phoneme presentation. During the Text, Task-Sensitive electrodes were overall left-lateralized ($p<.005$); Follow-up tests in the 4 targeted regions revealed that only the precentral gyrus reached significance ($p<.05$, fdr-uncorrected). There was no overall lateralization during Bi-phoneme presentation ($p>.05$). The overall proportion of Task-Sensitive electrodes was greater during Bi-phoneme presentation in both the left-hemisphere ($p<.001$) and right-hemisphere ($p<.001$). In the left-hemisphere targeted follow-up, this was true in precentral ($p<.001$), STG ($p<.001$), and Supramarginal ($p<.005$), and pars opercularis ($p<.05$, fdr-uncorrected)

During both the Text and Phoneme presentations, the Precentral generally had a greater proportion of Task-Sensitive electrodes than the other 3 targeted regions. For the left hemisphere targeted comparison, the precentral gyrus had a greater proportion of Task-Sensitive during Text presentation compared to the STG (*p*<.001) and the supramarginal (*p*<.05; fdr-uncorrected) but not the pars opercularis (*p*=.10). During Phoneme presentation, the precentral gyrus had a greater proportion than the STG (*p*<.001), Supramarginal (*p*<.001), and Pars Opercularis (*p*<.001).

Language-Preference: Text-Specific electrode proportion was left lateralized (*p*=.001) with the precentral gyrus being the only individual region to be left lateralized in the targeted follow-up tests (*p*=.01). There was no lateralization for Voice-Specific electrodes (*p*>.05). Overall, there were more voice-specific than text-specific electrodes in the left hemisphere (*p*<.05) and the right hemisphere (*p*<.001). In the targeted follow-up, the precentral gyrus displayed significantly more text-specific electrodes (*p*=.02, fdr-uncorrected) while the STG was significantly more voice-specific (*p*<.005). Neither the Supramarginal nor the Pars Opercularis reached significance (both *p*>.15).

In the targeted comparison, the precentral gyrus had significantly more text-specific electrodes in the precentral gyrus than the STG (*p*<.001) and the supramarginal (*p*<.05, fdr-uncorrected) but no significant difference between the precentral gyrus and the pars opercularis (*p*>.05). There were no significant differences between the precentral gyrus and the other regions for voice-specific proportion (all *p*>.10).

For the effect onsets, there were no significant hemispheric differences between text-selective onset (*p*>.10) or voice-selective onset (*p*>.5). Overall, voice-selective onsets were significantly faster than text-selective onsets (*p*=.002). Of the targeted follow-ups only the STG showed a faster onset for voice than text (*p*<.05, fdr-uncorrected).

Although the precentral gyrus did not reach significance in the targeted comparisons, we will note that it was near a trend for the Precentral being slower for Text-selective effects than both the Supramarginal (*p*=.054) and the Pars Opercularis (*p*=.054). For voice-selective onsets, the STG was faster than the precentral gyrus (*p*<.05, fdr-uncorrected) but no significant differences with the supramarginal or pars opercularis (both *p*>.20).

A critical question regarding text processing in the lateral temporal lobe is the presence of Text-selective effects in Voice-selective cortical regions. Here we find that a significant relationship for the presence of Text-selective effects in Voice-selective areas (*p*<.01). In the targeted follow-up, this was significant in the Pars Opercularis (*p*<.005), Precentral (*p*=.016, fdr-uncorrected), and the Supramarginal (*p*<.05, fdr-uncorrected) but not the STG (*p*>0.50). For comparison, the presence of Phoneme-selective electrodes was found in Text-selective regions as well (*p*<.001) but in the targeted follow-up only the Pars Opercularis reached significance (*p*<.005).

Letter & Phoneme Specificity: As there were only 8 Letter-specific electrodes found, as opposed to 35 Phoneme-specific electrodes, first we will discuss the statistical outcomes of the Phoneme-specific proportion distribution and timing followed by a description of the distribution of the letter-specific electrodes.

For phoneme-specific electrodes, there was no significant difference in proportion between hemisphere (*p*>.05). Overall, there was more phoneme-specific electrodes found than letter-specific electrodes (*p*<.001). In the targeted follow-up analyses, this was significant in the STG (*p*<.001) but not in the Precentral, Supramarginal or Pars Opercularis (all *p*>.05). In the targeted comparison, there were significantly more phoneme-specific electrodes in the Precentral than the Pars Opercularis (*p*=.01) but no difference with the STG or Supramarginal (all *p*>.05).

For phoneme-effect onset, there was no significant hemispheric difference (*p*>.20). In the targeted comparisons, there was no difference in phoneme-specific onset between the precentral gyrus and the STG or Supramarginal (all *p*>.10); There were no phoneme-specific effects in the Pars Opercularis to compare to.

Letter-specific effects were very sparse, totaling only 7 electrodes in the left hemisphere and 2 electrodes in the right hemisphere. The electrodes were in the ventral occipito-temporal (1 in the left lateral occipital, 1 in the left caudal fusiform, and 1 in the right caudal fusiform) and the lateral frontal (4 in the left precentral gyrus, 1 in the left Pars Opercularis, and 1 in the right precentral). While the greatest number of letter-sensitive electrodes were in the precentral gyrus it must be noted that in terms of proportion, the greatest proportion of letter sensitive electrodes were found in the occipito-temporal regions in both the left (lateral occipital had 8%) and the right (fusiform had 8%).

It is not possible to make statistical statements about letter specific timing, but the earliest letter-specific effect was in the left caudal fusiform at ~180ms, followed by the pars opercularis at ~220ms. The precentral letter-specific electrodes had a median onset time at ~420ms (with the earliest effect at ~340ms). The only region that had both letter-specific and phoneme-specific responses was the precentral gyrus. The comparison was underpowered, but the results did have a trend toward earlier onset of phonemes effects (median ~260ms) in this region than letter-specific effects (median ~420ms; *p*<.07).

Mismatch Effects: Similar to letter-specific effects, Mismatch priming effects were sparse, totaling 15 electrodes. These effects were concentrated mainly in the regions with which we have been focusing on with the STG (5), Precentral (3), Pars Opercularis (2), and the Supramarginal (1), and the fusiform (2). The earliest Mismatch effect was in the STG at ~160, with the median of the STG also being tied for the earliest at ~220ms with the Precentral. This was followed by the medians of the Supramarginal (~300ms), Fusiform (340ms), and Pars Opercularis (~390ms).

To find if the mismatch effects had a spatial relationship with phonemic representations, we next asked if there were more mismatch effects in Phoneme-specific regions than would be expected by chance. Indeed a significant relationships were found with mismatch overlap with Phoneme-specific (*p*=.005) effects. Targeted follow-up comparisons identified the STG (*p*<.01) and the Precentral (*p*=.026, fdr-uncorrected) having this relationship but not the Supramarginal (*p*=1) or the Pars Opercularis (no phoneme specific effects). For comparison, there was no evidence of a relationship between Mismatch effects and Letter-specific effects (*p*>.20).

Control Preference: Noise-selective electrodes were right-lateralized (*p*<.05). Targeted follow-up analyses revealed that both the STG (*p*<.01) and the pars opercularis (*p*<.03, fdr-uncorrected) were right-lateralized. However, the precentral gyrus was significantly left-lateralized (*p*<.05, fdr-uncorrected). Within the left hemisphere, comparing the two control trial types, false-font and noise-vocoded, showed a greater proportion of noise-vocoded—selective responses (*p*=.001). In the targeted follow-up analyses, this was true in the STG (*p*<.001), Precentral (*p*<.001), and Supramarginal (*p*<.05, fdr-uncorrected) but not for the pars opercularis (*p*>.20). In the targeted comparisons, the precentral gyrus had a greater proportion of Noise-selective responses than the STG (*p*<.005), Pars Opercularis (*p*<.005), and the Supramarginal (*p*<.05, fdr-uncorrected).

For noise-vocoded—selective onsets, there were no significant differences in timing between hemispheres. In the targeted comparison, the Precentral was slower than the Supramarginal (*p*<.05, fdr-uncorrected) but there no significant difference in timing between the onsets of noise-vocoded onsets in the precentral and the STG or Pars Opercularis (*p*>.20).

For the critical question of Noise-selective overlap with Text-Selective electrodes, a significant relationship was identified (*p*<.001). Targeted follow-up analyses identified the Precentral as having a significant relationship (*p*<.001) but not the STG (*p*>.20), Supramarginal (*p*>.40), or Pars Opercularis (*p*>.40). For comparison, there was no significant relationship between Noise-selective electrodes and Voice-Selective electrodes (*p*>.50).

Stimulation: A single patient had stimulation mapping of their left hemisphere. In this patient for noted movement, 7 electrodes neighboring elicited motor movement were found in the Precentral and 5 electrodes neighboring motor movement were found in the Pars Opercularis. All elicited motor movement was characterized with the oral muscles (tongue, pharyngeal, lips). For speech interruption, independent of oral muscle movement, 4 electrodes were identified in the STG, 5 in the Supramarginal, and 1 in the Precentral.

In the Precentral, 2 of the electrodes neighboring tongue motor cortex showed a Text-selective effect as well as a Noise-selective effect. Also neighboring oral muscle movement, as well as the 2 Text-selective electrodes, were 3 additional electrodes with a Noise-selective response (but no Text-selective response). None of these electrodes showed a Mismatch effect. The 1 speech interruption (non-motor) electrode in the Precentral was neighboring these electrodes displayed both a Text-selective and a Noise-selective response. Perhaps most interestingly, though not in directly tested cortex, a Letter-specific electrode was found neighboring electrodes identified as being overlaying this patch of oral motor muscle movement cortex.

In the STG, 2 electrodes which neighbored speech arrest cortex showed a Voice-selective response. Additionally, 1 electrode neighboring speech-arrest cortex showed a Noise-selective effect in each of the STG and the Supramarginal. No Text-Selective effects were found in Supramarginal or STG neighboring speech-arrest cortex.

Connectivity: For Phase-Locking Values, we focused on connectivity in two ways. The first was between the caudal fusiform and the 4 putative phonological areas and the second was between the Precentral and the other 3 putative phonological areas. This was done first during Trigram-presentation and then during Bi-Phoneme presentation.

For the caudal fusiform, 2 patients had a Task-Sensitive electrode in this region. Both patients' electrodes had a 180ms onset of Text-selectivity, the earliest recorded, and at a timing generally associated with the onset of widespread diffusion of processing across the cortx, marking both these electrodes as excellent assays into the network underlying task performance. Both electrodes had an onset of significant PLV with the Precentral. In addition, both had significant coupling with an electrode in the Supramarginal gyrus. But only one patient had significant coupling between the caudal fusiform and the STG and Pars Opercularis.

During Bi-phoneme presentation, both patients displayed connectivity during the early Text-selective sites and the Precentral, STG, and Supramarginal. However, neither patient displayed significant connectivity between the caudal fusiform and Pars Opercularis during this period.

The Precentral, displayed a similar muted connectivity during Text presentation, with both patients displaying the aforementioned connectivity between caudal fusiform and Precentral. However, 0 out of 4 patients displayed connectivity between the Precentral and the Supramarginal and only 1 patient displayed connectivity between the Precentral and the Pars Opercularis and STG. This 1 patient was the same one that showed a connection to between these areas and the caudal fusiform. The same electrodes in each of these regions that were significantly coupled with the Caudal Fusiform were the electrodes coupled with the Precentral.

During the Bi-Phoneme Presentation, the Precentral displayed much more widespread connectivity. The same 2 patients still displayed connectivity between the Caudal Fusiform. In addition, 4 out of the 5 patients displayed connectivity between the Precentral and STG, 3 out of 4 patients displayed connectivity between the Precentral and Supramarginal. The Pars Opercularis was more equivocal, with 2 out of 5 patients displaying connectivity.

To summarize, the Caudal Fusiform and Precentral show early connectivity which persists during the entirety of task performance. Connectivity is much more widespread during Bi-phoneme presentation, suggesting that for the 450ms of Text presentation, and therefore during the time of phonological re-coding, i.e. during initial Text encoding, the relationship of the Caudal Fusiform and Precentral Gyrus is paramount. This is later supported by a much more widespread network of connectivity when comparing the re-coded text-derived phonemes with the incoming auditorily-presented phonemes.

However, this tidy picture is somewhat complicated by 1 patient in which electrode pariings in the STG and the the Pars Opercularis displayed connectivity with both the Caudal Fusiform and Precentral during Trigram Presentation. In the Pars Opercularis, the connectivity was with an electrode which both displayed Text-selectivity and later displayed a Mismatch effect. In the STG, the story is slightly more complicated. In 1 electrode phase-locked to the Caudal Fusiform there was a Text-selective effect but no Mismatch effect. In a 2nd phase-locked electrode there was no response to Text, but a Mismatch effect. This suggests that will phase-coupling is overall sparser in the STG and Pars Opercularis, these regions do contribute to contribute to grapheme-to-phoneme conversion and do house representations from both modalities.

Discussion

Neuro-anatomical models of silent reading often omit the precentral gyrus as a contributor[6,19,29](but see[5]). Here we present evidence from a bi-modal phonological match/mismatch task demonstrating the central role the precentral gyrus plays in mediating visual and auditory phonology. The precentral gyrus had Text-selective responses, Voice-selective responses, Letter-specific responses, Phoneme-specific responses, Mismatch-effects, significant connectivity with the caudal fusiform during Text-presentation, and significant connectivity with both the fusiform and temporo-parietal areas during Phoneme-presentation. In one patient who underwent clinical stimulation, many of these effects were in cortex identified with oral muscle movements validating psychological theories that advocate for the role of articulatory phonological representations in text phonological re-coding[30–34]. This evidence establishes the precentral gyrus as a prominent locus of phonological re-coding.

The following discussion will comment on the ‘Where’ and ‘When’ questions regarding phonological re-coding. The data presented here will help to establish constraints for both cognitive and neuroanatomical models as the field moves toward a more mechanistic understanding of phonological re-coding during reading.

Where: STG versus Precentral Gyrus

As an encoding hub for auditorily-presented phonemes[21–23] the STG is a prime candidate for being involved in phonological re-coding. Previous intracranial studies have provided evidence for this candidacy, finding overlapping preference for the human voice in the STG and a response to visually presented words[27] as well as finding several neurons with correlated firing between phonemes and letters[24]. fMRI has also reported evoked BOLD activation during reading tasks in the STG[18,25,26]. As, roughly, the precentral gyrus is a primary seat of articulatory phonemic representations and the STG is a primary seat of encoding phonemes, these two regions stand in for a long-standing debate regarding the relative contributions of both articulatory and encoding phonemic representations to silent reading[2,55].

In the present task, we confirm the essential role the STG plays in phonemic encoding, with the STG displaying strong responsivity during the Bi-phoneme presentation and many Phoneme-selective and Phoneme-specific effects. However, the response to Text presentation was more subdued. Only 3 electrodes were identified which were Text-selective, a significantly smaller proportion than were Voice-selective. This is in contrast to the Precentral, which had a significantly higher proportion of Text-selective than Phoneme-selective electrodes and indeed had significantly higher proportion of Text-selective electrodes than the STG.

However, the STG and Precentral gyrus did show strong evidence of collaboration during the presentation of the Bi-phoneme, putatively in the comparison of the Text and Phoneme identity. Both the Precentral and STG had a median onset of 220ms for their Mismatch-effects, suggesting that by the end of the presentation of the first phoneme, both regions were aware that the Text & Bi-Phoneme did not match. In both regions, the mismatch effect significantly overlapped with Phoneme-specific effects. Indeed, during Bi-phoneme presentation both regions displayed significant PLV-coupling both with themselves and with the caudal fusiform. The earliest Mismatch-effect was found in the STG at ~160ms in a region which was completely unresponsive during Text-presentation, suggesting the need for a second, connected region to provide it with the Text-derived phonemic identity with which to compare to the Bi-phoneme. However, during Text presentation there was little connectivity between the Precentral and STG. Coupling this with the general lack of responsiveness to Text in the STG, in comparison to the significantly larger proportion of Text-selectivity in the Precentral, suggests that in the initial stages of visual phonological re-coding, as opposed to the bi-modal period of comparison, the precentral gyrus is able to function mostly independently of the STG to re-code the letter-representations into their phonemic representations.

Where: Pars Opercularis and Supramarginal versus Precentral Gyrus

Both the Pars Opercularis and Supramarginal gyrus neighbor rolandic regions, and both the Pars Opecularis[17,56,57] and Supramarginal[17,57] regions have been implicated as being involved in phonological processing. Here we validate that both areas have a role to play and that they have a relationship with the precentral gyrus.

Roughly, the effects in the Pars Opecularis tended to resemble its immediate neighbor the Precentral while the effect in the Supramarginal tended to resemble its immediate neighbor the STG. The Pars Opercularis was statistically indistinguishable from the Precentral in Text-selective effects. The Supramarginal had a significantly lower proportion of Text-selective electrodes than the Precentral, but unlike the STG the Text-selective effects significantly overlapped with Phoneme-selective effects. Both the Pars Opecularis (2) and Supramarginal (1) displayed Mismatch-effects, though they differed from the Precentral/STG Mismatch effects in that they were later (Supramarginal: 300ms, Pars Opercularis: 390ms).

For the patterns of connectivity, the Pars Opercularis displayed the least PLV coupling of the 4 putative phonological regions. During the text presentation, only a single subject demonstrated PLV coupling between the Pars Opecularis and Caudal Fusiform (1 out of 2) and Precentral (1 out of 5). Like the Precentral, the Supramarginal was significantly coupled with the fusiform in both subjects (2 out of 2) during both the Text and Bi-phoneme presentation. Similar to the STG, was not significantly coupled with the Precentral during Text presentation (0 of 4 subjects) but was significantly coupled during the Bi-phoneme comparison period (3 of 4 subjects). This pattern of results implicates both the Pars Opercularis and Supramarginal as playing a role in phonological re-coding, though less central than that of the Precentral Gyrus.

When: The Time-Course of Auditory Contributions to Visual Text Processing

The time-course of phonological re-coding is a key question in determining what role this process plays in lexico-semantic processing during silent reading. As mentioned, early psychological studies theorized that visual word identification was so fast and phonological re-coding so slow that the phonological route played little-to-no part in reading[10–12]. Visual word identification proceeds in the ventral temporal reading route in a feedforward posterior-to-anterior sweep from sensory to lexico-semantic processing[58,59]. Given the speed from when visual processing begins at 60ms in posterior visual cortex[60] to the first evidence of lexico-semantic knowledge in the antero-ventral temporal lobe at ~200-250ms[43,61–63], this assumption of rapid visual processing while reading has weight. However, while evidence for the beginning of lexico-semantic knowledge starts ~200ms, evidence also exists for a period of prolonged feedforward/feedback interaction in the antero-ventral temporal lobe with other cortical areas beginning from this time period[64,65]. In lateral areas, around the time letter-specific processing begins in the caudal occipito-temporal regions at ~160-180ms[43,66,67] there is an onset of widespread, simultaneous activity across the lateral cortex. This evidence for simultaneous and widespread activity and a long period of feedforward/feedback integration from iEEG aligns well with the rough time period from ~250-500ms associated with the N400 effect found in extracranial EEG which is taken to index lexico-semantic integration[68]. It is during this integrative period of feed-forward/feed-back interaction that phonological re-coding would be expected.

Here we find Text-selective effects beginning in the fusiform at ~140ms (median: 200ms), aligning well with the previous reports. Two subjects each had an electrode with a Text-selective onset at ~160ms which showed significant connectivity with the Precentral and Supramarginal during Text presentation and in one subject connectivity also with STG and Pars Opercularis. This supports the caudal fusiform, strongly associated with orthographic processing[35,69–71], as the hub in the onset of widespread lateral-network activity.

The Text-selective activity in the lateral regions was earliest in the Pars Opercularis at ~200ms (median 280ms), then Precentral at ~220ms (median: 390ms), STG at ~240ms (median: 340ms), and Supramarginal at ~260ms (median: 320ms). This pattern is consistent with widespread early and sustained processing in the dorsal (i.e. putative phonological) reading network. Letter-specific effects emerged later in the Precentral at ~340ms (median: ~420ms) compared to earlier letter-specific activity in the Caudal Fusiform at ~180ms (median 230ms) and the Pars Opercularis at ~220ms, suggesting that even though letter identity was known in a putative orthographic area and a putative Phonological area, longer processing was necessary before letter-identity was known in the Precentral, possibly related to a sustained processing of phonological re-coding.

The timing found here aligns well with a series of extracranial EEG studies attempting to identify the timing of phonological re-coding. They used masked, i.e. below perceptual threshold, phonological priming[2,3] with, such as ‘MADE’ primes ‘MAID’[72] or ‘BRANE’ primes ‘BRAIN’[73]. EEG places the pseudohomophone priming effect (‘BRANE’ primes ‘BRAIN’) during evoked components at both ~250ms and ~325ms[74]. In unmasked priming, simultaneous presentation of visual and auditory words that either match or mismatch leads to differences beginning at ~300ms[75]. For rhyme judgement tasks, differences emerged at ~320ms at temporal electrodes for pronounceable but not non-pronounceable stimuli[76]. Another rhyme judgement task presented an incongruity effect of rhyming/non-rhyming stimuli from 300-600ms which was not present for a matching/mismatching letter task[77,78]. Taken together, the extracranial electrophysiology studies provide evidence that phonological effects onset from ~250-350ms, depending on the paradigm used.

Conclusion

Why might the precentral gyrus play a central role in Phonological Re-coding? Early theories emphasize the role of articulation in silent reading[30–34]. Here we provide evidence for this theory by showing Text-selective responses, as well as overlapping Noise-Vocoded—

selective responses, in areas with oral muscle movement. Articulation is a key determinant in learning to read, a theory referred to as the ‘Self-Learning Hypothesis’[79]. Articulating words while reading lead to better learning[80,81] and disruption of the oral motor cortex by Centrotemporal Epilepsy seizures in childhood while learning how to read leads to decreased reading ability later in life[82–84]. Cognitive modeling of learning to read[8], as well as empirical evidence[85], shows a shift of the division of labor from early reliance on phonological information to later reliance on orthographic information. However, the cognitive model also emphasizes that despite the decreased relevance of phonological information, only when both types of information are utilized does the model reach peak performance[8]. This model-derived inference regarding the continued automaticity and influence on silent reading of phonological information is supported by behavioral data[3,86–88]. When searching for the neural correlate of this automatic PR, the precentral gyrus is highlighted during both unconscious priming[35] and speeded semantic decision tasks[43]. The functional relationship between precentral and caudal fusiform is likely formed when learning to read and remains a contributing factor to silent reading throughout the lifespan.

However, the empirical evidence presented here and elsewhere does not conclusively establish a mechanistic understanding of PR. To convincingly demonstrate this requires much finer spatial resolution allowing for the identification of cortical patches, and potentially individual neurons, representing specific overlapping letter/phoneme identities. Though controversial[89,90], functional cortical patches are estimated to be between 50-500um[91], much finer than standard clinical electrode width of 10,000um. However, new experimental carbon-based electrodes[92,93] which allow for the measuring of high-gamma power and retain high-SNR and the ability to stimulate down to a width of 50um may pave the way for recordings from the precentral gyrus to more fully ground the mechanistic intuitions hinted at in the present study.

Chapter 2, in part, is currently being prepared for submission for publication of the material. The dissertation/thesis author was the primary investigator and author of this material.

Eric Halgren is senior author. Additional co-author’s include Lucia Melloni, Orrin Devinsky, Werner Doyle, Xiaojing Wu, Daniel Friedman, Patricia Dugan, Thomas Thesen.

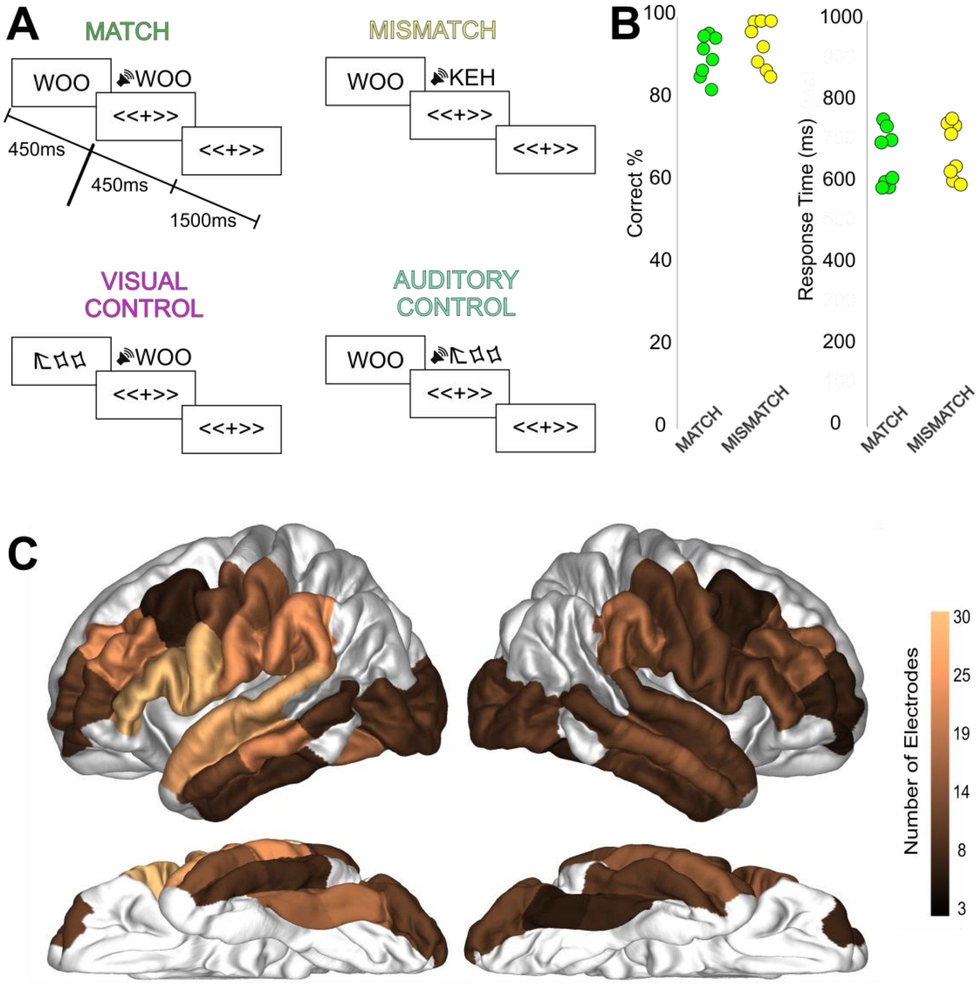

Figure 2.1: Task Design and Electrode Coverage. A) The sequence of visual-auditory stimulus presentation in the 4 trial types. B) Patient performance on Match and Mismatch trials, demonstrating a lack of difference between the two trial types. C) Electrode coverage highlighting coverage of perisylvian electrodes especially on the left side.

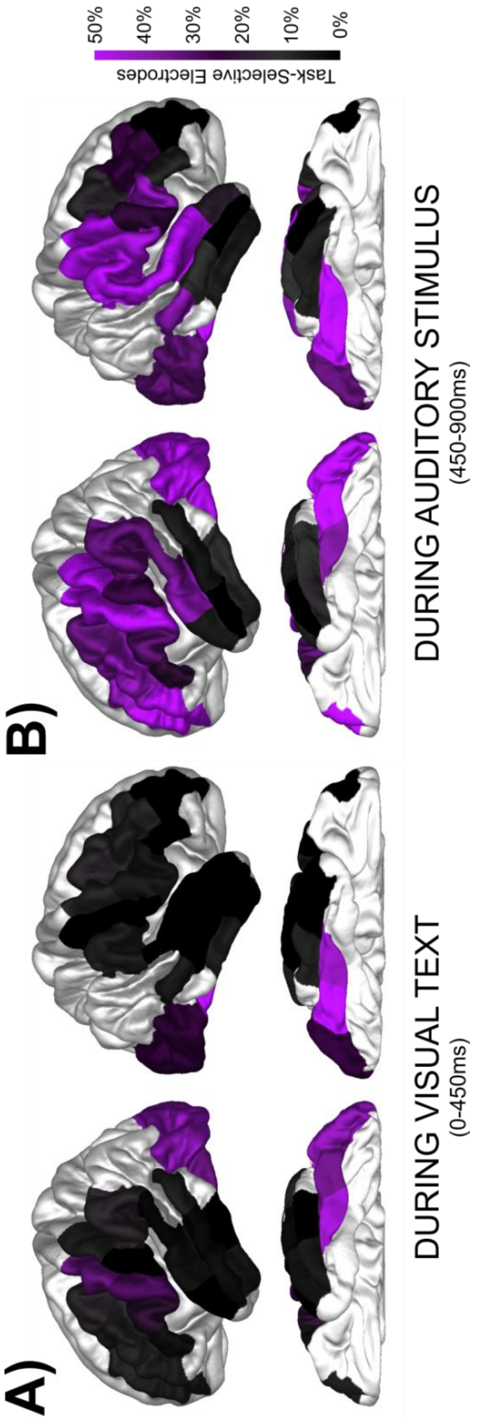

Figure 2.2: Task-Sensitive Electrode Distribution across the Cortex. A) Electrode demonstrating both a significant increase from baseline and a significant difference between the 4 trial types in a 1-way ANOVA during Text presentation from 0-450ms. B) Electrode demonstrating both a significant increase from baseline and a significant difference between the 4 trial types in a 1-way ANOVA during Bi-Phoneme presentation from 450-900ms.

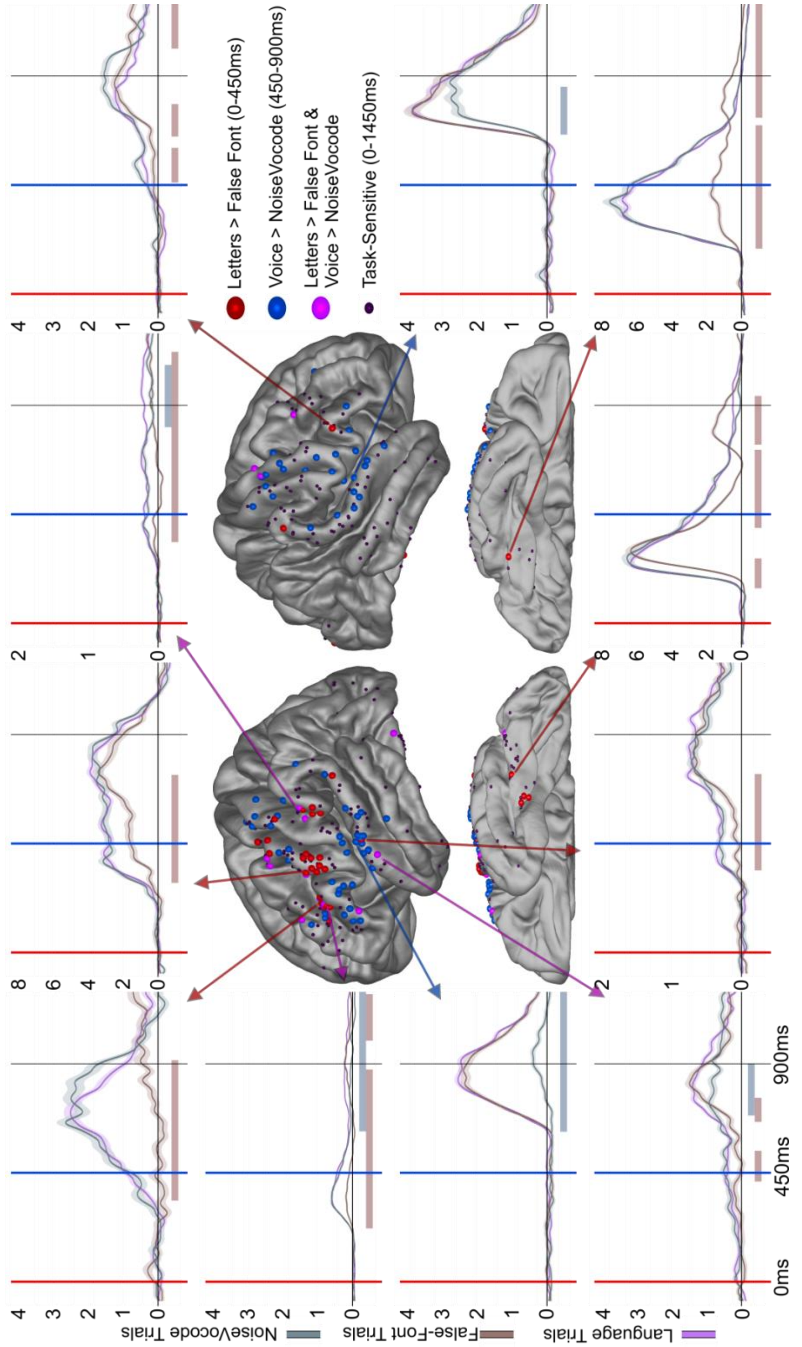

Figure 2.3: Language Selective Electrode Distribution across the Cortex. Electrodes displayed on the brain for Text-selective (red), Phoneme-selective (blue), and Bi-modal—selective (bright purple). Smaller electrodes represent sites that were Task-sensitive (dark purple) but did not prefer language stimuli to controls. Arrows from specific electrodes are color-coded for the electrodes effect and point to example waveforms illustrating typical waveforms for each region.

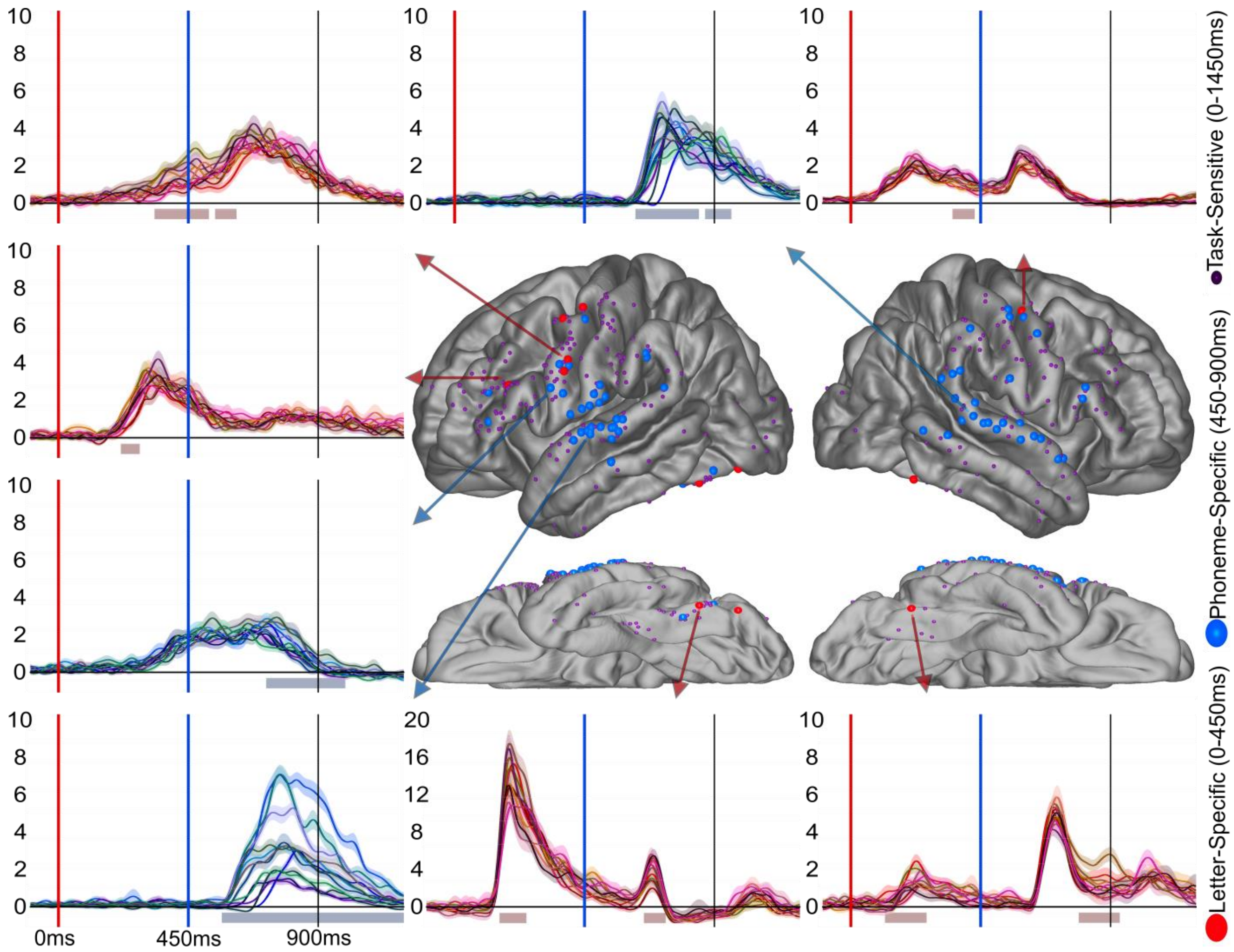

Figure 2.4: Language Specific Electrode Distribution across the Cortex. Electrodes displayed on the brain for Letter-specific (red) and Phoneme-specific (blue) effects. Smaller electrodes represent sites that were Task-sensitive (dark purple) but did not demonstrate letter or phoneme identity specificity. Arrows from specific electrodes are color-coded for the electrodes effect and point to example waveforms illustrating typical waveforms for each region.

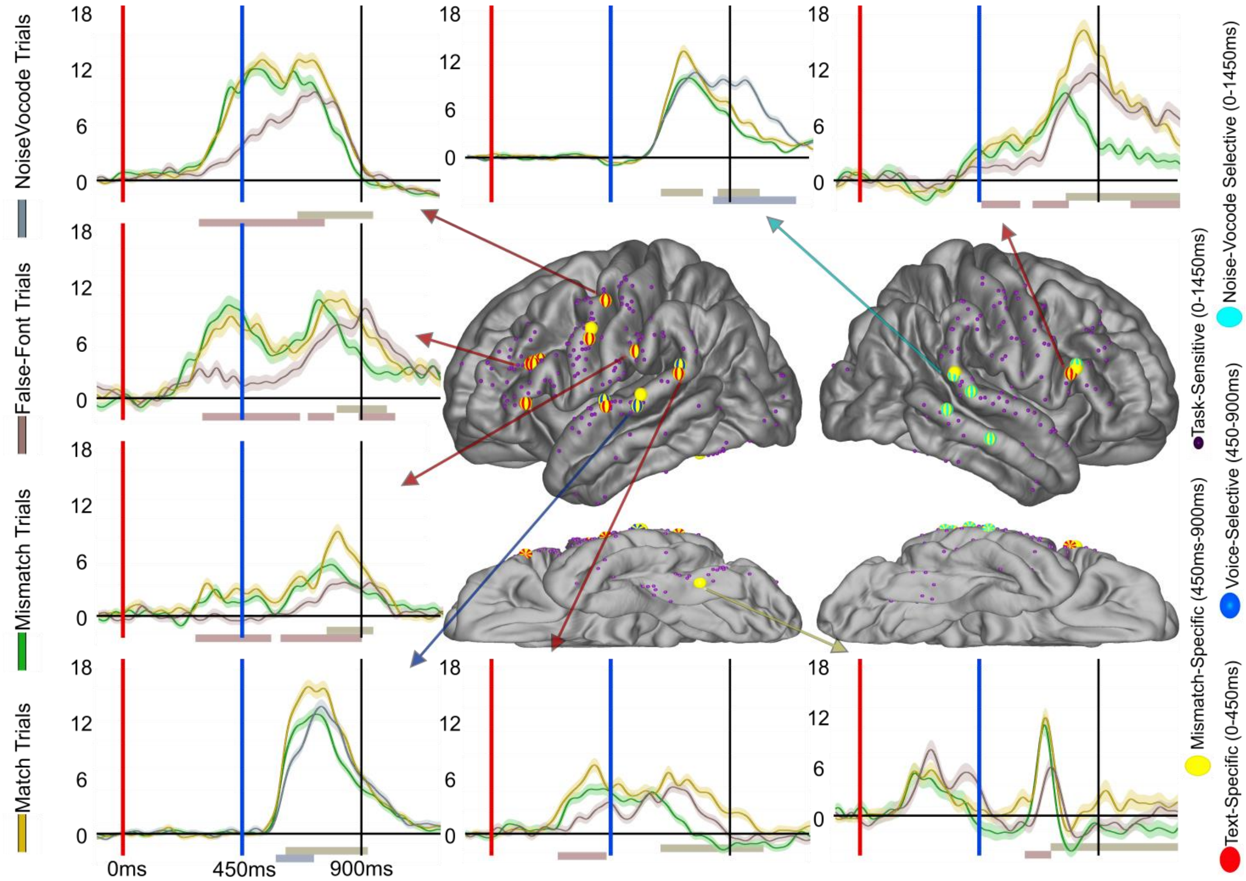

Figure 2.5: Mismatch Electrode Distribution across the Cortex. Electrodes displayed on the brain for the Mismatch effect (yellow) across the cortex. Overlapping Text-selective (red), Phoneme-selective (blue), and Noise-vocoded—selective (cyan) effects are noted with stripes. Smaller electrodes represent sites that were Task-sensitive (dark purple) but did not demonstrate a Mismatch effect. Arrows from specific electrodes are color-coded for the electrodes effect and point to example waveforms illustrating typical waveforms for each region.

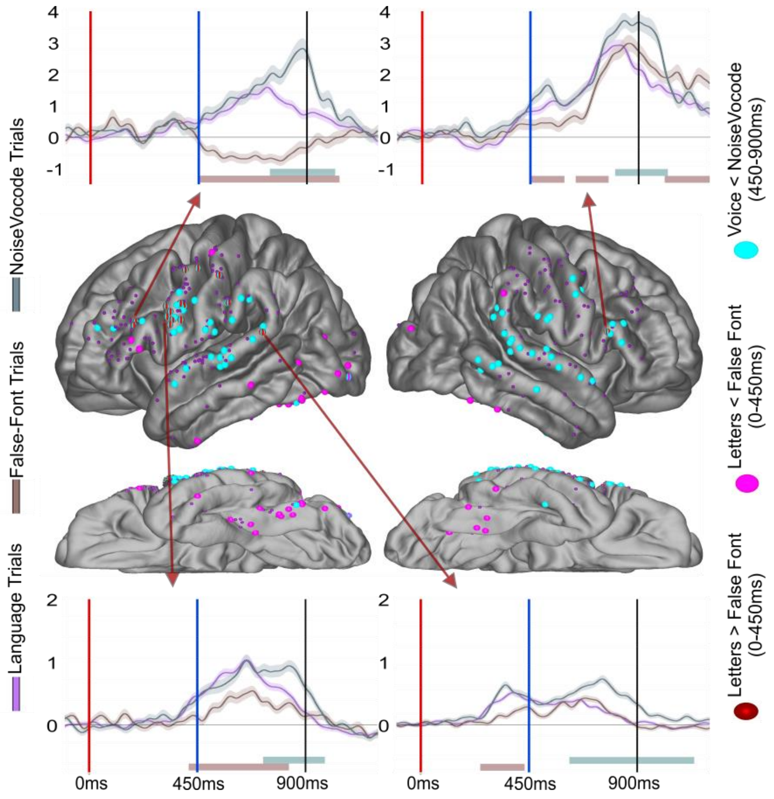

Figure 2.6: Illustration of the Overlap of Text-selective and Noise-vocoded—selective effects. Electrodes displayed on the brain for the Noise-vocoded-selective (cyan) electrodes. Overlapping Text-selective (red) effects are noted with stripes. Smaller electrodes represent sites that were Task-sensitive (dark purple) but did not demonstrate a Noise-vocoded—selective effect. Arrows from specific overlapping Noise-vocoded--selective and Text-selective electrodes point to example waveforms illustrating typical waveforms for each region.

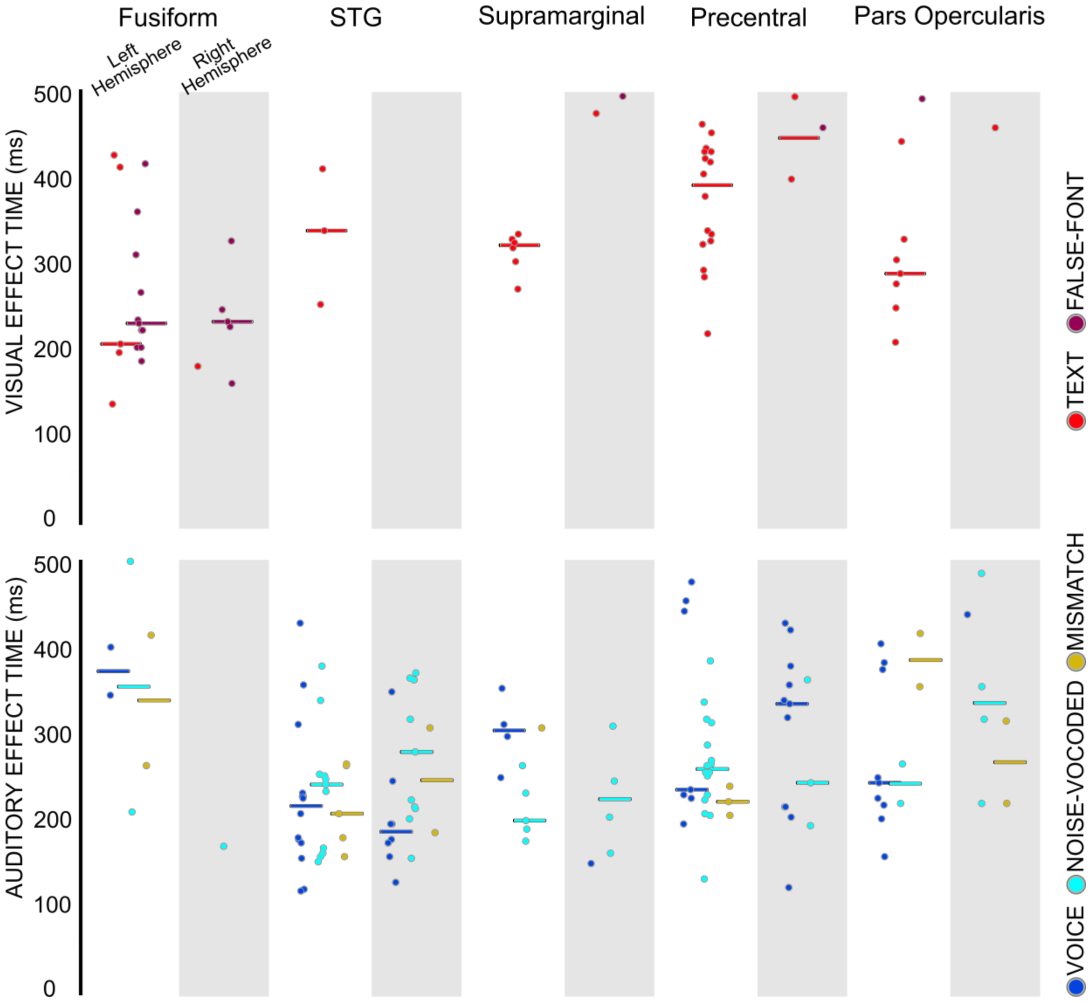

Figure 2.7: Effect onset timing from the Text presentation (top) and Bi-phoneme Presentation (bottom). The top displays onset of effects from Text display onset (0ms) for Text (red) and False-font—selective effects (magenta) for the left and right hemisphere. The bottom displays onset of effects from Bi-phoneme onset (450ms) for Phoneme-selective (blue), Noise-Vocoded—selective (cyan), and Mismatch effects (yellow) for the left and right hemisphere.

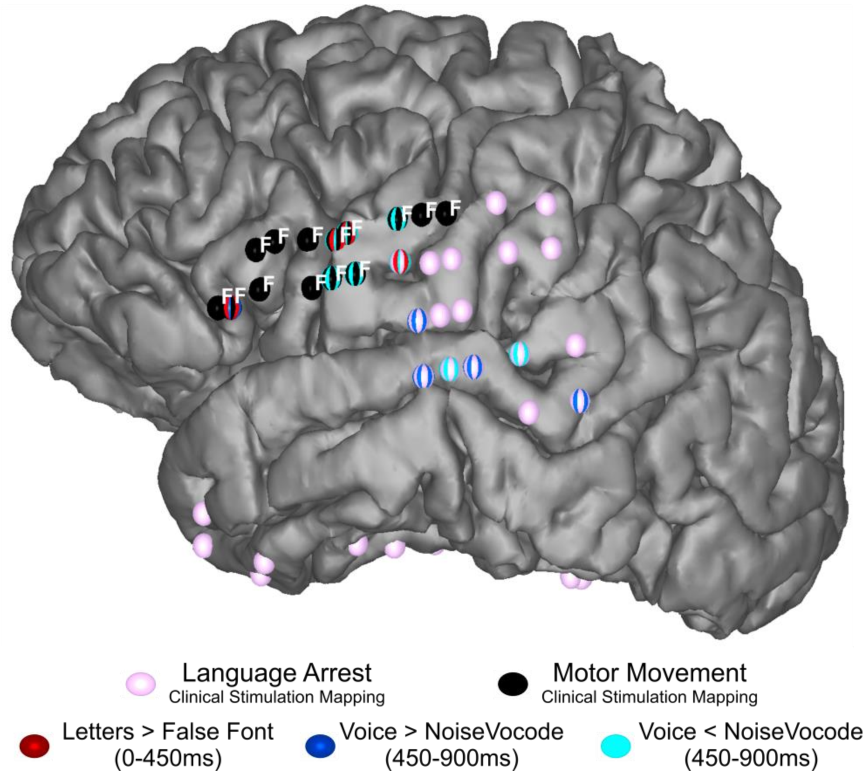

Figure 2.8: Stimulation results from one patient point toward overlapping Text-selective and Noise-Vocoded—selective effects with oral facial muscles. Electrodes illustrating stimulation evoked facial muscle movements (black) and speech interruption (pink). Overlapping Text-selective (red), Phoneme-selective (blue), and Noise-vocoded—selective (cyan) effects are noted with stripes.

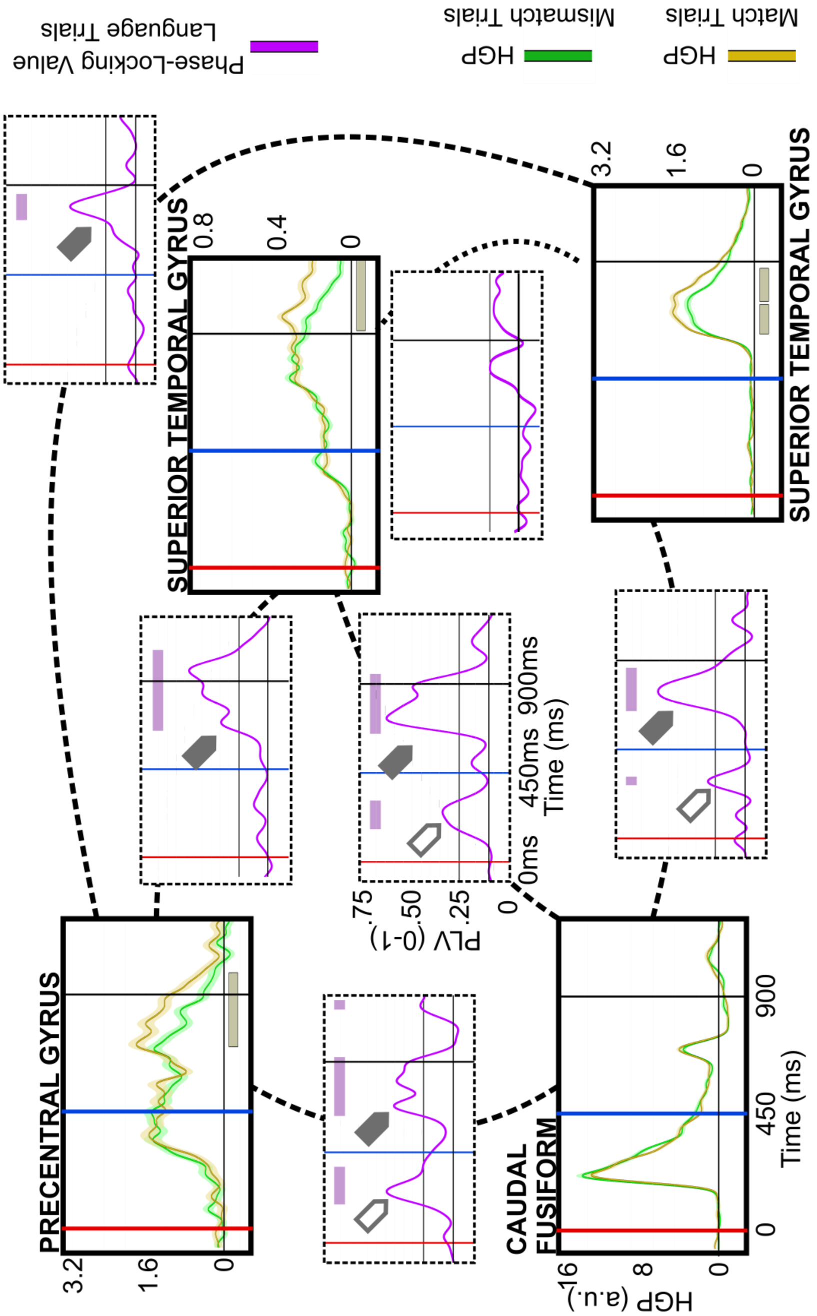

Figure 2.9: High-Gamma Power Responses and Phase-locking between the putative Phonological Re-coding network. Plots in solid lined boxes illustrate HGP differences between Match and Mismatch trials, illustrating Sensitivity to both Visual and Auditory phonemes at each electrode, except the Caudal Fusiform electrode. Dotted lines between electrodes show PLV values between each electrode. Empty arrows note the significant PLV connectivity between the caudal fusiform and both the Precentral Gyrus and STG in this patient during presentation of the visual text. Filled arrows note the significant connectivity between the caudal fusiform and these two areas again during the auditory phoneme presentation as well as significant connectivity between the Precentral Gyrus and STG during auditory phoneme presentation.

Table 2.1: Distribution of Task-Selective electrodes, and how many patients were contributed Language-Selective electrodes, in each region during text presentation (0-450ms) and auditory presentation (450-900ms).

		Left Hemisphere				Right Hemisphere			
	Region	Language-Selective (0-450ms)	Subjects	Language-Selective (450-900ms)	Subjects	Language-Selective (0-450ms)	Subjects	Language-Selective (450-900ms)	Subjects
Occipito-Temporal	Lateral Occipital	42% (5 / 12)	3 / 3	50% (6 / 12)	3 / 3	25% (3 / 12)	3 / 3	33% (4 / 12)	3 / 3
	Caudal Fusiform	35% (7 / 20)	2 / 3	60% (12 / 20)	2 / 3	60% (3 / 5)	2 / 2	60% (3 / 5)	2 / 2
	Middle Fusiform	44% (8 / 18)	4 / 4	39% (7 / 18)	3 / 4	43% (3 / 7)	2 / 3	57% (4 / 7)	2 / 3
	Middle ITG	0% (0 / 8)	0 / 4	13% (1 / 8)	1 / 4	9% (1 / 11)	1 / 5	9% (1 / 11)	1 / 5
	Rostral ITG	7% (1 / 14)	1 / 5	14% (2 / 14)	1 / 5	0% (0 / 11)	0 / 5	9% (1 / 11)	1 / 5
Perisylvian	Supramarginal	15% (6 / 41)	4 / 5	34% (14 / 41)	4 / 5	9% (2 / 22)	1 / 4	50% (11 / 22)	2 / 4
	Caudal MTG	9% (1 / 11)	1 / 4	9% (1 / 11)	1 / 4	8% (1 / 12)	1 / 4	42% (5 / 12)	4 / 4
	Middle MTG	3% (1 / 32)	1 / 5	6% (2 / 32)	2 / 5	0% (0 / 16)	0 / 5	13% (2 / 16)	2 / 5
	Rostral MTG	5% (1 / 20)	1 / 5	0% (0 / 20)	0 / 5	0% (0 / 18)	0 / 5	0% (0 / 18)	0 / 5
	Caudal STG	3% (1 / 38)	1 / 5	34% (13 / 38)	4 / 5	0% (0 / 13)	0 / 4	92% (12 / 13)	4 / 4
	Middle STG	6% (2 / 36)	2 / 5	42% (15 / 36)	5 / 5	0% (0 / 14)	0 / 4	50% (7 / 14)	4 / 4
	Rostral STG	0% (0 / 34)	0 / 5	9% (3 / 34)	3 / 5	0% (0 / 12)	0 / 5	17% (2 / 12)	2 / 5
Rolandic	Inferior Precentral	30% (11 / 37)	3 / 5	70% (26 / 37)	5 / 5	8% (1 / 13)	1 / 3	23% (3 / 13)	2 / 3
	Middle Precentral	35% (6 / 17)	3 / 5	71% (12 / 17)	5 / 5	12% (2 / 17)	1 / 4	71% (12 / 17)	4 / 4
	Inferior Postcentral	0% (0 / 29)	0 / 5	28% (8 / 29)	3 / 5	0% (0 / 13)	0 / 4	46% (6 / 13)	3 / 4
	Middle Postcentral	10% (2 / 21)	1 / 5	57% (12 / 21)	4 / 5	0% (0 / 13)	0 / 4	54% (7 / 13)	3 / 4
Frontal	Pars Opercularis	21% (8 / 39)	5 / 5	33% (13 / 39)	4 / 5	7% (1 / 14)	1 / 4	43% (6 / 14)	3 / 4
	Pars Triangularis	5% (2 / 38)	1 / 5	21% (8 / 38)	4 / 5	0% (0 / 18)	0 / 5	11% (2 / 18)	2 / 5
	Caudal Middle Frontal	14% (2 / 14)	2 / 5	36% (5 / 14)	3 / 5	14% (1 / 7)	1 / 3	14% (1 / 7)	1 / 3
	Middle Middle Frontal	10% (3 / 29)	2 / 5	41% (12 / 29)	3 / 5	11% (2 / 19)	1 / 4	26% (5 / 19)	2 / 4
	Rostral Middle Frontal	8% (1 / 12)	1 / 5	50% (6 / 12)	3 / 5	0% (0 / 7)	0 / 3	0% (0 / 7)	0 / 3

Table 2.2: Left Hemisphere Distribution of electrodes displaying each effect divided in region.

		Left Hemisphere							
		0-1500ms	0-450ms			450-900ms			450-1500ms
	Region	**Language-Selective**	**Text-Selective**	**FalseFont-Selective**	**Letter-Specific**	**Voice-Selective**	**Vocode-Selective**	**Phoneme-Specific**	**Incongruent**
Occipito-Temporal	Lateral Occipital	9	0	5	1	0	1	0	0
	Caudal Fusiform	15	1	6	0	1	1	2	2
	Middle Fusiform	9	4	4	1	0	0	0	0
	Middle ITG	2	0	0	0	0	0	0	0
	Rostral ITG	4	0	1	0	0	0	0	0
Temporal	Supramarginal	19	6	0	0	4	5	2	1
	Caudal MTG	2	0	1	0	0	0	0	0
	Middle MTG	3	0	1	0	1	0	1	0
	Rostral MTG	1	0	0	0	0	0	0	0
	Caudal STG	13	1	0	0	4	7	7	4
	Middle STG	17	2	0	0	9	3	7	1
	Rostral STG	4	0	0	0	1	1	0	0
Rolandic	Inferior Precentral	27	11	0	1	3	14	6	2
	Middle Precentral	12	5	0	2	4	2	2	1
	Inferior Postcentral	10	0	0	0	2	4	7	0
	Middle Postcentral	15	1	1	0	6	1	3	0
Frontal	Pars Opercularis	19	7	1	1	9	2	0	2
	Pars Triangularis	12	1	1	0	5	0	1	1
	Caudal Middle Frontal	8	1	1	0	2	0	0	0
	Middle Middle Frontal	16	3	0	0	4	1	0	1
	Rostral Middle Frontal	7	1	0	0	0	2	1	0

Table 2.3: Effect onset

				Left Hemisphere			
		0-450ms			450-900ms		450-900ms
Region	Text-Selective	FalseFont-Selective	Letter-Specific	Voice-Selective	Vocode-Selective	Phoneme-Specific	Incongruent
Fusiform	200ms (140-420)	220ms (180-400)	280ms (280)	370ms (340-400)	360ms (220-500)	440ms (440-440)	340ms (260-420)
Lateral Occipital		220ms (160-340)	260ms (260)		440ms (440)		
ITG							
MTG		320ms (300-340)		200ms (200)		200ms (200)	
STG	340ms (240-400)			220ms (120-420)	240ms (160-380)	180ms (120-440)	220ms (160-260)
Supramarginal	320ms (260-320)			310ms (260-360)	200ms (180-260)	260ms (180-340)	300ms (300)
Precentral	390ms (220-460)		420ms (340-420)	240ms (200-480)	260ms (140-380)	280ms (140-360)	220ms (220-240)
Pars Triangularis	420ms (420)	340ms (340)		280ms (180-380)		300ms (300)	380ms (380)
Pars Opercularis	280ms (200-440)	500ms (500)	220ms (220)	240ms (160-400)	240ms (220-260)		390ms (360-420)

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CHAPTER 3: The Separation of Lexico-Semantic Processing in Auditory and Visual Language: An Intracranial Study of Single-Word N400 Effects

Abstract

Visual language processing, i.e. reading, is conceived of as interacting networks focused on processing either the visual or auditory information encoded from text. The loci of the auditory information processing during reading is thought to be in perisylvian regions which overlaps with auditory language networks. Here we report evoked intracranial electrophysiology (iEEG) during a semantic decision task performed in both the visual and auditory sensory modalities. In both task-evoked High-Gamma Power (HGP; 70-170Hz) and the distribution of repetition effects in HGP and broadband local-field potentials (LFP) we find statistically significant overlap of ~50% of contacts. When examining phase-locking value (PLV) between electrodes however, we found a general separation of the networks with a statistically non-significant overlap of significant PLV coupling between the two modalities. Finally, we examined HGP from a Utah Array with a pitch of 400um (as opposed to the clinical electrode pitch of 10,000um) and found that even when Auditory-evoked and Visual-evoked activity was of a similar amplitude when averaged over a large patch of cortex, the amplitude of the smaller patches of cortex did not correlate. This leads to a picture of the perisylvian region as an area of both overlap and separation in Visual language and Auditory language networks.

Introduction

Visual language, i.e. reading, develops in the framework of an already existing auditory language network[1]. While early psychological theories posited that skilled readers could rely solely on visual identification of word[2–4], decades of behavioral[5,6] and lesion studies[7] have led to computational model agreement that both visual and auditory information contribute to reading[1,8,9]. Neuroanatomical models roughly map these two information processing stream onto distinct but interacting networks in the cortex. Visual word identification is thought to be centered along the ventral occipito-temporal lobe[10,11] and auditory word identification is centered in perisylvian areas including the posterior temporo-parietal region and inferior frontal gyrus[12–16]. However, despite evidence of strong phonological influences on visual language processing in early readers, as reading skill increases phonological influences decrease[17]. These observations coupled with disagreements regarding the locus of lexico-semantic processes during reading as primarily visual[8] or auditory[5,6] leads to questions regarding how fully the putative auditory language network is involved in adult reading. Here we use the spatio-temporal precision of intracranial electrophysiology (iEEG) to record from the cortical surface during both a visual and auditory lexico-semantic decision task. Our goal is to characterize the separation and/or overlap of processing evoked by visual and auditory language processing in the perisylvian regions, i.e. the putative dorsal reading route.

N400 Effects: A window into the process of lexico-semantic integration

As strong phonological theorists highlight that the phonological reading network is chiefly concerned with word-level meaning and identity[5,6], a main focus will be at the level of lexico-semantic integration. There are a vast number of behavioral assays into the processing underlying the encoding of single word lexico-semantic identity and its integration into the ongoing cognitive context. Electrophysiologicaly, these assays produce effects during a temporal window containing an overlapping series of cognitive processes that are part of a complex referred to as the N400. The N400 is a widespread electrophysiological component indexing lexico-semantic processing beginning ~250ms, peaking around ~400ms, and continuing to ~600ms. During this time, there are assumed to be many simultaneous cognitive operations accessing and integrating word identity and meaning[18,19]. This component is particularly sensitive to meaning integration with the ongoing context, with increased difficultly indexed by sentential semantic violations[20], word expectation probability[21–24], surrounding semantic context[25–27], and priming[28–32], but not for non-semantic operations such as syntactic mismatches[33].

A wide variety of stimuli elicit N400 effects, including objects[34], mathematical symbols[35], and spatial location[36], and the similarity between difference contexts such as single word versus sentential effects[37] has led to a theory of an encompassing a-modal lexico-semantic system[19]. For our purposes of comparing visual and auditory language processing, though the N400 shows qualitative differences in waveform between visual and auditory words, the effects appear roughly the same for language presented in both the auditory and visual modalities[19]. N400 processes intersect for both visual and auditory language, evidenced by cross-modal priming, either sequentially[38,39] or simultaneously[40]. This is often taken as proof that many of the simultaneous ongoing processes are in common between visual and auditory language, with a logical location for these overlapping cognitive operations being located in the putative phonological route during reading with which were are interested.

Auditory Contribution to Visual Language Processing: Feed-Forward & Feed-Back Interaction

Early psychological theories emphasized the putative speed of visual word identification as a reason why a putatively slower phonological route did not contribute to visual word identification[2–4]. With visual processing beginning at ~60ms in the posterior ventral temporal lobe[41] reports of lexico-semantic encoding effects during visual word processing onsetting by ~200-250ms in the antero-ventral temporal lobe[42–45] do support this characterization of fast visual encoding. However, just as the suite of N400 processes recorded extracranially extend in time for 100s of milliseconds, the onset of N400-like lexico-semantic effects at ~200-250ms begins a period alternating feed-forward and feed-back flows of information in the anteroventral temporal lobe[46,47]. The general timecourse of lexico-semantic processing in the ventral visual route is illustrated by a study which found the onset of putative feedforward activity at the terminal of the ventral reading route begins at ~120ms and the onset of repetition priming at ~220ms[46] which extended for 100s of millisceonds. This temporal window of feed-forward/feed-back processing extending for 100s of milliseconds beginning ~200ms aligns well with reports of activity in the putative dorsal reading route of a widespread simultaneous onset of processing starting at ~150ms[48].

Present Study

Models of reading take it as a given that visual and auditory language systems are highly interactive, but assume varying degrees of overlap between visual and auditory language regions in lexico-semantic processing[1,8,9]. The strongest theories of phonology assume that the already developed auditory lexico-semantic network serves as the main, or only, lexico-semantic system with the visual language network appended via various phonological re-coding processes[1,5,6]. Here we investigate the actual degree of overlap in the dorsal reading route, i.e. perisylvian language areas, using the spatial and temporal precision of electrophysiology recorded directly from the cortical surface. Patients performed both a visual and auditory lexico-semantic decision task allowing us to assess the degree of overlap and independence of visual and auditory language processing networks.

Methods

Electrocorticographic (ECoG) recordings were obtained from 12 patients (9 males, mean age 34.6, age range 20-73, mean age of onset: 13.7) undergoing intracranial EEG monitoring as part of treatment for pharmacologically resistant epilepsy. One patient was left-handed and had a WADA revealing the right hemisphere as the dominant language hemisphere. Their electrodes are treated as part of the 'left hemisphere' for the purposes of this study with the 'left hemisphere' standing in for 'dominant hemisphere'. All procedures were approved by the Institutional Review Board at New York University and written informed consent was obtained from all participants. Electrode placement was determined by clinical criteria to identify seizure activity and eloquent tissue. Each patient was implanted with subdural platinum-iridium electrode arrays embedded in silastic sheets (AdTech Medical Instrument Corp). Data included arrays of grids (8x8 contacts) and strips (1x4 to 1x12 contacts). Contacts had a diameter of 4mm with 2.3mm exposure. Center-to-center spacing between contacts was 10mm for grids and 5mm for micro-grids. Recordings were acquired using a Nicolet One EEG system sampled at 512 Hz and bandpass filtered between 0.5 and 250 Hz.

Electrode localization

Electrode localization was done through co-registration of pre- and post-implant MRI images, followed by manual and automatic localization of electrodes[49]. Coordinates were co-registered to a standard MNI template and anatomical parcellations were determined using the Desikan-Killiany atlas[50]. Long gyri were split into 3 parts, either inferior/middle/superior (Pre-central gyrus, post-central gyrus) or caudal/middle/rostral (fusiform, ITG, MTG, STG, Middle-Frontal, Superior-Frontal). Parcellations were excluded if ≤ 5 electrodes had task responsive effects. Three-dimensional reconstructions of cortical surfaces in figures were created using FreeSurfer[51]. Localization into a brain region was performed in each subject's native brain. Subject average electrode location, used for display purposes only, were obtained using FreeSurfer surface-to-surface calculations with the fsaverage brain. Figure 1C shows the electrode coverage throughout the cortical parcellations, highlighting our coverage of relevant left-hemisphere perisyvlian regions as well as lateral occipital, inferior frontal gyrus, and ventral temporal regions. Regions with <5 electrodes were excluded from analysis.

Task Design

Figure 1A displays a schematic of the task. In two independent but symmetric tasks performed separately, patients performed a silent semantic decision either with words presented visually or with words presented auditorily. Words represented were concrete objects, loosely broken into 'animate' (such as animals, body parts, etc.) and 'inanimate' (such as tools, clothes, etc.). Patients were asked to make a size judgement regarding each word presented, either that it was larger or smaller than ~1 ft. Words were chosen (such as cricket, tiger, car, nail) to make this a relatively easy choice.

In each task, words were split into "novel words" (50% of trials, all words unique) and "repeated words" (50% of trials, 10 words all repeated equally). The repeated words were intermixed with the novel words during presentation. The visual and auditory word lists were each a unique group of words, matched on word frequency (auditory: 13.28 per million and visual: 12.51 per million)[52]. The auditory task had slightly shorter words (1.4 syllables, 5.2 letters) than the visual task (2.1 syllables, 6.6 letters) due to presentation timing constraints. The repeated words were chosen to be representative of their respective category with respect to word frequency and length.

Auditory words were recorded by a native male speaker and were equated for sound onset and duration (500ms), as well as amplitude level by digitally editing the recorded waveforms. Presentation of auditory words occurred every 2.2s. Visual words were presented for 300ms with white text on a black background on a computer screen. A fixation point was present between word presentations. Presentation of visual words occurred every 2s.

The repeated words represent our assay into lexico-semantic processing, as they represent full repetition priming, which has been used effectively to measure the N400 processes as described in the introduction. In addition to N400 effects, repetition priming leads to multiple well-documented empirical regularities, with decreased neuronal activity previously found in task-engaged regions using fMRI[53], unit firing[54], and iEEG[55]. These repetition priming effects remain over long periods of time (>hours)[53,56,57]. The decreased activity is thought to be arelatively automatic part of processing as they persist in amnesiacs[58], occur during anesthesia[59], and when the repeated stimulus is non-attended[60]. Due to this dissociation from overt top-down systems of memory and attention, repetition priming is judged to be a good assay of the timing and location of neural representational traces. The repetition priming occurring here is moderately long range, with multiple intervening stimuli and many seconds passing between each occurrence of an individual repeated stimulus. The number of intervening items decreases the facilitation of repetition priming for known words down to a stable floor after 3 intervening non-primes[61], further suggesting that that remaining repetition effects we measure are related to long-lasting representational traces. In this particular study, the representational traces relate to linguistic identities. As the method of repetition occurring here is full repetition, these representational traces relate to both sub-lexical and lexico-semantic level representations.

The decrease in neuronal firing to repeated stimuli is understood partially in terms of the feed-forward, feed-back interactions we are interested in[62]. This proposal is that feed-back predictions decrease feed-forward activity. In support of this theory, evidence has been found that when frequent repetitions are expected repetition effects are stronger[63]. How these feed-forward/feed-back connections interact is suggested by a study which found decreased neuronal firing after repetition priming but the remaining spikes were more synchronized to local LFP[64].

Data Processing

Data were preprocessed using MATLAB (MathWorks) and the Fieldtrip toolbox[65]. We used an average reference to reduce noise. Data was epoched to the onset of lip movement for visual trials and to the onset of auditory input for auditory and audiovisual trials. Epochs were transformed from the time domain to the time–frequency domain using the complex Morlet wavelet transform. Constant temporal and frequency resolution across target frequencies were obtained by adjusting the wavelet widths according to the target frequency. The wavelet widths increase linearly from 14 to 38 as frequency increased from 70 to 170 Hz (high gamma band activity), resulting in a constant temporal resolution of 16ms and frequency resolution of 10 Hz. For each epoch, spectral power was calculated from the wavelet spectra, normalized by the inverse square frequency to adjust for the rapid drop-off in the EEG power spectrum with frequency, and averaged from 70 to 170 Hz, excluding line noise harmonics. This data was smoothed by a moving window matching the temporal characteristics of the wavelet. Each trial epoch was demeaned with a baseline from -250 to 0m.Trials containing artifacts were identified b0y amplitude and variance, visually inspected for artifacts and removed from data.

Task Effect Analysis

Task-Responsive (High-Gamma Power): Electrodes that had significantly increased High-gamma activity from a baseline of 0 to either the Visual stimuli or the Auditory stimuli stimulus conditions between 25-to-600ms (Task-Responsive electrodes) were identified using a timepoint-by-timepoint t-test corrected for temporal false-discovery rate at p<.05[66]. This test was run separately for Auditory and Visual, leading to Visual-responsive electrodes, Auditory-responsive, or Bimodal-responsive (i.e. Visual-responsive & Auditory-responsive).

Repetition-Effect (High-Gamma Power): To understand which electrodes were measuring cortex sensitive to repetition priming, pairwise one-way ANOVAs were next run to determine if a significant difference between novel and repeated stimuli existed using High-Gamma Power. ANOVAs were run run timepoint-by-timepoint, temporally corrected using a bootstrapped shuffling of trial identity 1000 times[65]. The significant time points for the repetition effect were masked by significant time-points that were also increased from 0 (i.e. Task-Responsive). Electrodes were only included if they were Novel greater than Repeated. This test was run separately for Auditory and Visual, leading to Visual- repetition electrodes, Auditory-repetition, or Bimodal- repetition (i.e. Visual- repetition & Auditory- repetition).

iN400-Effect (Local-Field Potentials): This was an additional analysis into the repetition effects more closely matching the N400 literature. To understand which electrodes were measuring cortex sensitive to repetition priming in the lower broadband frequencies, pairwise one-way ANOVAs were next run to determine if a significant difference between novel and repeated stimuli existed. ANOVAs were run run timepoint-by-timepoint, temporally corrected using the bootstrapped shuffling method. Electrodes were only included if they were Novel greater than Repeated. This test was run separately for Auditory and Visual, leading to Visual-iN400 electrodes, Auditory-iN400, or Bimodal-iN400 (i.e. Visual-iN400 & Auditory-iN400).

Regional Comparisons

Comparisons between regions are difficult in iEEG due to sparse coverage that varies between participants due to clinical considerations. However, studies with large numbers of patients note that while locations of interest, such as language, vary in exact anatomical location they are located in generally similar regions relative to neuroanatomical landmark[67]. For this reason, this study will make use of non-parametric statistics to compare both proportion of electrodes and timing of electrodes between regions of critical interest when effect numbers provide the power to do so.

For proportion of electrodes, 8 regions will be compared to the total pool of electrodes from other included regions (minus the region being tested's electrodes) to see if the region is more/less involved than the total pool of responses. Fisher's Exact Test will be used to make this test. These 8 regions tested are typically focused on in neuroanatomical models of reading will be included in the statistical tests: Fusiform, Lateral Occipital, STG, MTG, Supramarginal, Precentral Gyrus, Pars Opercularis, and Pars Triangularis. Therefore the corrected p-value is $p<.006$ (.05 divided by 8). As this is a stringent threshold, the total number of datapoints (i.e. significant electrodes) for some conditions is low, and we are using non-parametric statistics which have lower power, p-values $p>.006$ but $p<.05$ will be noted as well, but marked as uncorrected.

Effect onset comparisons will use the same general will also compare effect onset timings between regions statistically is difficult because of the variable number of effects per region causes differences in power between regions. However, despite these difficulties some regularities emerged. These timing analyses will mirror the targeted/exploratory structure of the regional distribution analyses and share their p-value corrections. All tests run will be a ranksum non-parametric test.

Overlap Comparisons

A key question in this work is the overlapping/separation of Visual and Auditory language cortical representations. We sought to assess whether the 8 regions described above could be regarded as having a significant overlap of effects (such as having overlapping Visual-responsive and Auditory-responsive effects). For this purpose a binomial test was run for these regions. For example, to asses if the Visual-responsive effects in a region overlap significantly above chance with the Auditory-responsive effects in the region, we used the following method. We ran the binomial test comparing the number of overlapping Visual-responsive and Auditory-responsive effects (i.e. Bimodal-Responsive) and the number of overall Visual-responsive effects, compared to an expected chance level of the overall proportion of Auditory-responsive effects.

Amplitude

High-gamma power is an indirect measure of neuronal population firing[68], so the measured amplitude of HGP at an electrode gives an indirect measure of the aggregate surrounding neuronal population firing. To understand whether overlapping effects reflect similar levels of neuronal involvement, high-gamma power amplitude was also compared within the 8 targeted regions. If the same neuronal populations underlie lexico-semantic, or phonological, cognitive operations in both visual and auditory language, similar amplitude would be expected during both tasks. An amplitude difference would suggest less tuning for language in one modality versus the other.

To assess amplitude, for both visual and auditory trials, the average waveform for novel words was z-scored relative to its baseline (the same time-window as used for baselining in data analysis). Only novel words were used to avoid confounds from the repetition effect. Then the highest value was found for each electrode in both modalities during the time window of 50-to-600ms (to allow for differences in timing in the network flow of information during visual and auditory linguistic processing). The same targeted regions were compared as in regional analysis. The statistical procedure was the same for the timing, using a ranksum non-parametric test.

Connectivity

To test the putative network identified in individual electrodes with HGP effects, we used Phase-Lag Value (PLV) calculated pairwise between electrodes as decribed in [69] to test whether

significant functional connectivity could be inferred between electrodes. PLV measures the consistency of the relative phase of LFPs in two locations. High PLV indicates consistent synchronization of the synaptic currents in pyramidal apical dendrites between the cortical locations underlying the intracranial sensors. Significant PLV was determined by creating a distribution of all PLV values from a baseline period (-300-to-0ms) for each subject. Only if the obtained PLV value after stimulus presentation was $p<.00005$ based on the subject's own baseline distribution was a pairwise connection judged to be significant. PLV was run separately for Visual trials and for Auditory trials.

Results

Task Responsive Electrodes (High-Gamma Power)

First, we establish the distribution and timing of Visual-responsive electrodes to understand what cortical areas are engaged by the semantic decision task. The Visual responsive electrodes were left-lateralized ($p<.001$). For the overall distribution in the left hemisphere, there was a breakdown into roughly three regions. The occipito-temporal regions had the greatest proportion, with both the Lateral Occipital ($p<.01$) and Fusiform ($p<.01$) having greater proportion of electrodes. Overall, these regions were also faster than the pooled onsets in both the Lateral Occipital ($p=.007$, fdr-uncorrected) and Fusiform ($p=.008$, fdr-uncorrected). Next was frontal perisylvian regions such as the precentral gyrus, pars opercularis, and pars triangularis (all $p>.05$) not distinguishable from the pooled responses. The Pars Opercularis was also slower than the pooled regions ($p=.001$). Finally, there were lateral temporal regions that were less involved with the STG ($p<.05$, fdr-uncorrected), MTG ($p<.001$), and Supramarginal ($p<.05$, fdr-uncorrected) having a lower proportion than the pooled proportion.

Next, we examined the Auditory-responsive electrodes and their relationship to Visual-responsive electrodes. Auditory-responsive electrodes responsive electrodes were left lateralized as were the Visual-responsive electrodes ($p<.001$). In the left hemisphere, overall Auditory-responsive electrodes were a greater proportion than Visual-Responsive electrodes (*p*< .005). Follow-up analyses revealed that the occipital-temporal regions that showed greater proportions of Visual-responsive electrodes had a greater proportion of Visual-responsive than Auditory-responsive electrodes: Lateral Occipital (*p*<.005) and Fusiform (*p*=.007, fdr-uncorrected). Similarly, the lateral temporal regions that had decreased proportions for Visual-responsive electrodes showed greater Auditory-responsive effects: MTG (*p*=.004) and STG (*p*<.001). For effect onset, we examined the timing differences in the onset of Visual-responsive and Auditory-responsive effects. Overall, in the left hemisphere there was no difference in the onset of Visual-responsive and Auditory-responsive effects (*p*>.50). Follow-up analyses identified the Lateral Occipital (*p*=.02, fdr-uncorrected), Fusiform (*p*=.02, fdr-uncorrected), and ITG as having faster Visual-responsive onsets while the STG (*p*=.03, fdr-uncorrected) had faster Auditory-responsive electrodes.

Focusing on Bimodal-responsive electrodes, they were also found to be left lateralized (*p*<.001). Analyses of the distribution of Bimodal-responsive electrodes in the left hemisphere found that only the Precentral (*p*=.01, fdr-uncorrected) had a greater proportion of effects that the average. The MTG (*p*=.02, fdr-uncorrected) and Pars Opercularis (*p*=.01, fdr-uncorrected) had a lower proportion of Bimodal-responsive electrodes. To see if the Bimodal-responsive electrodes showed a difference in onset between Visual-responsive and Auditory-responsive effects, subtracted the two onset times. This differences in timing found in Bimodal-responsive electrodes matched the overall onset time differences. Visual-responsive onsets were faster in the Lateral Occipital (*p*=.008, fdr-uncorrected) and Fusiform (*p*=.03, fdr-uncorrected while Auditory-responsive onsets were faster in the STG (*p*=.01, fdr-uncorrected).

Finally, we assess the critical question regarding whether the Bimodal-responsive electrodes we did find evidenced a significant relationship between Visual-responsive and Auditory-responsive electrodes. We focused on whether there were more Visual-responsive electrodes also displaying an Auditory-responsive effect than would be expected by chance. Overall there was strong overlap of Auditory-responsive effects in electrodes with Visual-responsive effects (*p*<.001) with 58% of Visual-responsive electrodes also showing an Auditory-responsive effects. This effect was significant in the STG (*p*<.001, 100%), Precentral (*p*<.001, 77%), and Supramarginal (*p*=.02, fdr-uncorrected, 100%).

Repetition Effects (High-Gamma Power)

In examining how many of the Visual-responsive electrodes additionally showed evidence of a HGP repetition effect, it was found that 23 out of the 96 (24%) were Visual-repetition. Like Visual-responsive electrodes, Visual-repetition electrodes were left lateralized (*p*<.001). In the left hemisphere, only the Pars Triangularis showed an increase relative to the average proportion (*p*<.05, fdr-uncorrected). No differences were found between regions for onset of Visual-repetition effects (all *p*>.10*).*

Next, we examined the Auditory-repetition electrodes and their relationship to Visual-repetition electrodes. Similar to the visual modality, Auditory-repetition electrodes were left lateralized (*p*=.005). In the left hemisphere, Auditory-Repetition effects were a greater proportion than Visual (*p*<.001). Follow-up targeted analyses, the STG (*p*<.001), Precentral gyrus (*p*<.05, fdr-uncorrected), and MTG (*p*=.05, fdr-uncorrected) displayed a greater proportion of Auditory-repetition versus Visual-repetition effects; There were no areas with significantly greater proportion of Visual-repetition electrodes. An analysis of the onset of repetition effects revealed no timing differences between Visual and Auditory effects (all *p*>.25).

Focusing on Bimodal-Repetition effects, the distribution of Bimodal-repetition electrodes, they were left lateralized (*p*<.05). Among regions, these Bimodal-repetition effects were distributed with no regions with either a significantly increased or decreased proportion relative to the average (all *p*>.15). Additionally, there was no evidence for any region's Bimodal-repetition effects being faster or slower than any other region (all *p*>.15).

Finally, we assess the critical question regarding whether the Bimodal-repetition we did find evidenced a significant relationship between Visual-repetition and Auditory-repetition electrodes. We focused on whether there were more Visual-repetition electrodes also displaying an Auditory-repetition effect than would be expected by chance. Overall there was strong overlap of Auditory-repetition effects in electrodes with Visual-repetition effects (*p*<.001) with 52% of Visual-repetition electrodes also showing an Auditory-repetition effects. This effect was significant in the Precentral Gyrus (*p*=.007, 57%) and the Supramarginal Gyrus (*p*<.05, fdr-uncorrected, 100%). In the lateral temporal lobe (MTG, STG) there were not enough electrodes to statistically determine if there were an overlapping relationship; However, what Visual-repetition electrodes were found were overlapping with Auditory-repetition electrodes.

Repetition Effects: Local-Field Potentials

Having examined repetition effects using High-gamma power, we next examined repetition effects from broadband low-frequency activity. Similar to both previous effects, the Visual-iN400 was left lateralized (*p*<.001). For distribution of effects, there were no regions with an increase relative to the average (all *p*>.05). However, the STG did have a significant decrease relative to the average (*p*<.05, fdr-uncorrected). There were no significant onset difference between regions (all *p*>.05)

Next, we examined the Auditory-iN400 electrodes and their relationship to Visual-iN400 electrodes. Like the Visual-iN400 the Auditory-iN400 effects were left-lateralized (*p*<.001). Mirroring the HGP repetition effects, in the left hemisphere Auditory-iN400 electrodes were a greater proportion than Visual-iN400 electrodes (*p*<.001). Follow-up analyses revealed that this effect was significant in the STG (*p*<.001). Overall, in the left hemisphere there was no overall difference in the onset of Visual-responsive and Auditory-responsive effects (*p*>.50). However, follow-up targeted analyses reveleated that Visual-iN400 effects were faster than Auditory-iN400 effects (*p*<.05, fdr-uncorrected).

Focusing on Bimodal-iN400 electrodes, they were left-lateralized (*p*<.001). In the left hemisphere, the distribution of Bimodal-iN400 electrodes did not show any region having a greater proportion of effects than any other region (all *p*>.05). When comparing the overlap of Visual-iN400 and Auditory- iN400 effects, we focused on whether there were more Visual-iN400 electrodes also displaying an Auditory- iN400 effect than would be expected by chance. Overall there was strong overlap of Auditory- iN400 effects in electrodes with Visual- iN400 effects (*p*<.001) with 54% of Visual-repetition electrodes also showing an Auditory-repetition effects. This effect was significant in the Pars Opercularis (*p*=.002, 80%), Supramarginal Gyrus (*p*=.003, 100%), STG (*p*<.05, fdr-uncorrected, 100%), Fusiform (*p*<.05, fdr-uncorrected, 100%), and MTG (*p*<.001, 100%).

Amplitude

Due to High-gamma power correlating well with overall neuronal activity, we attempted to assess whether the measured neuronal populations had equal evoked neuronal activity by each language modality. Overall, there was no significant difference in amplitudes between Visual and Auditory stimuli (*p*>0.40). Follow-up comparisons revealed that the occipito-temporal regions, the Fusiform (*p*=.005) and Lateral Occipital (*p*<.01, fdr-uncorrected), had a greater amplitude for Visual trials than for Auditory trials. In contrast, the STG (*p*<.001) had a greater amplitude than for Auditory trials than Visual trials. This lines up well with the proportion of effects being different in these two regions in the Task-responsive electrodes distribution.

Restricting our analyses to just Bimodal-responsive electrodes largely confirmed this difference in amplitude in core-modal areas. Both the Lateral Occipital (*p*=.003) and Fusiform (*p*=.03, fdr-uncorrected) had greater amplitude for Visual trials in Bimodal-responsive electrodes. For Auditory trials, the STG showed a trend toward larger Auditory amplitudes (*p*=.06) while the neighboring Supramarginal also showed greater amplitude for Auditory trials (*p*<.05, fdr-uncorrected).

Unimodal versus Bimodal Effects

There is a significant relationship between Visual effects and Auditory effects for responsive, repetition, and iN400 electrodes. However, overall the amount of overlap is ~50% meaning that at least that many Visual effect electrodes are Unimodal. Here we compare Uni-modal and Bi-modal electrodes to assess whether there are distinguishing features between them, such as proportion, timing, or amplitude that could explain why some cortical patches are unique for one modality or the other versus being involved in both the processing of both modalities.

For responsive effects, in comparing the distribution of Uni-modal versus Bi-modal electrodes it was found that overall Uni-modal electrodes were a greater proportion than Bi-modal electrodes (*p*<.001). Follow-up analyses identified both the STG (*p*<.001) and Precentral (*p*=.008, fdr-uncorrected) had a significantly greater proportion of Unimodal-responsive electrodes than Bimodal-repsonsive electrodes. To assess if one modality's Unimodal-responsive electrodes were driving the effects, we split the Unimodal-responsive electrodes into Visual-unimodal and Auditory-unimodal. There was no difference overall between Visual-responsive Uni-modal electrodes and Bi-modal responsive electrodes (*p*>.15) but Auditory-responsive Uni-modal electrodes were a greater proportion than Bi-modal responsive electrodes (*p*<.001). This was significant in both of the individual regions as well, with Auditory-unimodal electrodes having a greater proportion than Bimodal electrodes in the STG (*p*<.001) and Precentral (*p*<.05, fdr-uncorrected). For timing, there was an overall significant effect of Uni-modal electrodes being faster than Bi-modal electrodes (*p*<.05) but no individual regions reached significance.

Next, we examined the amplitude of these Task-responsive electrodes to see if the overall neuronal activity would distinguish between the Unimodal and Bimodal electrodes. However, there were no significant amplitude differences between Bi-modal and Uni-modal electrodes in either the Visual (*p*>.20) or the Auditory (*p*>0.10) modalities. No individual region was significant either.

For Repetition effects, overall Unimodal-repetition effects were greater than Bimodal-repetition effects (*p*<.001). In targeted follow-up analyses this pattern was found for STG (*p*<.001), and Precentral Gyrus (*p*=.008, fdr-uncorrected). .Like Task-responsive effects, the difference in overall Unimodal-repetition electrodes and Bimodal-repetition electrodes appears to be driven by the prevalence of Auditory-unimodal effects. Visual-unimodal electrodes were not significantly different Bimodal-repetition electrodes (*p*>.15) but overall Auditory-unimodal effects were a greater proportion than Bimodal-repetition effects (*p*<.001). Follow-up analyses again identified both the STG (*p*<.001) and the Precentral Gyrus (*p*<.05, fdr-uncorrected) as displaying this effect. There were no onset differences between Unimodal-repetition effects and Bimodal-repetition effects (all *p*>.30).

For iN400 effects, overall Unimodal-repetition effects were greater than Bimodal-repetition effects (*p*<.001). In targeted follow-up analyses this pattern was found for STG (*p*<.001), Precentral Gyrus (*p*<.001), and Pars Triangularis (*p*<.05, fdr-uncorrected). For the third time, the difference in overall Unimodal-iN400 electrodes and Bimodal-iN400 electrodes appears to be driven by the prevalence of Auditory-iN400 Unimodal effects. Overall, Auditory-unimodal effects were a greater proportion than Bimodal-repetition effects (*p*<.001), which was significant in both the STG (*p*<.001) and the Precentral Gyrus (*p*<.05, fdr-uncorrected). There was no significant difference between Visual-Unimodal and Bimodal electrodes (*p*>.10). Overall, there was no difference in the onset of Bimodal-iN400 and Unimodal-iN400 effects.

Connectivity

For Visual-responsive electrode pairs, 2 regions showed almost identical levels of interregional connectivity: the Fusiform (33 significant pairs, ~15%), Lateral Occipital (33, ~16%). Lesser connected regions were the Pars Opercularis (17, 9%), Precentral (32, 7%), and MTG (20, 6%). For Auditory trial connectivity, the greatest proportion of connections was found in the Pars Opercularis (26, 14%) followed by the Supragmarginal (15, 10%) and STG (55, 9%). Comparing the connectivity of the two 'core' areas for the opposite modality, some Auditory connectivity was found in the Fusiform (11, 5%) but none in the Lateral Occipital (0, 0%). Additionally, very low amounts of Visual connectivity was found in the STG (13, 2%) and Supramarginal (2, 1%).

In a direct comparison of overlapping electrode pairs for Auditory pairs in the Visual connectivity network, this was not above chance (*p*=.22; 7 pairs, 9%). However, despite not being above chance, the spatial locations did show an intriguing pattern. directly overlapping electrode pairs were found in the Pars Opercularis (4), Precentral (2), Fusiform (3), and STG (3).

Utah Array

Of the 96 sharp contacts recorded from in 1 subject's STG, 80 were judged to have High-Gama signal. Taking the average HGP of these electrodes revealed that the overall recorded HGP was responsive to both Auditory trials above baseline and to Visual trials above baseline, though the time course was different. The Auditory significant increase began at ~60ms while the Visual significant increase began at ~400ms. Overall, the peak amplitude was roughly equal between the two modalities with the peak Visual-responsive value being ~1.27x greater than the peak Auditory-responsive value.

However, examination of the HGP distribution of effects and the distribution of amplitudes reveals that the average being similar between the two modalities does not indicate that the individual channels are similar. The overall distribution of effects revealed that there were 8 Visual Unimodal-responsive contacts, 20 Auditory Unimodal-responsive contacts, 26 Bimodal-responsive contacts, and 26 channels with no significant response. The heterogeneity of effects is mirrored by a heterogeneity of amplitudes. Most strikingly, the correlation of amplitudes is non-significant (r = -.029, *p*=.83). This is illustrated by the largest Auditory-responsive amplitude was 8.1x greater than the Visual-responsive amplitude in the same electrode. Similarly the largest Visual-responsive amplitude was 3.9x greater than the Auditory-responsive amplitude in the same electrode.

Discussion

The overlap and separation between visual and auditory language networks is a critical question in determining the division of labor between visual- and auditory-centric routes of processing. Here we present evidence from electrophysiology recorded directly from the cortical surface during semantic decisions performed in both the visual and auditory sensory modalities. A remarkably consistent pattern of activity evoked high-gamma power and in repetition effects found in both high-gamma power and broadband local field potentials. Initially unimodal areas converge near primary sensory cortex converge onto distributed bimodal processing areas. However, while the visual language network shows statistically significant overlap with the auditory language network, it is far less prevalent in perisylvian areas than the auditory language network and there are still many unimodal visual language electrodes. The complexity presented by this question were highlighted by a probe with 25x spatial precision, showing that even when high-gamma activity across a large cortical patch is roughly equal for the visual and auditory modalities, smaller patches within the larger patch revealed no correlation in evoked amplitude. Finally, when examining evidence of network connectivity across regions, a general separation of visual and auditory connectivity was found, suggesting a mostly independent and non-overlapping flow of information in the two language networks.

The Visual Language Network

Our two main assays into cortical function were overall evoked-responsiveness and repetition effects. Evoked responsiveness includes all stimulus-evoked activity and therefore includes both sensory-related as well as linguistic electrophysiological activity. The distribution of visual language evoked HGP was proportionally greatest and the fastest onset in the occipito-temporal route. These areas are strongly associated with the orthographic processing of visual text[11,45,70,71]. Specialized cortical patches proceed along the ventral surface of the brain in an anterior sweep from sensory to low-level visual to lexico-semantic processing[10,45].

In the perisylvian regions, dissociation between lateral temporal and frontal regions was found. The lateral temporal regions displayed a decreased proportion of responsiveness while the frontal regions displayed an average proportion of responsivity. The responses that were found in perisylvian regions did not display onset differences in general, except the Pars

Opercularis which was slower than other regions. The frontal regions involved in which we found responsitivity are generally divided into regions supporting phonological or semantic functions. The Pars Triangularis[72–76] is associated with semantic processing while the Pars Opercularis[74,75,77–79] and Precentral Gyrus[70,80–85] are typically associated with phonological processing.

Our second assay was repetition effects, which are evidence of emerging cortical representations of linguistic identities. Though the neural basis for repetition effects are not wholly agreed upon, theories emphasize a combination of feed-forward/feed-back interaction[62] and long-term sensitivity to representational traces[53,56,57]. Due to our use of full repetition, these representational traces will include both sub-lexical identities, such as phonemes and letters, as well as word-level lexico-semantic identities. These levels of expected repetition effects map well onto the two chief two cognitive operations that are assumed to take place in the dorsal reading route perisylvian regions during Visual Language. The first process is phonological re-coding, the process of representing phonological codes derived from print, and the second process is lexicosemantic processes, largely assumed to be in common with Auditory language lexico-semantic processes. Visual language repetition effects were found to be evenly distributed across regions with no onset timing differences. This is consistent with the conception of the N400 as indexing a series of simultaneous and distributed overlapping properties. The only weak effect that was found was an increase in HGP repetition effects in the Pars Triangularis, which was mentioned previously is theorized to be a loci of lexico-semantic processing.

Functional Overlap and Separation of Visual and Auditory Language Networks

Our primarily perisylvian electrode coverage, placed entirely for clinical regions, was well-placed to probe the overlap and separation of the dorsal reading network and the auditory Language network, which is focused on the perisylvian regions[86,87]. We found that auditory-evoked language activity was consistently more widespread than visual-evoked language activity. This increased responsivity and repetition effects to auditory language was driven primarily by effects in the STG and the MTG, and to a lesser extent the Precentral Gyrus. Part of this increased responsiveness to auditory words in these regions is likely due to many steps, such as decoding phonetics from the voice in the STG[88–90], that would be unnecessary for Visual Language processing. The increased proportion of auditory-evoked language activity relative to visual-evoked language activity, particularly in the lateral temporal regions of STG and MTG, are in regions that generally were proportionally less active during visual language processing.

However, despite the generally greater proportion of Auditory-responsive electrodes, the Visual-responsive electrodes that were found in perisylvian regions did significantly overlap with Auditory electrodes. Overall, the statistically significant overlap only accounted for 58% of Visual-responsive electrodes. This overlap of Task-responsive effects was statistically significant in the STG (100% of Visual-responsive effects overlap with Auditory-responsive effects), Supramarginal (100%), and Precentral Gyrus (77%). Interestingly, each of the Precentral Gyrus[70,80–85] and STG[91–93] have been associated with Phonological Re-coding, or the phonemic level of representation.

The overlap of Repetition effects largely mirrored the Task-responsive effects. There was an increased proportion of Auditory repetition effects relative to Visual repetition effects in both LFP and HGP, with the STG consistently showing greater Auditory repetition effects. However, there were no significant differences found in timing of the effects between the Visual and Auditory modalities. Again, there was a statistically significant overlap of Auditory and Visual Language for both LFP and HGP repetition effects, with the portion of overlapping Auditory electrodes in Visual-electrodes was slightly over half (HGP: 52%, LFP: 54%). For HGP, the overlap of repetition effects was significant in similar regions to the Task-responsive overlap with significant overlap in the Precentral Gyrus and Supramarginal. There was a general lack of Visual repetition effects in lateral temporal areas, so while the overlap was not statistically significant, but the effects that were present were overlapping in the STG and MTG. Repetition effects in LFP were much more widespread, with statistically significant overlap in Pars Opercularis, Supragmarginal, STG, Fusiform, MTG.

Overlapping and Separable Neural Populations

In the putative dorsal reading network we found a mix of Visual Unimodal, Auditory Unimodal, and Bimodal effects in pretty much every region. Strong proposals have been made regarding the cortex as functionally multi-sensory[94], but mixes of Unimodal and Bimodal effects in association cortex has been reported in animal studies[95]. In our study, in all cases the proportion of Unimodal electrodes was greater than Bimodal electrodes, and this was driven mainly by an increased number of Auditory Unimodal electrodes, as the number of Visual Unimodal and Bimodal electrodes were roughly equal.

However, it has been reported that even neurons which respond only to one modality may have their responses modified by information presented in a second modality[96,97]. If a future study could with cross-modal language stimuli presentation found that the putative unimodal responses from our study are indeed modified by information from the other modality, this would suggest that there is indeed a supramodal language network but one that is not typically recruited by visual language presentation. This lack of recruitment, and the resulting pattern of overlap/separation, seen in the fully trained English readers in this study may be driven by the relative orthographic depth in English[98]. Orthographically deep languages like English have a less consistent relationship between phoneme identity and letter identity. Therefore, a high amount of error-related feedback from the auditory processing system during learning may overall decrease visual language recruitment of, and perhaps overlap with, the auditory language system. This has been found in cross-language studies, both behaviorally[99,100] and in imaging studies where greater perisylvian activity is found in languages with more consistent phoneme-letter relationships than English[434].

The idea of a single group of neurons collectively representing a single concept has had a strong influence on thinking about neural processing and neural organization[101]. In models of reading, linguistic identities have taken both localist[8] or distributed[1] representations, but there is general agreement about the identities being represented. There are sensory features, sub-lexical identities (letters for visual, phonemes for auditory), and lexico-semantic identity. Recently, there have been advances in understanding the phonetic features represented in the STG[88–90] but in general, questions about neural representations in humans are hampered by questions regarding spatial specificity. Though the concept of cortical columns in association cortex are still controversial[102–104], studies in motor and sensory cortex have implied columnar width to be ~50-500um[105,106]. With clinical electrodes typically encompassing 10,000um this means that even if we, very dubiously, assume that only neural populations directly underneath the electrode are being measured this means smearing together activity from >400 columns. The real number of measured columns is likely much higher.

Here we attempted to make inferences about neural population based on high-gamma amplitude, based on the evidence that high-frequency activity is tied to neuronal population firing[68]. Greater amplitude in one modality or the other would indicate either that spatially more columns were involved or that the involved columns' activity was more driven by that modality. For example, it is possible the even overlapping effects we have identified may conceal different amounts of the underlying neural activity between modalities.

What we found overall was there was no overall difference amplitudes between visual and auditory stimuli. However, in individual regions several differences emerged. Occipito-temporal regions, the Lateral Occipital and Fusiform, Visual words evoked greater HGP amplitude whereas in the STG Auditory words evoked greater HGP. However, in cortex in regions away from these two unimodal areas near primary sensory cortex there were no overall differences in amplitude. This adds to the picture of each modality having a Modal-specific area near primary sensory with other associative cortex playing a more balanced role in each language network.

However, the possible inadequacy of this level of spatial specificity for characterizing neural population similarity is hinted at in the one patient in which we obtained measurements at a pitch of 400um (instead of the 10,000um typical of clinical electrodes). In this patient, the overall average amplitude of the elecctrode, somewhat analogous to the signal picked up by a typical clinical electrode, was roughly equal. However, when examining the individual probes no correlation was found between the amplitudes. Therefore, a definitive, spatially specific answer to questions about overlapping and separable neural representations of linguistic identity remain elusive, for now. A path forward is suggested by new experimental carbon-based electrodes[107,108] which allow for the measuring of high-gamma power and retain high-SNR and the ability to stimulate down to a width of 50um.

Network Connectivity

So far, we have discussed isolated patches of cortex and the overlap and separation of Visual and Auditory language processing in these patches. But the wide spatial distribution of responses necessarily indicates a distribution spatial network to match. That the sensory information flow for auditory and visual language differs indicates that the flow of information in the brain may be an area of difference between Visual and Auditory language. This flow of information differs not just in the separate location of the primary sensory cortices, but the temporal flow of information. Auditory information is sequentially presented in time with important information regarding phonemic identity present in temporally-neighboring form of coarticulation[109,110]. In contrast, visual letters that are foveated are seen simultaneously and a good deal of letters to the right and left in parafoveal view additionally receive processing[111–113]. Given these differences in the temporal and spatial presentation of information, it is not clear that even cortically overlapping visual and auditory language patches would share network relationships with regards to the neural flow of information.

In this study we used PLV to assess whether significant connectivity between responsive electrodes was found. As would be expected, the Visual language network connectivity mainly was centered on occipito-temporal cortical locations. Other significant nodes included the Pars Opercularis, Precentral, and MTG. The Auditory language network appeared to be focused mainly in the STG, Supramarginal, and Pars Opercularis. However, the number of overlapping electrode pairs with significant connectivity in both modalities was not statistically discernable from chance. The areas that did show overlapping electrode-pair connectivity were the Pars Opercularis, Precentral, Fusiform, and STG. Three of those are putative phonologically related regions, which makes some sense to find overlapping connectivity. The fusiform is typically associated with the ventral reading route, but overlapping semantic activity for Auditory and Visual language has been reported in this region[44]. The relative dissociation of network activity between Auditory and Visual language processing does call into question that assumption that after phonological re-coding, the auditory processing of visual text follows a similar network to the processing of Auditory Language.

Conclusion

Early, lesion-based models of reading[114], models of reading development[1], and strong phonological theories[5,6] all emphasize the overlapping of visual language processing with an initially auditory language network. In assessing why certain patches along the ventral visual route develop specialization for visual language processing, a key determinant appears to be connectivity with perisylvian areas[115]. However, here we present mixed evidence of both a significant overlap and of a significant separation between the two language networks. A key question is whether the largely settled visual language network and its relationship to auditory language of partial overlap and partial separation we report here is a valid description of the relationships between the two language systems during learning to read. Perhaps an initially heavily overlapping visual language network settles into this less overlapping pattern as an end-state as auditory information exerts less influence on visual lexico-semantic processing.

Additionally, the spatial specificity needed to answer questions regarding the exact overlapping and separable neural populations is still under development. These considerations and constraints leave many questions to be addressed regarding the exact distribution of visual language cortical representations in perisylvian regions and precisely how they relate to the pre-existing perisylvian auditory network.

Chapter 3, in part, is currently being prepared for submission for publication of the material. The dissertation/thesis author was the primary investigator and author of this material. Eric Halgren is senior author. Additional co-author's include Ksenija Marinkovic, Lucia Melloni, Orrin Devinsky, Sydney Cash, Werner Doyle, Daniel Friedman, Patricia Dugan, and Thomas Thesen.

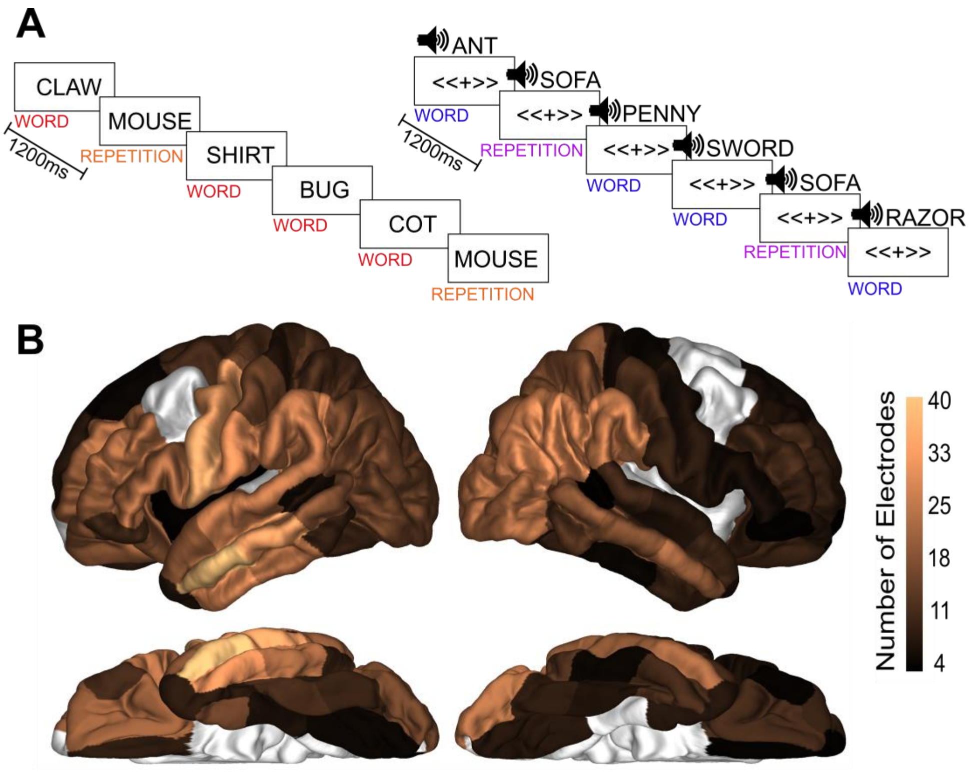

Figure 3.1: Task Design and Electrode Coverage. A) The sequence of presented words in both the Visual (left) and Auditory (right) version of the semantic decision task. Patients were asked to make a size judgements about the presented word (either smaller than 1 foot or larger than 1 foot). Word lists were unique in each sensory modality. Half of the words were unique (WORD) and half the stimuli were words that were repeated throughout the task. B) Electrode coverage highlighting coverage of perisylvian electrodes, especially on the left side.

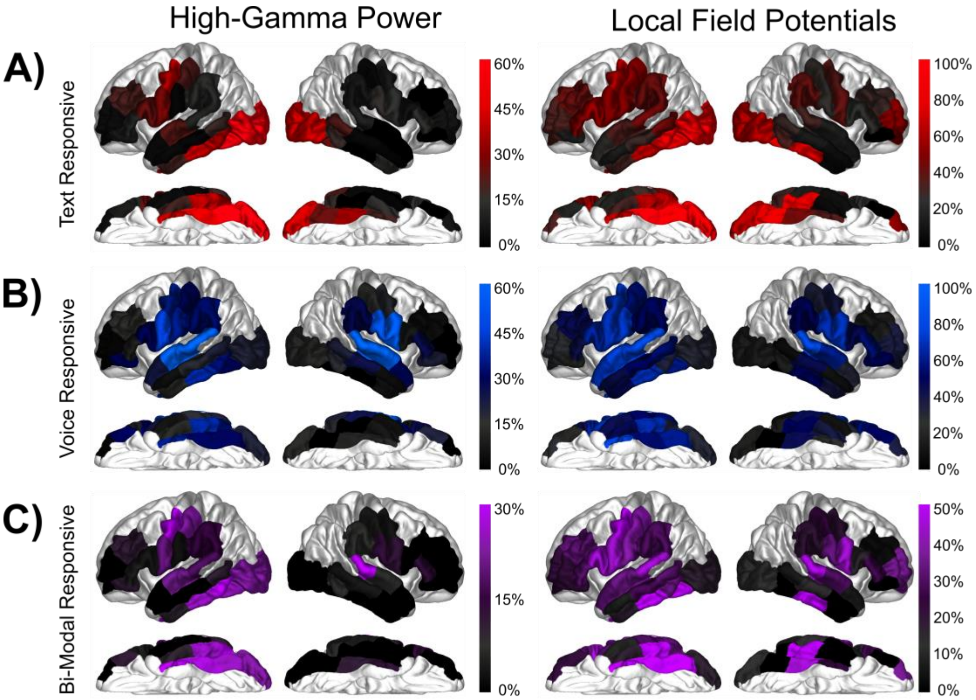

Figure 3.2: Proportion of electrodes with task-evoked increases in HGP and LFP during the visual task, auditory tasks, and during both. A) Proportion of electrodes in each parcellation demonstrating a significant increase from baseline in HGP (left) and LFP (right) from 0-600ms to visually presented text. B) Proportion of electrodes in each parcellation demonstrating a significant increase from baseline in HGP (left) and LFP (right) from 0-600ms to auditorily presented words. C) Proportion of electrodes in each parcellation demonstrating a significant increase from baseline in HGP (left) and LFP (right) from 0-600ms to both visually-presented text and auditorily-presented words.

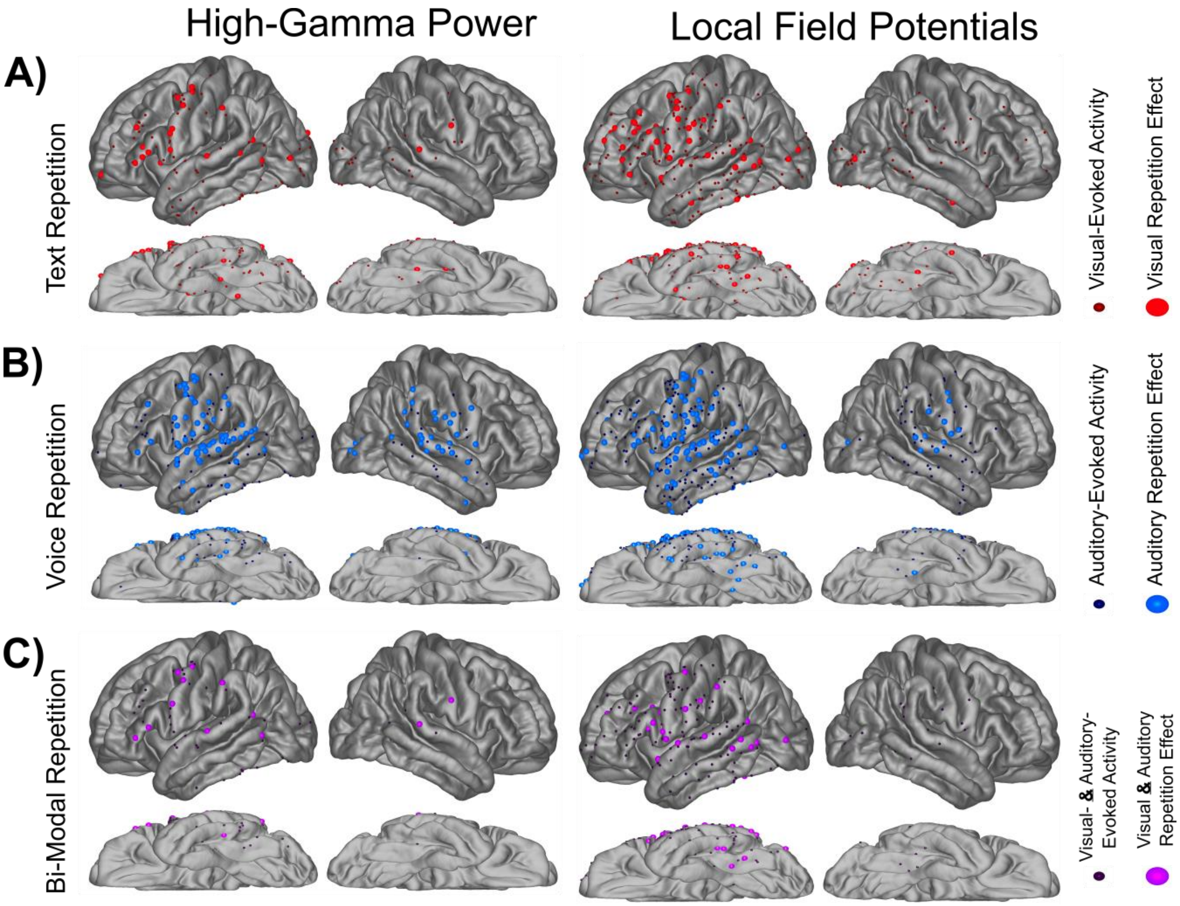

Figure 3.3: Location of electrodes with repetition effects in HGP and LFP to Text, to Voice, and to both. A) Display of electrode location (approximate, morphed to an average brain for display purposes) which demonstrate both a significant increase from baseline and a repetition effect in HGP (left) and LFP (right) from 0-600ms to visually presented text. Large bright-red electrodes show a repetition effect while small dark red electrodes showed only an increase from zero. B) Display of electrode location (approximate, morphed to an average brain for display purposes) which demonstrate both a significant increase from baseline and a repetition effect in HGP (left) and LFP (right) from 0-600ms to auditorily presented words. Large bright-blue electrodes show a repetition effect while small dark blue electrodes showed only an increase from zero. C) Display of electrode location (approximate, morphed to an average brain for display purposes) which demonstrate both a significant increase from baseline and a repetition effect in HGP (left) and LFP (right) from 0-600ms to both visually presented text and auditorily presented words. Large bright-purples electrodes show a repetition effect while small dark purple electrodes showed only an increase from zero.

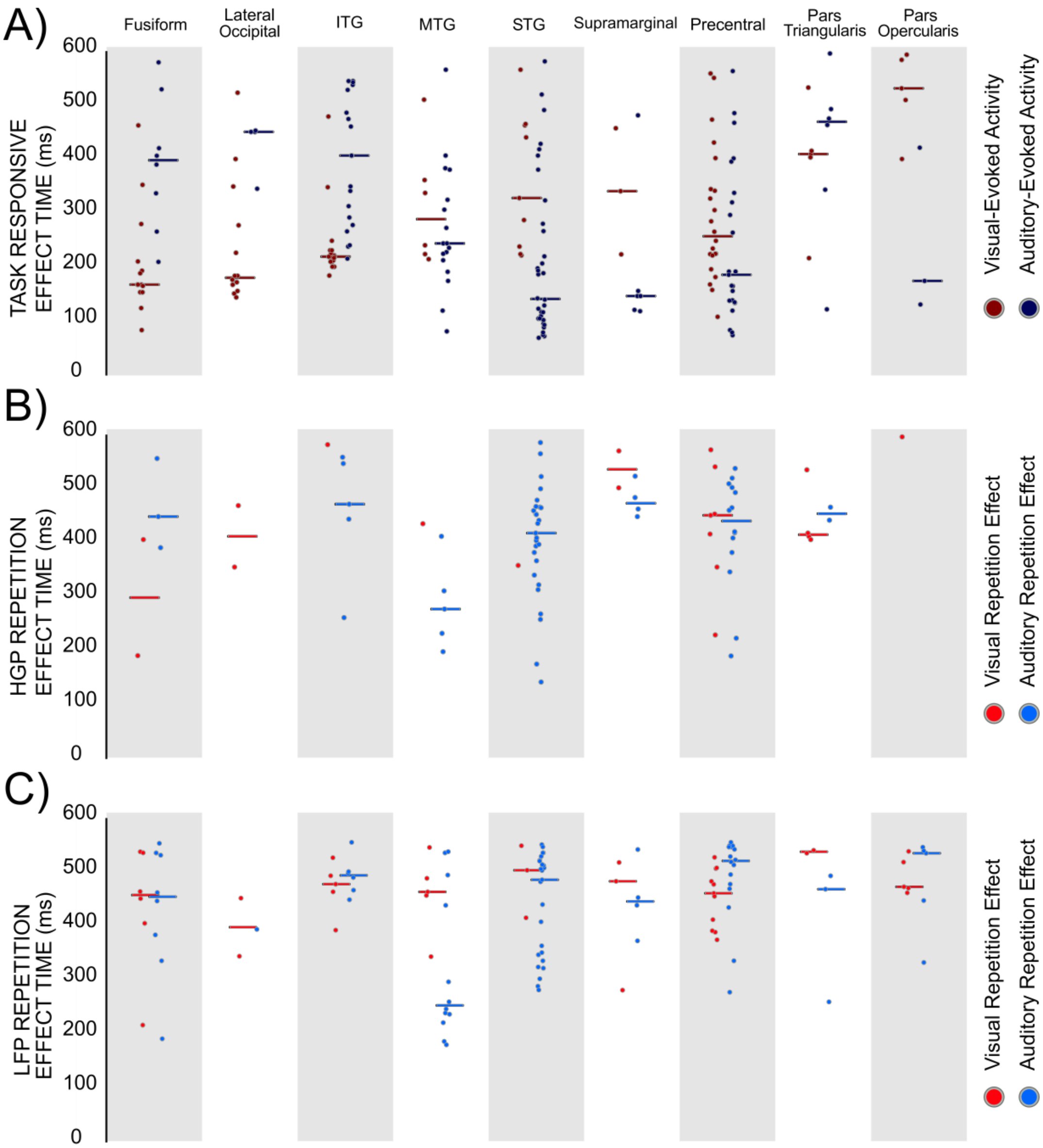

Figure 3.4: Timing of Task-Evoked changes in baseline, Repetition effects, and Lexical Frequency effects across region for text and voice presentation. A) Circles are the onset of effects for HGP significant increases from 0. Dark red circles are visual-evoked and dark blue circles are auditory-evoke. The lines are the median for each effect onset. B) Circles are the onset of effects for HGP significant differences between Novel and Repeated words. Bright red circles are visual-repetition effects and bright blue circles are auditory-repetition effects. The lines are the median for each effect onset. C) Circles are the onset of effects for LFP significant differences between Novel and Repeated words. Bright red circles are visual-repetition effects and bright blue circles are auditory-repetition effects. The lines are the median for each effect onset.

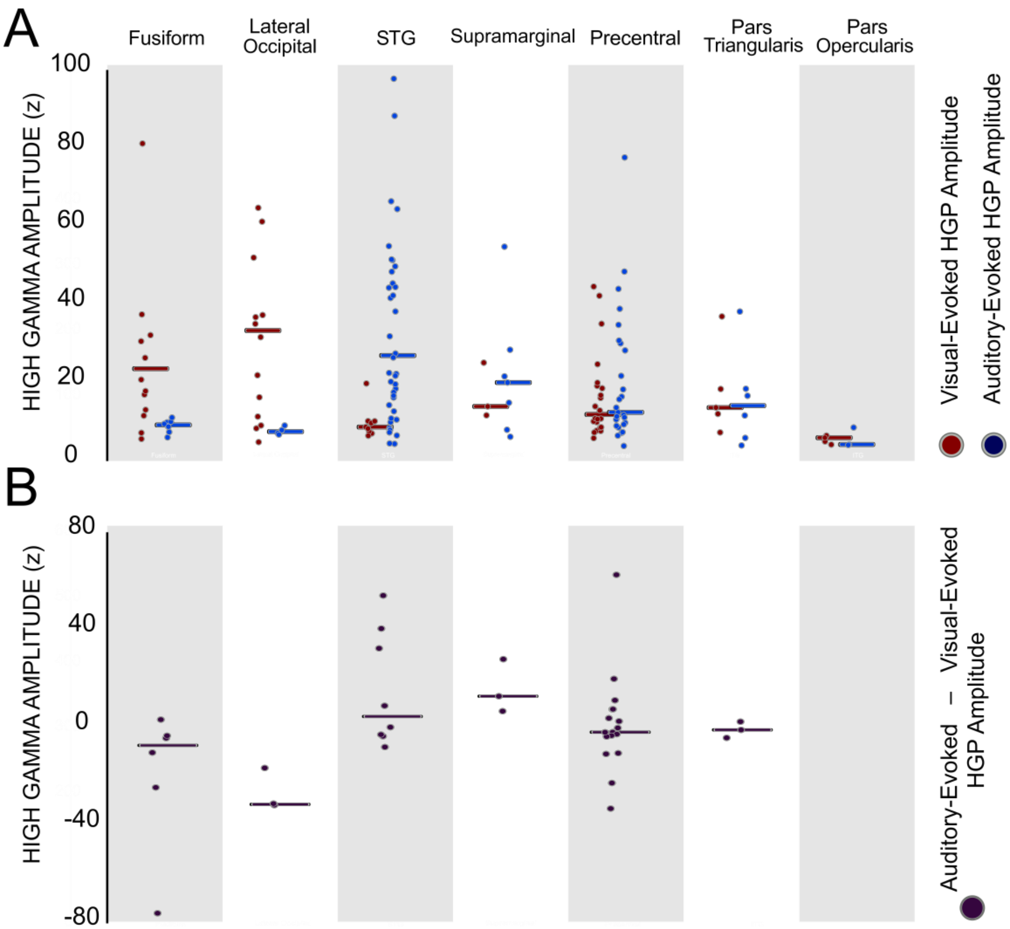

Figure 3.5: Amplitude of evoked HGP across regions for text and voice presented words. A) High-gamma amplitude evoked by Visual words (red) and Auditory words (blue) is displayed. Amplitude is the peak z-score found on an electrode between 0-to-600ms. Z-score was calculated with the variance from a baseline period (-300-to-0ms). B) High-gamma amplitude evoked by Visual words (red) is subtracted from High-gamma amplitude evoked by Auditory words across Bimodal-responsive electrodes is displayed. Amplitude is the peak z-score found on an electrode between 0-to-600ms. Z-score was calculated with the variance from a baseline period (-300-to-0ms).

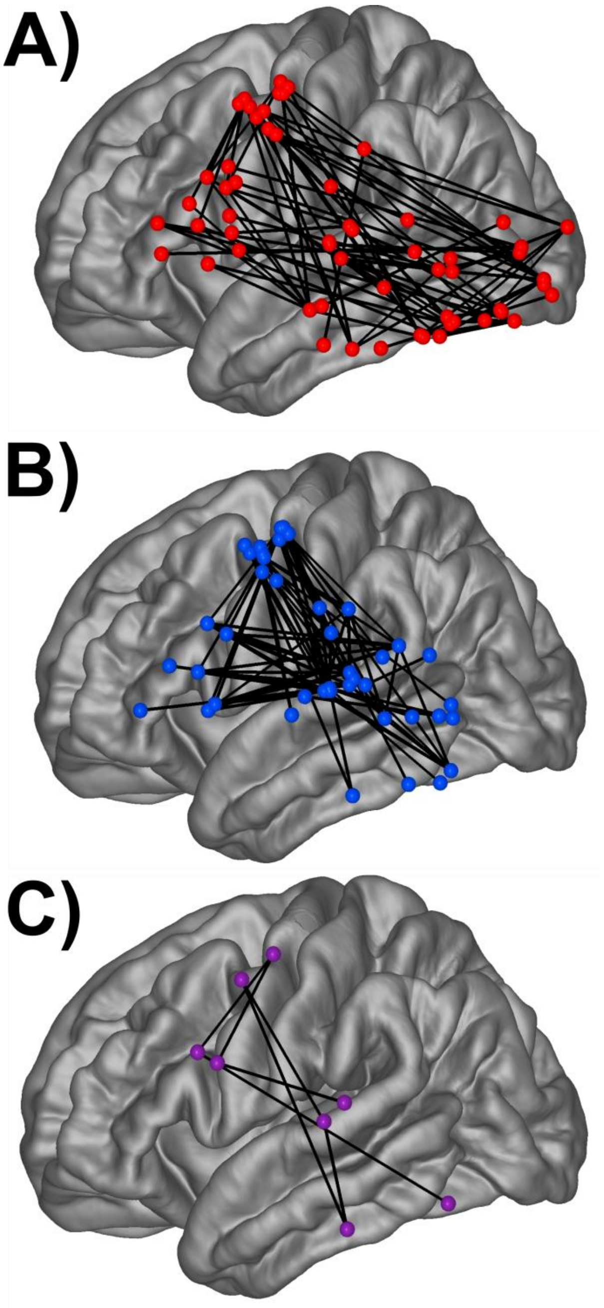

Figure 3.6: Phase locking between the precentral gyrus, STG, and Fusiform during text- and voice-presentation of words. A) Electrode pairs displayed had a significant phase-locking value (PLV) averaged from 6-12Hz during presentation of Visual words for at least 50ms during 0-to-600ms. Only electrodes which were Task-responsive were included. B) Electrode pairs are displayed had a significant PLV averaged from 6-12Hz with at least one electrode during presentation of Auditory words for at least 50ms during 0-to-600ms. Only electrodes which were Task-responsive were included. C) Electrode pairs are displayed had a significant PLV averaged from 6-12Hz with at least one electrode during both presentation of Auditory words and presentation of Visual words for at least 50ms during 0-to-600ms. Only electrodes which were Task-responsive were included.

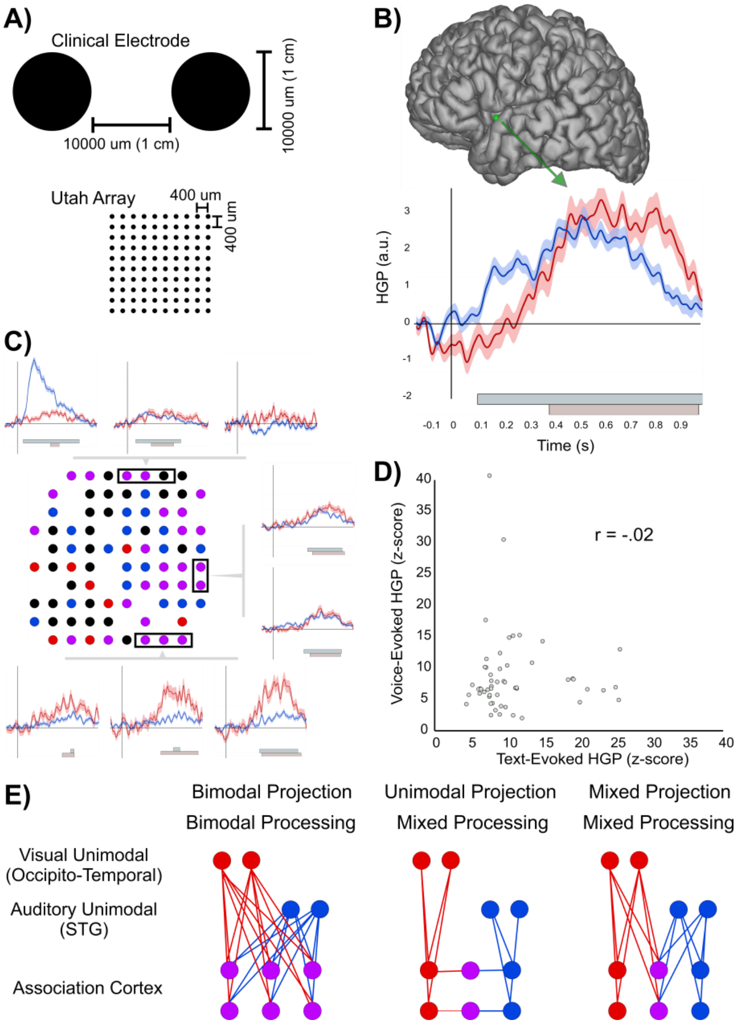

Figure 3.7: Fine-grained spatial resolution of overlapping text- and voice-evoked High-Gamma Power as measured by Utah Array. A) Illustration of the difference in pitch between a typical clinical electrode and the Utah Array. A typical clinical electrode is 10,000um in pitch while the Utah array is 400um, or 25x spatial resolution. B) In one patient's anterior STG we recorded during a patient's performance of our Visual and Auditory semantic decision task. Averaging HGP across the electrode, both significant Auditory-evoked (blue bar) and Visual-evoked (red bar) HGP was found of roughly similar amplitude, though differing time course. C) We looked at each electrode that had a HGP signal (blank spots in grid did not have high-gamma signal). We found a mix of Bimodal-responsive (purple dots), Visual-responsive (red dots), Auditory-responsive (blue dots), and non-responsive (black dots). Black boxes in the top, middle, and bottom point to example waveforms illustrating a variety of response amplitudes across the electrode. D) A scatterplot of amplitudes across task-responsive electrodes in the Utah array. The correlation between amplitudes is non-significant. E) Three potential models of association cortex distribution and their projections from Visual Unimodal and Auditory Unimodal areas. The classical model is that a-modal (or supramodal) association cortex receives overlapping input from Unimodal areas and performs supramodal processing. Our data of mixed Unimodal and Bimodal responses suggests this view is inadequate. However, we do not have definitive data to resolve two alternative models. The first is when Unimodal responses in Association cortex reflect Unimodal input, followed by Bimodal processing. The second possibility in the mixed processing reflects overlapping projections, leaving some patches receiving unimodal input while other receive Bimodal input.

Table 3.1: Distribution of Visual- and Auditory-evoked electrodes, and how many patients were contributed Language-Selective electrodes, in each region.

		Left Hemisphere					
	Region	Visual-Responsive (0-600ms)	Subjects	Auditory-Responsive (0-600ms)	Subjects	Bimodal-Responsive (0-600ms)	Subjects
Occipito-Temporal	Lateral Occipital	70% (14 / 20)	6 / 8	20% (4 / 20)	2 / 8	20% (4 / 20)	2 / 8
	Caudal Fusiform	78% (7 / 9)	4 / 5	11% (1 / 9)	1 / 5	11% (1 / 9)	1 / 5
	Middle Fusiform	44% (4 / 9)	4 / 5	22% (2 / 9)	2 / 5	22% (2 / 9)	2 / 5
	Middle ITG	36% (8 / 22)	3 / 6	50% (11 / 22)	3 / 6	27% (6 / 22)	3 / 6
	Rostral ITG	21% (7 / 33)	1 / 7	15% (5 / 33)	2 / 7	6% (2 / 33)	1 / 7
	Parahippocampal	75% (3 / 4)	2 / 3	0% (0 / 4)	0 / 3	0% (0 / 4)	0 / 3
	Entorhinal	24% (4 / 17)	4 / 7	6% (1 / 17)	1 / 7	0% (0 / 17)	0 / 7
Perisylvian	Supramarginal	11% (3 / 28)	3 / 8	25% (7 / 28)	4 / 8	11% (3 / 28)	3 / 8
	Caudal MTG	15% (3 / 20)	2 / 8	45% (9 / 20)	4 / 8	15% (3 / 20)	2 / 8
	Middle MTG	3% (1 / 35)	1 / 10	17% (6 / 35)	3 / 10	0% (0 / 35)	0 / 10
	Rostral MTG	5% (2 / 44)	1 / 9	7% (3 / 44)	2 / 9	0% (0 / 44)	0 / 9
	Caudal STG	11% (3 / 28)	2 / 9	71% (20 / 28)	7 / 9	11% (3 / 28)	2 / 9
	Middle STG	17% (5 / 29)	3 / 7	72% (21 / 29)	6 / 7	17% (5 / 29)	3 / 7
	Rostral STG	5% (1 / 19)	1 / 5	16% (3 / 19)	3 / 5	0% (0 / 19)	0 / 5
Rolandic	Inferior Precentral	22% (8 / 37)	6 / 10	41% (15 / 37)	8 / 10	19% (7 / 37)	6 / 10
	Middle Precentral	37% (14 / 38)	7 / 8	32% (12 / 38)	8 / 8	26% (10 / 38)	7 / 8
	Inferior Postcentral	0% (0 / 34)	0 / 9	35% (12 / 34)	6 / 9	0% (0 / 34)	0 / 9
	Middle Postcentral	16% (3 / 19)	2 / 8	26% (5 / 19)	4 / 8	5% (1 / 19)	1 / 8
Frontal	Pars Opercularis	19% (5 / 27)	2 / 8	11% (3 / 27)	3 / 8	0% (0 / 27)	0 / 8
	Pars Triangularis	20% (5 / 25)	3 / 7	24% (6 / 25)	3 / 7	12% (3 / 25)	2 / 7

Table 3.2: Number of electrodes displaying each effect divided in region.

		Left Hemisphere					
	Region	Text Repetition (HGP)	Text Repetition (LFP)	Voice Repetition (HGP)	Voice Repetition (LFP)	Bimodal Repetition (HGP)	Bimodal Repetition (LFP)
Occipito-Temporal	Lateral Occipital	2	2	0	1	0	1
	Caudal Fusiform	0	0	0	1	0	0
	Middle Fusiform	1	2	0	3	0	2
	Middle ITG	1	3	3	4	1	2
	Rostral ITG	0	0	2	2	0	0
	Parahippocampal	1	0	0	0	0	0
	Entorhinal	1	2	1	2	0	1
Perisylvian	Supramarginal	2	3	4	4	2	3
	Caudal MTG	1	4	3	5	1	4
	Middle MTG	0	0	3	5	0	0
	Rostral MTG	0	1	1	2	0	0
	Caudal STG	1	1	17	11	1	1
	Middle STG	0	1	15	11	0	1
	Rostral STG	0	1	1	5	0	1
Rolandic	Inferior Precentral	3	6	6	10	1	3
	Middle Precentral	4	5	9	7	3	1
	Inferior Postcentral	0	3	7	10	0	1
	Middle Postcentral	0	0	1	4	0	0
Frontal	Pars Opercularis	1	5	0	5	0	4
	Pars Triangularis	4	2	2	3	2	0

Table 3.3: Timing of effect onset divided in each cortical region.

	Left Hemisphere					
Region	**Text-Responsive HGP (ms)**	**Text -Repetition HGP (ms)**	**Text -Repetition LFP (ms)**	**Voice-Responsive HGP (ms)**	**Voice-Repetition HGP (ms)**	**Voice-Repetition LFP (ms)**
Fusiform	160 (80 - 400)	250 (160 - 340)	410 (200 - 480)	350 (200 - 500)	380 (320 - 460)	410 (180 - 500)
Lateral Occipital	150 (120 - 440)	350 (300 - 400)	350 (300 - 400)	380 (280 - 380)	-	360 (360)
ITG	180 (160 - 400)	480 (480)	440 (360 - 480)	340 (180 - 460)	400 (220 - 460)	440 (400 - 500)
MTG	240 (180 - 420)	360 (360)	420 (300 - 500)	200 (60 - 480)	200 (60 - 340)	230 (160 - 480)
STG	280 (180 - 480)	300 (300)	460 (380 - 500)	100 (60 - 480)	340 (80 - 480)	440 (100 - 500)
Supramarginal	280 (180 - 380)	450 (420 - 480)	440 (260 - 460)	120 (100 - 400)	390 (380 - 440)	400 (340 - 480)
Precentral	220 (100 - 460)	380 (200 - 480)	420 (340 - 480)	150 (60 - 480)	340 (60 - 440)	460 (100 - 500)
Pars Triangularis	340 (180 - 440)	340 (340 - 440)	480 (480 - 480)	390 (100 - 500)	370 (360 - 380)	420 (240 - 440)
Pars Opercularis	440 (340 - 500)	500 (500)	420 (420 - 480)	140 (120 - 360)	-	480 (300 - 500)

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PART 2: Future Directions in Intracranial Electrophysiology

CHAPTER 4: Development and Translation of PEDOT:PSS Microelectrodes for Intraoperative Monitoring

Abstract*:*

Recording neural activity during neurosurgical interventions is an invaluable tool for both improving patient outcomes and advancing our understanding of neural mechanisms and organization. However, increasing clinical electrodes' signal-to-noise and spatial specificty requires overcoming substantial physical barriers due to the compromised metal electrochemical interface properties. The electrochemical properties of PEDOT:PSS based interfaces surpass those of current clinical electrocorticography electrodes. Here, we demonstrate robust PEDOT:PSS microelectrode arrays for safe intraoperative monitoring of human brain. PEDOT:PSS macro and micro-electrodes measured similar differential neural modulation under various clinical conditions, even with 4 orders of magnitude smaller electrode area. Furthermore, the PEDOT:PSS electrodes exhibited more differential power than clinical electrodes for mid-band frequencies (15 – 50 Hz) indicating better sensitivity. We report the first evoked (stimulus-locked) cognitive activity with changes in amplitude across pial surface distances as small as 400 μm, potentially enabling basic neurophysiology studies at the scale of neural micro-circuitry.

Introduction

Electrocorticography (ECoG) is preferred in clinical and experimental mapping of brain activity due to its higher spatial resolution and sensitivity compared to electroencepholography (EEG) and magnetoencephalography (MEG), yet retains their greater temporal resolution compared to functional magnetic resonance imaging (fMRI)[1]. In the clinical context, ECoG is used for precise localization of eloquent cortex in neurosurgical cases for tumors, epileptogenic foci, and vascular abnormalities. This functional localization can be confirmed using ECoG electrodes by electrical stimulation producing a temporary, functional lesion. In the experimental context, most clinical ECoG can resolve activity to less than a millimeter with a high degree of certainty, relative to fMRI, MEG, and EEG [2], which rely upon modeling and reconstruction techniques to estimate signal source locations. Furthermore, ECoG can measure not only field potentials (which like MEG and EEG are mainly due to currents in the apical dendrites of pyramidal cells), but also measure high-frequency power, which reflects neuronal population firing[3].Consequently, the use of ECoG in clinical environments is critical for improving neurosurgical patient outcomes – estimated to be 111,000 patient cases per year in the US only –,[4] for localizing a wide variety of cortical task-related activity, and for implementing brain-machine interfaces (BCI)[1,5-10].

However, current clinical ECoG electrodes face physical limits to the number of electrode sites, spatial resolution (centimeter scale), and electrode diameter (millimeter scale), and thus cannot resolveneural activity that changes multiple times over the course of a millimeter[11]. This limitation has important implications for surgical tissue resection, as current surgical methodology requires high precision in identifying the boundaries between diseased and eloquent cortex. In addition to these design limitations, current clinical electrode arrays are constrained to non-conformal electrode-carriers/substrates and to less-optimal metal (e.g. PtIr) electrochemical interfaces[12].To fully exploit the advantages of ECoG in both clinical and experimental mapping of detailed neural activity, significant advances at the electrochemical, mechanical and biocompatibility fronts of electrode/tissue interfaces must be made [13-15]. The needed advances includes (1) the development of a high-quality electrochemical interface with low impedance (high signal to noise ratio (SNR) recording), (2) high charge injection capacity (safe/efficient stimulation) [16-18], (3) compliant mechanical properties for mimicking the curvilinear brain surface and to compensate for brain micromotion in order to reduce tissue damage [19-21], and (4) enhanced biocompatible electrode/tissue interfaces to minimize biofouling [13,22,23].

Here we focus on the development of high-SNR neural recordings to increase the spatial specificity at which neural activity can be measured. Several novel materials and strategies have been employed, focusing on increasing SNR by lowering electrode impedance. Nanostructured materials such as nanowires, carbon nanotubes and graphene [24-26] as well as surface-modified metallic electrodes (Pt, Au, and Ir) with porous surfaces and higher geometrical surface area are among those explored [17,27-29]. Several difficulties hold back these efforts. For nanostructured materials, current fabrication processes are relatively complicated and are less scalable than planar microelectrodes and therefore face challenges for translation to clinical practice. For metallic electrodes, their relatively high electrochemical impedances and site-to-site variability can result in significant electrophysiological recording losses.

Conductive polymers (CPs) on the other hand offer excellent possibilities for advancing electrode/tissue interfaces. CPs have significantly lower microelectrode impedance than inorganic microelectrodes due to their combined ionic-electronic conductivity[30]. In addition, by minimizing the mechanical mismatch at electrode/tissue interface, they permit long-lasting functional neural interface [31-33] with diminished biofouling [34,35]. When built on thin flexible films of polyimide or parylene, they conform to the curvilinear brain tissue[36] and their transparency permits their accurate placement on the cortical surface in desired regions. In particular, poly(3,4-ethylenedioxythiophene):poly(styrenesulfonate)(PEDOT:PSS) is considered as a forefront alternative due to its low electrochemical impedance over a wide range of frequencies of cortical activity that is of interest [30,37], its excellent chemical stability [38], and its biocompatibility [39,40]. However, to date, there is only one group who has demostrated PEDOT:PSS utilization in intraoperative monitoring. Their pioneering work reported single units from a human brain and began to explore the spatial specificity capabilities of PEDOT:PSS devices[41,42]. Here we expand on these efforts by thoroughly benchmarking PEDOT:PSS electrodes against clinical electrodes and by demonstrating background, functional, and pathological recordings, the complete suite of mapping that is necessary for clinical translation of PEDOT:PSS into intraoperative monitoring.

The objective of our work is to advance PEDOT:PSS microelectrode arrays for high fidelity electrophysiological recordings in human subjects. To accomplish this, we first studied the structural and surface integrity of the devices for suitability in safe intraoperative monitoring from human subjects. Here, we refined earlier fabrication procedures[43,44] for which we optimized the autoclave sterilization for clinical use,[45] and obtained high yield with a narrow distribution of microelectrode electrochemical characteristics. We benchmark PEDOT:PSS electrodes characteristics against clinical PtIr and pure Pt electrodes, correlate clinical recordings from PEDOT:PSS and clinical electrodes to their electrochemical properties, and present the first recording of stimulus-locked neural activity from human subjects using PEDOT:PSS microarrays. By employing high yield PEDOT:PSS microelectrode arrays, not only was high SNR obtained, but evidence of spatially modulated activity across the scale of cortical microcolumns was measured. These changes, measured in high-gamma amplitude across 400μm pitch electrodes, demonstrate the spatial specifity afforded by the low impedance, small electrode diameter, and fine electrode pitch of the fabricated PEDOT:PSS devices.

Methods:

Device fabrication

4-inch glass wafers (Specialty Glass Products) were used as a substrate carrier for the thin parylene C layers. The glass wafers were first solvent cleaned by rinsing with acetone/isopropanol (IPA)/deionized (DI) water/IPA, then were subjected to ultrasonic agitation in IPA for 5 min, and were then rinsed again with acetone/IPA/DI water/IPA. Diluted Micro-90 (0.1 %) as an anti-adhesion layer was spun-cast at 1500 rpm on the glass wafer to facilitate the separation of the device after the device fabrication is completed. A first parylene C layer (~3 μm) was deposited by chemical vapor deposition using a PDS 2010 Parylene coater system. Metal lead patterns were defined and exposed using a Karl Suss MA6 mask aligner using NR9-3000 negative resist. Temescal BJD 1800 electron beam evaporator was used for the deposition of 10 nm Ti adhesion layer and 100 nm Au contact layer, and lift-off process in acetone followed. O_2 plasma (Oxford Plasmalab 80 RIE) was then applied for 2 min (150 W RF power) to activate the surface of parylene C for enhancing the adhesion of the subsequent encapsulating parylene C layer. A ~3μm parylene C layer was then deposited and followed by coating another Micro 90 anti-adhesion layer.This time, a slightly higher concentrated Micro-90 (1 % as opposed to 0.1 % for the first layer) was spun-cast at 650 rpm for 10 seconds on this 2nd parylene C layer for ease of separation of the subsequent layers. A 3rd parylene-C layer was then deposited, followed by the spin-coating and patterning the thick 2010 SU-8 photoresist layer which developed with a SU-8 developer. O_2 plasma was used to etch the openings in the 3rd and then 2nd parylene C layers prior to the deposition of PEDOT:PSS. After the O_2 plasma etching step the exposed Au surface was cleaned using moderate soniction while the device was immersed in DI water. 20 mL aqueous dispersion of PEDOT:PSS (PH 1000 from Clevios) was mixed with ethylene glycol (5 mL), dodecylbenzene sulfonic acid (DBSA, 50 μL) and 1 wt% of (3-Glycidyloxypropyl)trimethoxysilane (GOPS) and the solution was spun-cast at 650 rpm for 30 seconds and pre-baked at 95 °C for 1 min. The third parylene C layer was then mechanically peeled off in all regions except where PEDOT: PSS made contact with the Au surface on the microarray and macrodot regions. Finally, the devices were cured at 140 °C for 1 hour and immersed in DI water to remove any Micro-90 residue from the PEDOT:PSS and parylene C surface. Fabrication of the platinum microarrays followed similar procedure to that of PEDOT:PSS devices except for the PEDOT:PSS deposition which was not carried out. For the Pt devices, a 10 nm Ti adhesion layer and 100 nm Pt contact layer were deposited by sputtering (Denton Discovery 18 Sputter System).

Device characterization:

The devices were imaged using an FEI SFEG ultra high resolution (UHR) scanning electron microscope (SEM) at 10 kV accelerating voltage and a magnification of with 4702X. To reduce electron charging in the specimen, a 15 nm thick Ti layer was deposited on the back of the device and that electrically connected to the stage of the system providing a runaway path for impinging electrons. A Veeco Scanning Probe Microscope was used to take atomic force microscopy (AFM) images in non-contact tapping mode. Electrochemical impedance spectroscopy (EIS) was performed using a GAMRY interface 1000E in phosphate buffer saline (PBS) solution, using three electrodes configuration, i.e., Ag/AgCl electrode as a reference, a large platinum electrode as a counter elelectrode, and PEDOT:PSS/Pt microarray/macrodot as the working electrode. Sinusoidal signals with 10 mV rms AC voltage and zero DC voltage were applied and the frequency was swept from 1 Hz to 10 kHz.

Electrophysiology Methods

Acquistion:

Patients S1-S3 undergoing clinical mapping of eloquent cortex provided informed consent to have the microarray placed on their pial surface and to participate in a 10 minute task. The PEDOT microarray was placed on the superior temporal gyrus (STG): anterior STG for Subject 2 (S2) and posterior STG for Subject 1 & 3 (S1, S3). UC San Diego Health Institutional Review Board (IRB) reviewed and approved study protocol.

Patient S4 provided informed consent to have microarray placed on their pial while unconscious. The electrode was implanted on the lateral surface of the temporal lobe across the superior and middle temporal gyrus. The Partners Human Research Committee reviewed and approved the IRB protocol at Brigham and Women’s Hospital.

S2 read visual words, repeated auditory words, and named visual pictures. S3 saw a 3-letter string (GUH, SEE) and then heard an auditory 2-phoneme combination, making a decision whether the visual and auditory stimuli matched. Interspersed were visual control trials in which a false font was followed by a real auditory stimulus and auditory control trials in which a real letter string was followed by a 6-band noise-vocoded 2-phoneme combination.

We used our clinic compatible, open source electrophysiology (ephys) system based on Intan technology (Los Angeles, CA) to record acutely during neurosurgery. The details of the system have been published [56]and the design files and software are freely available on *https://github.com/TNEL-UCSD/nacq* and is briefly discussed below.

The system is capable of recording 256 channels at 20 kHz and features 5 kV RMS power isolation. The purpose of an isolator is to protect the patient from hardware malfunctions and/or power surges. The system consists of an adapter, amplifier & digitizer (Intan RHD2164), power isolator and USB buffering board (RHD2000). The adapter has switches, which can connect a subset of electrodes to reference (REF) or ground (GND). Typically, 2 macrodots are connected to REF while GND is connected to an external needle probe (The Electrode Store, Buckley, WA) that is inserted in the scalp near the craniotomy.The signals are then amplified and digitized by the RHD2164, passed through the power isolator, then buffered and sent via USB to a laptop.

Since ephys components are within several feet of the surgical site, these components were sterilized via standard methods at each of the participating hospitals. The adapter and RHD2164 were sterilized using an electronics friendly process called Sterrad. Sterrad is a low temperature sterilization method that uses hydrogen peroxide plasma to eliminate microbes. We found that there were no obvious effects to the hardware the first three to five sterilization runs.

The clinical recording system is an Xltek 128 channels (Natus Neurology, Pleasanton, CA). For patients S1-S3, the sampling frequency is 500 Hz (70 Hz cutoff) and for S4, it is 250 Hz (83.33 Hz cutoff). Clinical signals are referenced using a bi-polar configuration, which enhances signal differences between recording channels. On the other hand, research electrodes were measured with a uni-polar configuration which results in measuring signals with less differences.

Analysis & Statistical Methods:

The following software and toolboxes were used: MATLAB, EEGLAB and the Fieldtrip, Chronux toolboxes.

In **Figure 3**, power spectral densities were estimated using Welch's method (pwelch) using a Kaiser Window of length 0.75 seconds with $\beta = 4$. An entire time period of 10 seconds was used with 50% between windows. Confidence intervals (c.i.) were computed by pwelch and the expression for c.i. is equation 5.3.64 from Statistical and Adaptive Signal Processing : Spectral Estimation, Signal Modeling, Adaptive Filtering and Array Processing .[57] The time-frequency plot was generated using short-time Fourier transform method with Slepian tapers (mtspecgramc from the Chronux toolbox). The moving window is of length 400 msec and step 40 msec. A time-bandwidth product of 5 and 5 tapers were used. The power was converted to units of dB then z-scored across to highlight temporal dynamics.

Figure 4 uses the same method to compute PSDs as Figure 3. The only difference is that a time period of 20 seconds was used.

For the analysis in **Figure 5**, the data was low-pass filtered at 400Hz and then downsampled to 1000 Hz.[58] To remove noise, the average signal of the microdot electrodes was subtracted from each channel (average re-reference) and each channel was then bandstopped around line noise and its harmonics. Next, the data was epoched to the onset of stimulus presentation (visual word/picture/auditory word onset for S2, visual word onset for S3) and for each trial the baseline from -300ms-to-0ms was subtracted. Trials judged to have artifactually high amplitude or variances were removed from the dataset. To investigate differences between stimulus classes in the high-frequency band, amplitude was obtained using a 4th-order Butterworth bandpass filter from 70-170Hz and then taking the analytic amplitude from the Hilbert transform and smoothed with a moving window. ANOVAs were run between stimuli classes and corrected for multiple comparisons with false-discovery rate.[59] S2 had 60 trials for each condition (visual word, auditory word, visual picture). S3 had 157 trials for the human voice and 80 trials for noise-vocoded stimulus. For the time-frequency plots, epochs were transformed from the time domain to the time–frequency domain using the complex Morlet wavelet transform. For the HFB frequencies, constant temporal and frequency resolution across target frequencies were obtained by adjusting the wavelet widths according to the target frequency. The wavelet widths increase linearly from 14 to 38 resulting in a constant temporal resolution of 16 ms.

Results:

Device Benchmarking

To realize the fully conformal, high-density PEDOT:PSS microelectrode array, we utilized parylene C as an insulating and flexible substrate carrier for the sensing electrodes and the metalization lines. The device consisted of an array of 56 microelectrodes (arranged in an 8-by-7 grid) and 6 macrodots (arranged in a 1-by-6 strip) of which a subset was used as reference. The macrodots have the same 3 mm diameter as commonly used clinical electrodes (eg. Ad-Tech Medical Inc.) and are arranged in the same form factor (strip shape with 1cm spacing) as shown in **Figure 1**a. The microelectrodes have 50 μm diameter microdots and are spaced 400 μm center-to-center yielding an array that has a footprint of 3.25 mm x 2.85 mm. Extension to higher density and channel counts is possible with either passive wiring[41] or active multiplexing electronics[46]; here we focus on the clinical translation of PEDOT:PSS by recording μECoG intraoperatively. We use this design to directly compare clinical recordings obtained by standard PtIr electrodes, similarly sized PEDOT:PSS macrodots, and the scaled PEDOT:PSS microdot arrays.

The fabrication process on 4” glass carrier wafers is discussed in detail in the experimental section. **Figure1**b-d show optical microscope images of the microarray after Ti/Au 10 nm/100 nm evaporation, parylene C chemical vapor deposition and selective etching above the Ti/Au microdots, and definition of PEDOT:PSS above the Ti/Au pads by a spin-cast and peel-off process. **Figure 1**e shows a scanning electron microscope image (SEM) of one 50 μm diameter microdot.

To confirm the structural integrity of the microdots and their interfaces with both parylene C and underlying metal contacts, a critical safety factor for use in clinical procedures, we performed focused-ion-beam (FIB) slicing at the edge of the microdot of **Figure1**e. The parylene C layers embed the edges of the metal contact and is etched at its center where only PEDOT:PSS was deposited as shown in **Figure 1**f. The spin-casting approach for depositing PEDOT:PSS enables an intimate contact with the underlying metal and the sidewall of the etched parylene C, forming a tight and fully biocompatible neural interface device. After autoclave sterilization at 121°C for 20 min in steam, we performed atomic force microscopy (AFM) on the PEDOT:PSS surface for two purposes: (1) validate that insignificant morphological changes occur post sterilization, and (2) no nanoscale voids exist in the PEDOT itself such that the electrochemical interface is only PEDOT:PSS and not a mixed PEDOT:PSS and metal one as is the case when PEDOT:PSS is electrodeposited on metal contacts. **Figure 1**g shows the AFM images on PEDOT:PSS film after autoclave showing a relatively smooth and continuous surface with a root mean square surface roughness of 1.22 nm. These cumulative structural studies support the integrity of PEDOT:PSS on parylene C for safe intraoperative monitoring of brain activity.

For high fidelity recordings, the yield and reproducibility in device fabrication is important. Our refined fabrication process (see Methods) resulted in a high yield of functional microelectrodes (>96% functional) and a very narrow distribution of their impedances. Specifically, as shown in **Figure 2**a, conventional fabrication procedures lead to a 1 kHz average impedance of 19.81 ± 6.94 kΩ whereas the refined procedure for 3 separate devices resulted in average impedances of 12.68 ± 0.35 , 12.12 ± 0.4 and 13.1 ± 0.45 kΩ (**Figure 2**a). Since clinical electrodes are not manufactured with microscale electrodes, we fabricated a comparison set of Pt microarrays in a similar fashion to our PEDOT:PSS arrays to compare impedance profiles. In contrast to PEDOT:PSS devices, Pt microelectrodes demonstrated a broader distribution of impedances with average impedance at 1 kHz of337.52 ± 37.02 kΩ, 290.23 ± 35.2 kΩ and 316.64 ± 27.18 kΩ (**Figure 2**b). The Bode plots of the electrochemical impedance spectroscopy (EIS) for one of these device types (MGS-112 with PEDOT:PSS contacts) and (Pt3 with platinum contacts) are depicted in the inset of **Figure 2**a and **Figure 2**b respectively and demonstrate nearly identical electrochemical characteristics for all of 56 PEDOT:PSS microdots and non-uniform characteristics for Pt microdots in the array. EIS characterization of Pt and PEDOT:PSS micro/macro electrodes are shown in **Figure 2**c-d (clinical electrode EIS spectra are shown in supporting information **Figure S**2). The impedance of PEDOT:PSS microarrays (50μm diameter) displayed mostly capacitive characteristics below 100Hz; above 100 Hz faradaic processes dominate the EIS spectra. Across frequencies of interest for physiological analyses (1Hz-10kHz), PEDOT:PSS microelectrodes exhibited impedances >10X lower than impedances measured for Pt microelectrodes. The impedance of Pt microarrays on the other hand displayed a nearly fixed dependence on frequency with mixed capacitive and faradaic processes. For the larger 3mm diameter macrodots, the impedances become significantly lower and are dominated by series resistances for PEDOT:PSS and faradaic resistance for Pt (detailed models with size dependencies will be published elsewhere[47]).

Human Electrocorticography

Having shown the favorable characteristics of our PEDOT:PSS electrodes compared to Pt electrodes, next we assessed our electrodes' ability to measure human electrophysiological activity. We performed intraoperative recordings in both anesthetized patients and patients undergoing clinical mapping of eloquent cortex during epilepsy and tumor resection surgery. The recordings reported consist of testing with four individuals: three at UC San Diego (UCSD) Thornton Hospital (La Jolla, CA) and one at Brigham and Women's (BW) Hospital (Boston, MA). At UCSD, we performed recordings using PEDOT:PSS from Subject 1 (S1) both while awake and while unconscious, and from Subjects 2 and 3 (S2 & S3) while performing a cognitive task. At BW, Subject 4 (S4) was unconscious during the recordings.

As an initial analysis, we demonstrate that PEDOT record comparable activity to current clinical electrodes (**Figure 3**). Here we compare electrophysiology from the macrodot Pt (clinical electrodes), *versus* the macrodot and microdot PEDOT:PSS electrodes during two different states for S1 when the electrodes were implanted on the anterior superior temporal gyrus. The first state is awake and is engaged in an audio-visual task (see methods for details) versus the second state of anesthesia with Propofol and Dexmedetomidine. As expected there were readily observable differences in electrophysiological recordings between the two states as illustrated in power spectral densities (PSD) (**Figure 3a-c**), time-frequency plots and time series (**Figure 3d-g**). There is markedly higher power in the anesthetized condition and in particular in the 12 – 17 Hz range, indicative of spindle-like activity (**Figure 3a-c**). Spindling has been reported in deeply anesthetized patients under the drug Dexmedetomidine [48]. Time-frequency plots also appear to show spindling and other dynamic neural activity (**Figure 3d and 3e**). Clinical ECoG using standard of care electrodes (3 mm Pt) were recorded alongside PEDOT ECoG. A PSD of a clinical electrode shows comparable effects to those measured by the PEDOT electrodes: (1) increased power during the anesthetized condition and (2) a prominent peak around the alpha range for the task condition. However, there are differences between the clinical and PEDOT electrodes in terms of the differential power of the two conditions. The PSDs are significantly different from each other based on their 95 % confidence interval (c.i.) up to 30 Hz and 42 and 44 Hz, for a clinical, macro and micro electrode, respectively (**Figure 3a-c**). This suggests that PEDOT electrodes are more sensitive at sensing neural activity which is consistent with the presented EIS plots (**Figure 2 and S2**). This demonstrates that physiologically expected effects observed in the clinical ECoG are also seen in micro PEDOT electrodes and that they may be sensed with higher fidelity.

Another example of consistent physiological effects observed across electrode types is shown in Figure 4. S4 was undergoing a standard non-dominant temporal lobe resection. Prior to removal, clinical and PEDOT electrodes were placed on the lateral surface of the temporal lobe across the superior and middle temporal gyrus. After recording under usual anesthetic conditions, a dose of Methohexital (Crtl + H) was administrated with the intention of increasing epileptiform activity.[49,50] As expected, this caused a significant increase in epileptiform activity after several minutes as illustrated in the time traces across the electrode types (Figure 4a and 4b). The time traces are taken over two windows: T_1 which was shortly after the Methohexital (Crtl + H) dose and T_2 which occurred 200 s after T_1. PSDs for T_1 and T_2 are plotted for clinical, PEDOT macro and micro (**Figure 4c-e**, respectively) showing the same trend: more activity in $T_{2.}$ Additionally, there is a larger power difference measured by the PEDOT electrodes than the clinical electrodes again indicating that they are more sensitive to higher frequency (> 15 Hz) neural activity. Insets of **Figure 4c-e** show snippets of an interictal epileptic discharge (IED) that occurred concurrently across the electrodes with different waveform morphologies. PEDOT electrodes showed a larger increase from baseline power due to Methohexital (Crtl + H) demonstrating their potential clinical utility.

To further examine spatial specificity, we analyzed stimulus-locked cognitive activity in two patients. Recordings were made from the anterior superior temporal gyrus for S2 (**Figure 5**a) and from the posterior superior temporal gyrus for S3 (**Figure 5**d) while each was awake for the clinical mapping of eloquent cortex. While awake, each also performed a short task (see methods). S2 verbally responded on >95% of naming trials and S3 made a correct match/mismatch decision on 98% of trials.

Spectrograms demonstrated increases in high-frequency power specific to certain stimuli classes: auditory words for S2 (**Figure 5**c) and noise-vocoded stimuli for S3 (**Figure 5**f)[51]. The most consistent difference across electrodes was in the frequency ranges commonly referred to as ‘high-gamma’, here defined as 70-170Hz (**Figure 5**c & **5**f show the responses for 3 neighboring example channels from each subject). This high-frequency band amplitude (HFB) is highly correlated with population neuronal firing rates[52]. To better assess this HFB response, we looked at the response averages across electrodes.

Of the 56 micro-contacts, 42 in S2 and 34 in S3 were functional, as determined by impedance < 60,000 ohms. While reference autoclave experiments here and in ref. 37 showed negligible influence on the microarray impedances (**Figure 2**), some of the microarray dots displayed higher impedances after transportation and autoclave by hospital personal as determined by impedance measurements just prior to the recordings. In S2, 16 of 42 good electrodes demonstrated a significant ($p<0.05$ false-discovery rate corrected) increase to auditory words relative to visual words and pictures (38% of electrodes). In S3, 31 of 34 electrodes demonstrated a significant increase ($p<0.05$ false-discovery rate corrected) to auditory noise-vocoded trials relative to human voice trials (91% of electrodes). S3 also saw a visual bigram prior to the auditory stimulus, but showed no significant response across electrodes to visual stimuli.**Figure 5**b & **5**e show the HFB of the six example electrodes chosen from a 3x2 portion of the grid, demonstrating that the presence of an effect and the variability of the effect size can vary across distances as small as (400μm).

Discussion*:*

Here we report the fabrication of a highly reproducible, high-yield PEDOT:PSS microarray, demonstrate PEDOT:PSS possesses superior impedance characteristics compared to Pt clinical electrodes, and show the first PEDOT:PSS recorded stimulus-locked human cognitive activity. A variety of structural studies confim PEDOT:PSS is safe for implantation and our microaray had a high yield of functional microelectrodes (>96% functional) with a very narrow distribution of impedances. Microelectrodes measured similar electrophysiological phenomena as macrodots made of either PEDOT:PSS or Pt across anesthesized, awake, and pathological states despite the microelectrode's 4 orders of mangitude smaller area. PEDOT electrodes exhibited larger differential power among various conditions (**Figure 3 and 4**) than clinical electrodes indicating they have more senestivity. Finally, we demonstrated that the PEDOT:PSS microelectrode array was capable of resolving differences in cognitive responses across cortical tissue over distances as small as 400μm.

In other cases, PEDOT micro-electrodes recorded highly similar signals as compared to the clinical electrodes as shown in **Figure 4a** and **4b**. This can partly be attributed to referencing schemes (see methods), but is undoubtedly a result of sensing signals much closer to each other(400μm – 3mm vs 1 –5 cm) [53,54]. Measuring highly similar signals has advantages and disadvantages, which change depending on use case. An advantage for measuring highly similar or redundant signals is that they may help denoise a collective signal or feature when combined intelligently. For example, interictal epileptic discharges, IEDs, are difficult to detect using automated algorithms and even challenging for trained electrophyiologists. IED detection might be improved if there were multiple redundant views of the signal which could increase detection confidence. This concept has been used by electrophysiologists to better detect action potentials from single units (eg. tetrode designs). This potential motivates investigation of high density or mixed density surface probe designs, even if sensed signals appear to be highly similar.[42]

As electrode development pushes towards decreasing contact size to increase spatial specificity, PEDOT:PSS contacts facilitate high SNR recordings and have a number of favorable characteristics. The spin-casting approach used in our fabrication provides a consistent electrochemical interface and insignificant morphological changes post-sterilization[45]. This approach leads to a very high yield of functioning electrodes (>96%) with a narrow range ofimpedances. The EIS impedances for PEDOT:PSS are smaller than those for Pt which in turn results in lower noise power spectral density than those of Pt (**Figure 2**e-f). This difference is significant because cognitive processes that are generally observed at low frequencies (theta, gamma, and low frequency oscillations) need to be measured with the lowest possible electrode noise. Additionally, important information about neuronal firing in the high-frequency bands has a very low amplitude, making it critical to maximize SNR.

Combining these reliably low impedances with several other favorable characteristics makes PEDOT:PSS a strong contender for leading the next generation of neural electrochemical interfaces. These additional characteristics include high charge injection capacity (safe/efficient stimulation) [16-18], compliant mechanical properties for mimicking the curvilinear brain tissue and to compensate brain micromotion in order to reduce tissue damage [19-21], and enhanced biocompatible electrode/tissue interfaces to minimize biofouling [13,22,23]. With higher channel counts being achievable via passive wiring or active multiplexing, PEDOT:PSS presents a great opportunity to achieve high-density, high-SNR arrays, with greatly increased spatial specificity.

Despite the promise of PEDOT:PSS for neural recording, we are only aware of one group which displayed human neural recordings from a PEDOT:PSS device[41,42]. They demonstrated that PEDOT:PSS electrodes with an area of 10 x 10 μm^2 can sense a wide variety of neurophysiological activity including low frequency oscillations (beta, delta and spindle activity) and high frequency action potentials. They validated these neurophysiological signals by showing they are modulated by other neurophysiological signals and coarse conditions such as awake or under a variety of anesthesia, similar to our results in Figure 3. However, they have not demonstrated how the sensed neurophysiology is modulated by sensory stimulus or cognitive processing, which is one of the main contributions of this work. Interestingly, we did not detect action potentials, which may have been caused by excessive CSF between the pial surface and probe, which acts as a spatial low pass filter. In [42], they suggest adding openings homogenously throughout the probe to allow CSF to flow over the probe as well as minimizing the amount of CSF near the probe [42]. Additionally, the device presented in our study has a larger electrode size (50 µm diameter vs 10 µm diameter), which may have prevented the electrodes from sensing action potentials. Finally, the neurogrid device makes use of a tetrode-like design, concentrating 4 electrodes every 2000µm as opposed to our grid placing 1 electrode every 400µm. Future studies will need to determine optimal electrode design, which will undoubtedly vary for different clinical and experimental questions.

Finally, we examined the ability of PEDOT:PSS microgrid arrays to measure stimulus-locked cognitive responses to audiovisual stimuli. Neural responses to stimuli showed increases in power in high frequencies, likely related to neuronal firing[52]. These increases proved to reliably discriminate different stimuli, both between language modalities (S2) and within a single language modality (S3). Further, the high-frequency amplitude and effects differed within a displacement of 400 μm, demonstrating the great spatial specificity possible with PEDOT:PSS micro-electrodes.

The utility of high-density, high-SNR arrays with high spatial resolution is straightforward within the context of basic science. PEDOT:PSS micro-arrays can extend the ability of intracranial research to identify precisely the borders of functional regions and tease apart the information processing micro-circuitry operations within these regions. Perhaps more important is the great potential for PEDOT:PSS clinical applications as well and the potential for higher SNR and higher spatial resolution ECoG toimprove patient outcomes for surgical brain resections. The current gold standard for sparing eloquent, motor, and sensory cortex during resections is direct cortical stimulation to map brain function.In addition to this gold standard, recent work demonstrates the potential use of recorded HFB activity as a complementary method for functional mapping.[55] The surgeon often faces a very difficult tradeoff of maximizing resection extent to remove pathological tissue and thus improve the patient's health, while preserving as much function as possible. The coarse spacing, limited channel count, and non-conformability of the currently used electrode substrate constrain the resolution of the information available to make a decision about this tradeoff. PEDOT:PSS electrodes provide safe and efficient stimulation in addition to their high-SNR recording ability and conformable characteristics. Using future arrays combining the excellent stimulation and recording capabilities of PEDOT:PSS, neurosurgeons would be more confident in the functional boundaries of the exposed cortex, and thus be able to make a more informed decision of which tissue to resect. Development of these arrays is facilitated by the fact that PEDOT:PSS electrode fabrication allows quickly iterated designs. Eventually, working together, surgeons and researchers will be able to develop arrays that are effective for optimizing post-surgical outcomes[13–15].

Chapter 4, in part, has been published in Advanced Functional Materials in 2017. The dissertation/thesis author was a co-primary investigator. Eric Halgrenwas a co-senior author. Additional co-authors include Mehran Ganji, John Hermiz, Nick Rogers, Joseph Snider, George Malliaris, Ilke Uguz, Milan Halgren, Atsunori Tanaka, Sang Heon Lee, David Barba, Daniel Cleary, Sydney Cash, Shadi Dayeh.

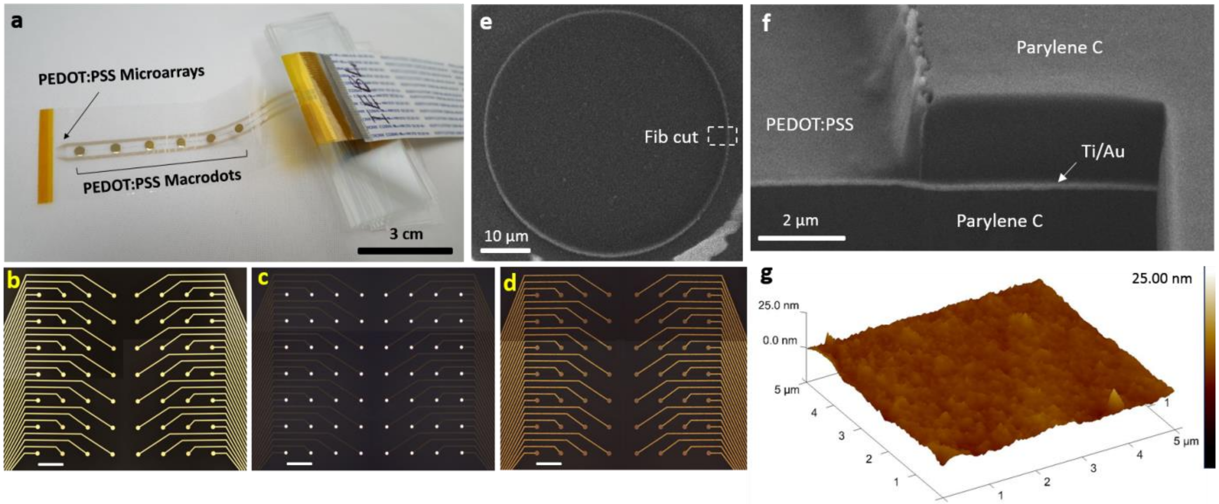

Figure 4.1: Structural and morphological characterization of PEDOT: PSS electrophysiology device.(**a**) A picture of the fabricated electrophysiology PEDOT: PSS device on thin film parylene C layer showing the location of microarrays with 56 microdots at the top of the probe and above the 6 macro REF electrodes. Optical microscope image of the microelectrodes after (**b**) Ti/Au deposition and lift-off process, (**c**) selective parylene C oxygen plasma etching to expose the gold electrodes and (**d**) definition of PEDOT: PSS layer on top of the metal electrode sites (scale bars 400 µm). (**e**) Top view SEM image of the circular PEDOT:PSS microelectrode with 50 µm diameter. The white contrast in the lower right of the image is the result of electron charging on parylene C and does not signify a morphological detail. The dashed white box highlights the the location of FIB cut. (**f**) Slanted view SEM image showing the cross-section of the device and the stacked layers highlighting conformal and intimate contact between the different layers of the device and exposure of PEDOT:PSS as the only electrochemical interface. (**g**) 3D AFM topography image of a 5×5 µm scan area of PEDOT: PSS film after autoclave sterilization showing smooth and uniform morphology (compared to before sterilization, not shown) and absence of voids in the film.

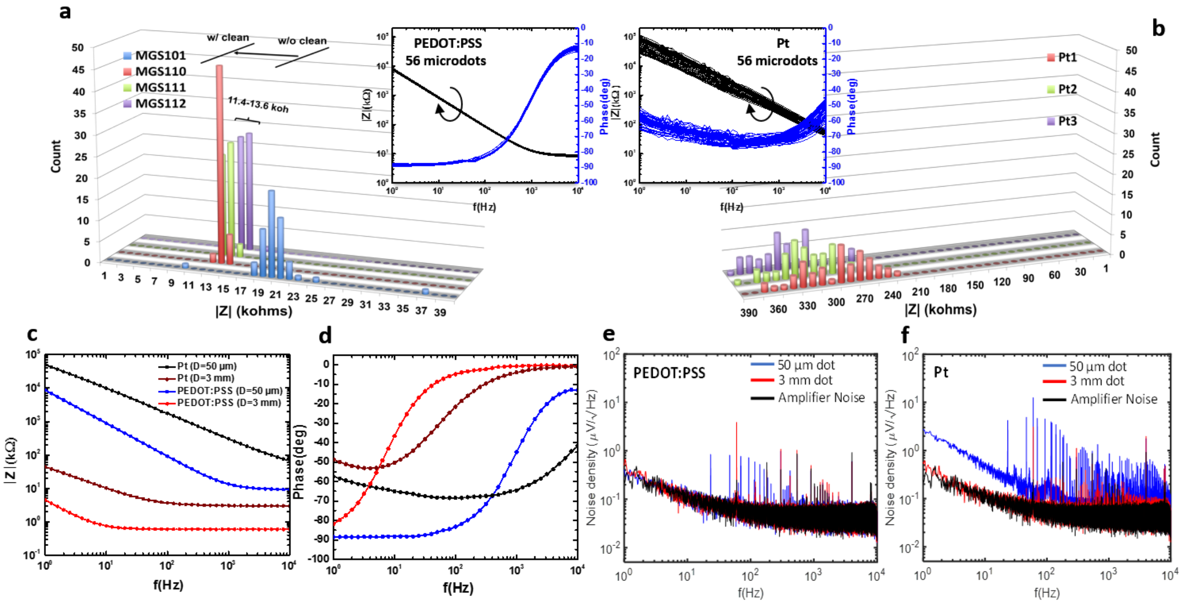

Figure 4.2: Electrochemical comparison of Platinum and PEDOT:PSS electrodes. (**a**) The 1kHz impedance histogram for three optimized PEDOT:PSS devices i.e. MGS 110, MGS 111 and MGS 112, with 55, 54 and 56 working channels out of 56 microdots, respectively and for the non-optimized PEDOT:PSS (MGS 101) (**b**) The 1kHz impedance histogram for three Pt devices i.e. Pt1, Pt2 and Pt3 with 52, 54 and 56 working channels out of 56 microdots, respectively. The inset of (**a**) and (**b**) show EIS spectra for all 56 microdots of MGS 112 and Pt3 displaying robust and uniform characteristics of PEDOT:PSS microdots compare to non-uniformity of Pt microdots. (**d**) Impedance and (**c**) phase spectra for micro and macro PEDOT:PSS and Pt electrodes showing distinctive electrochemical behavior (see text) and lower impedances for PEDOT:PSS. (**e**) The noise density of micro/macro PEDOT:PSS and (**f**) Pt electrodes showing that PEDOT:PSS noise is low and is masked by the amplifier noise whereas Pt microdot noise is significantly higher, particularly in the low frequency regime (theta, gamma, and low frequency oscillation bands) where cognitive field potentials are located.

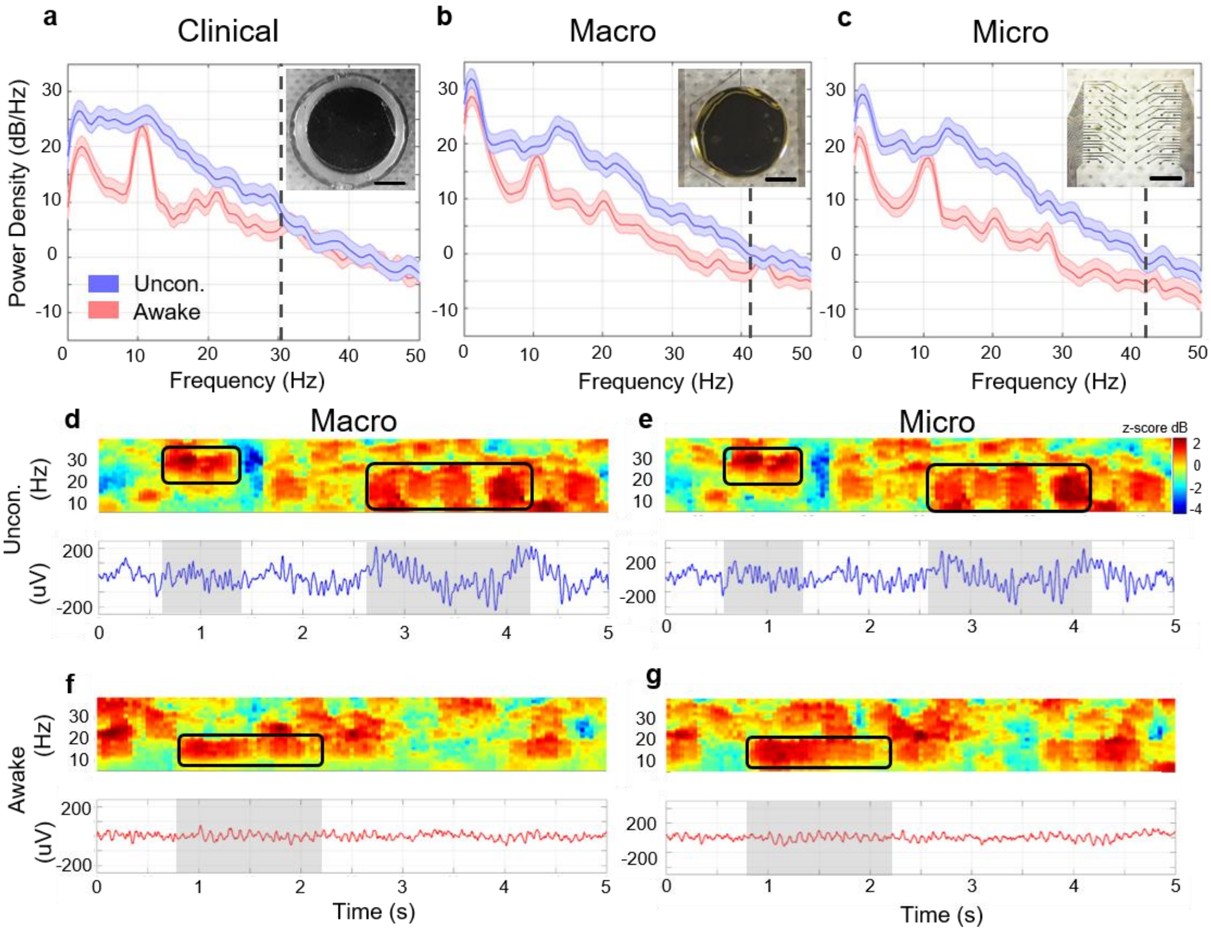

Figure 4.3: Awake vs Unconscious ECoG differences in clinical, PEDOT macro and micro electrodes. Power spectral densities (PSD) between the two conditions (awake vs unconscious) for (**a)** clinical electrode, (**b)** PEDOT macro and (**c)** microdot. Inset of (**a**) shows optical image of clinical Pt macrodot and (**b**), (**c**) show optical image of PEDOT:PSS macrodot and an array of 56 microdots (scale bars 1 mm). The dark blue and red lines are average PSD estimates from overlapping time windows and the lightly colored shaded regions are the 95% c.i. (see methods). The two conditions are deemed significantly different from each other at a particular frequency if c.i. bands do not overlap. The dashed black line at 30, 42 and 44 Hz for a-c mark the frequency at which the PSD difference between the two conditions start to become insignificant for frequencies > 15 Hz. Time-frequency and corresponding time series are shown for a sample 5 sec window for the awake (**d** and **e**) and unconscious condition (**f** and **g**). The rectangles highlight increases in beta (20 - 30 Hz) and spindling activity (12 - 17 Hz). Color axis represents standard deviations away from the mean for each frequency. The time window per condition for macro and micro are nearly identical.

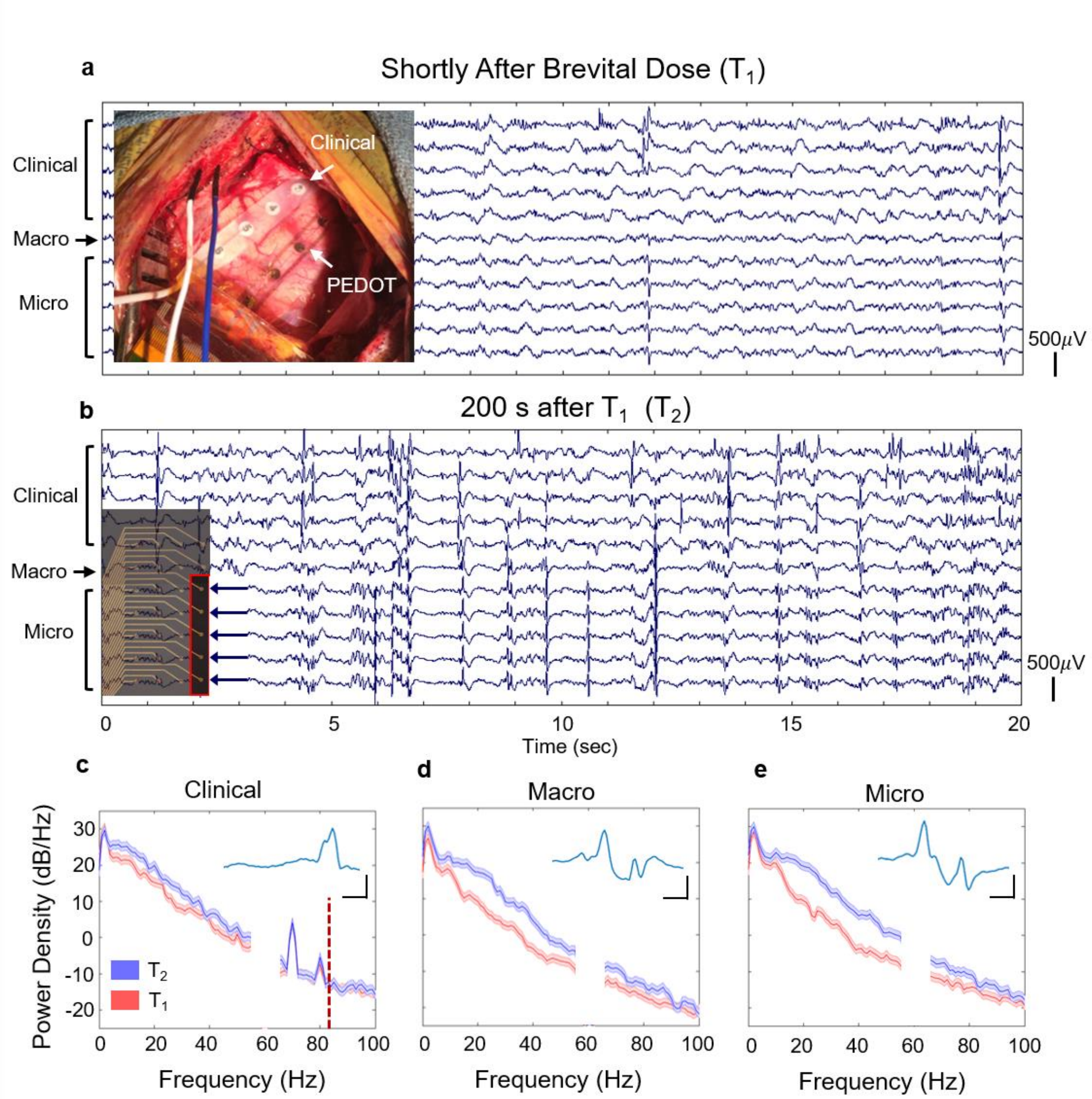

Figure 4.4: Methohexital induced differences in clinical, PEDOT macro and micro electrodes. (a) Simultaneously captured ECoG traces from clinical, PEDOT macro and micro electrodes shortly after Methohexital dose (T_1) and **(b)** 200 seconds after $T_{1,}$ (T_2). Inset in (a) shows the clinical and PEDOT ECoG probes implanted over the superior and middle temporal gyrus. Inset in (b) shows which micro-electrodes are plotted for a-b. Power spectral densities of a **(c)** clinical, **(d)** macro and **(e)** micro electrode taken from T_1 (red) and T_2 (blue). The dark blue and red lines are average PSD estimates from overlapping time windows and the lightly colored shaded regions are the 95% c.i. (see methods). The two conditions are deemed significantly different from each other at a particular frequency if c.i. bands do not overlap. The dashed red vertical line in (c) indicates the upper passband cutoff frequency for the clinical system. Insets from (c-e) show an interictal epileptic discharge (IED) captured concurrently across the three electrode types. Scale bars are 200 μV (vertical) and 50 ms (horizontal).

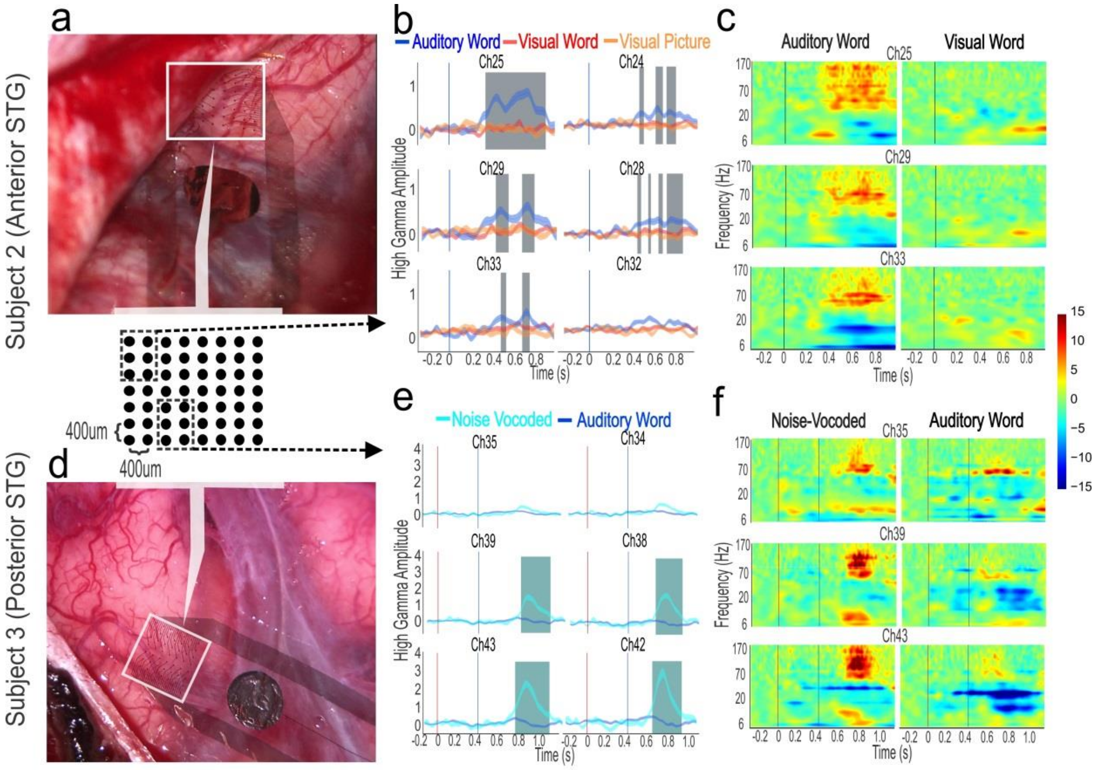

Figure 4.5: Neural activity varies across distances as small as 400um. (a & d) Electrode placement from the two subjects who performed cognitive tasks. Activity from six neighboring electrodes (3x2 electrodes) from the 8x7 electrode array are displayed to illustrate high-frequency amplitude variation. The white box highlights device placement (device partially obscured in subject 1 by the dural flap). (**b & e**) High-frequency amplitude for the 3x2 channels confirming significant differences in Hilbert analytic amplitude from 70-170Hz between stimuli classes (shaded regions are anova fdr-corrected significant differences). For subject 1, the blue line indicates stimulus onset. For subject two, the red line indicates visual stimuli onset (to which no response was found across the electrodes) and blue line indicates auditory stimulus onset. Shaded error bars are standard error of the mean for each stimulus condition. (**c & f**) Time-frequency plots from three of the example channels (3x1) in response to different stimuli classes demonstrating strong differences in higher frequencies. Displayed is trial-averaged power determined by wavelets.

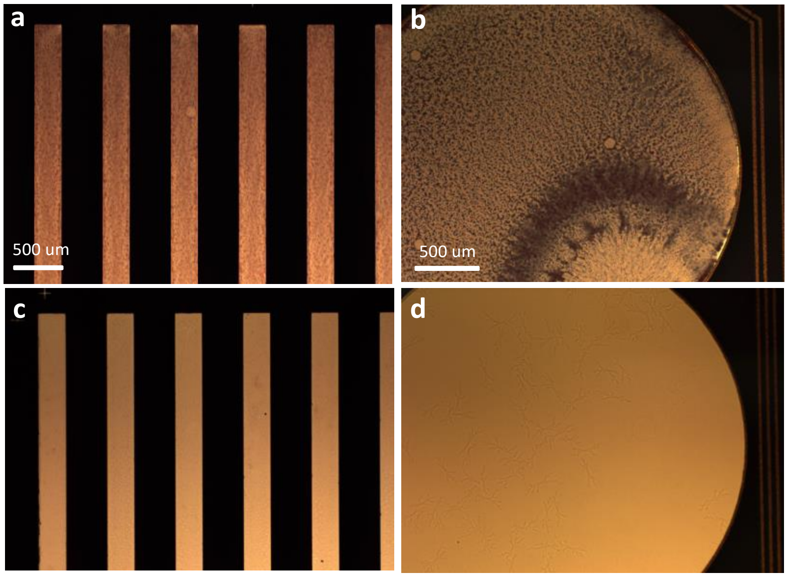

Figure 4.6: Optimization (cleaning) process of Au surface prior to PEDOT deposition. Optical microscope images of (**a**) contacts pads and (**b**) macro-dot after parylene C etching without cleaning showing residual particles from the anti-adhesion layer (micro-90) that is used in the process. Optical microscopy images of the same (**c**) contacts pads and (**d**) macro-dot after a cleaning step using DI water and light sonication step resulting in clean Au metal surfaces before PEDOT: PSS deposition.

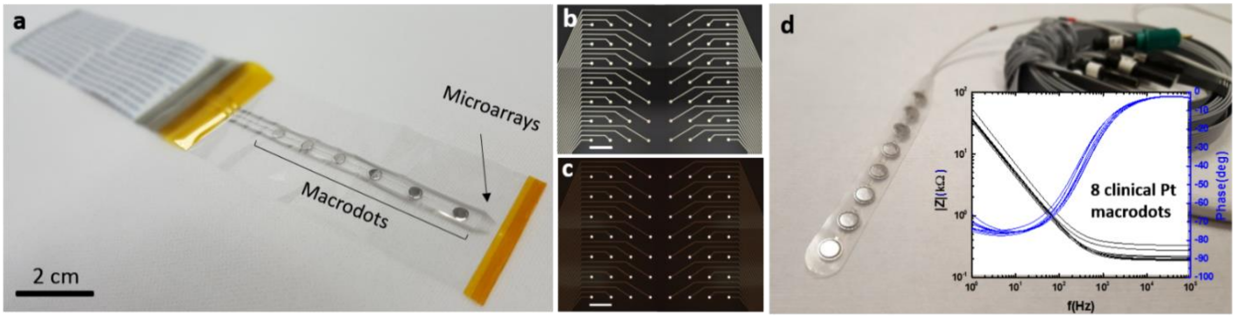

Figure 4.7: Structural characteristics of the platinum neural probe. (**a**) A picture of the fabricated platinum electrophysiology device on thin film parylene C layer with the same form-factor compared to that of PEDOT: PSS devices, showing the location of microarrays with 56 microdots at the top of the probe and above the six macro REF/GND electrodes. Optical microscope images of the microelectrodes after (**b**) Ti/Pt deposition and lift-off process, (**c**) selective parylene C etching, using oxygen plasma, showing exposed platinum microelectrodes (scale bars 400 µm). (**d**) A picture of the Ad-Tech clinical probe with 8 Pt macrodots. The inset shows the EIS (phase and magnitude) results of Pt macrodots.

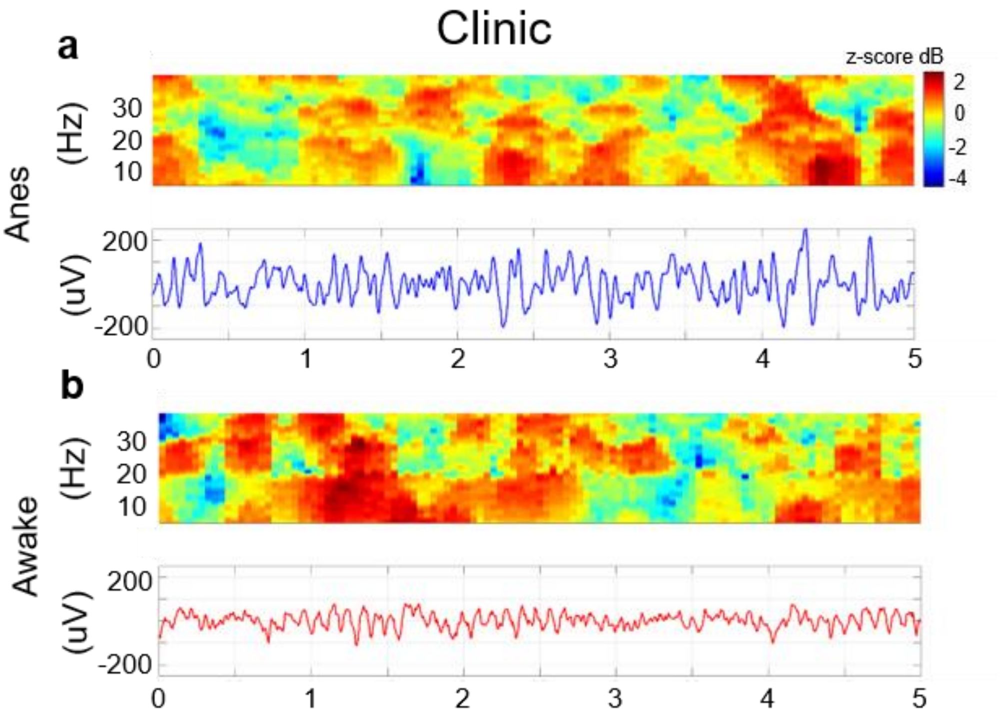

Figure 4.8: Awake vs Anesthesia Clinical ECoG electrode. Same plots as Figure 3 D-G, but for clinical ECoG. Time-frequency and time series for (a) task and (b) anesthetized condition. Note, the time windows between the PEDOT and clinical recordings may be misaligned by 2-3 seconds as they were recorded on separate systems without time syncing information.

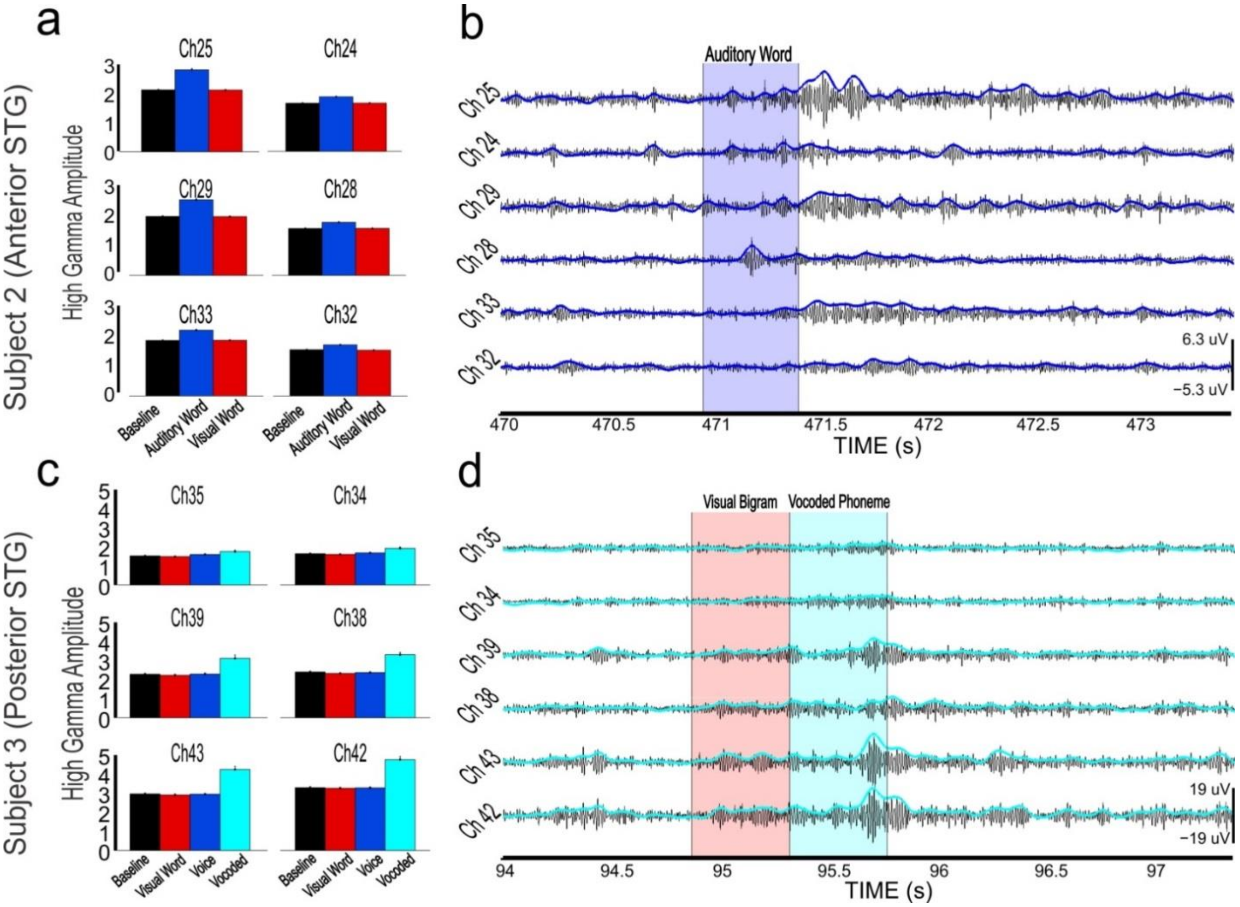

Figure 4.9: Basal High-Frequency Activity and Single Trial Example. (**a & c**) Integrated amplitude of high-frequency band activity from figure 5b & 5e (70-170Hz) with no baseline subtraction. Baseline period was -500ms-to-0ms, and each stimulus class used a 500ms epoch after stimulus presentation. Error bar is standard error of the mean. This demonstrates difference in basal high-frequency amplitude over short distances in addition to the previously shown differential responsitivity to specific stimulus classes. (**b & d**) Single trial for each subject of data bandpassed from 70-170Hz with a smoothed Hilbert analytic amplitude overlaid for the six channels from a & c. Shaded regions represent stimulus duration for the two different patients.

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CHAPTER 5: Toward a Database of Intracranial Electrophysiology during Natural Language Presentation

Abstract

Intracranial electrophysiology (iEEG) studies using cognitive tasks contribute to the understanding of the neural basis of language. However, though iEEG is recorded continuously for ~7 days during clinical treatment, due to patient considerations task time is often limited. To increase the usefulness of iEEG recordings for language study, we provided patients with a tablet pre-loaded with media filled with natural language (movies, podcasts, etc.), wirelessly synchronized to clinical iEEG. This iEEG data collected and time-locked to natural language presentation in media is particularly applicable for studying the neural basis of combining words into larger sentence and dialog contexts. Here we validate this approach by reporting pilot analyses involving words heard during a movie, tagging syntactic properties and verb contextual probabilities. Event-related averages of high-frequency power (70-170Hz) identified bilateral perisylvian electrodes with differential responses to syntactic class and a linear regression identified activity associated with contextual probabilities, demonstrating the usefulness of aligning media to iEEG. We imagine future multi-site collaborations building an 'intracranial neurolinguistic corpus'.

Introduction

Intracranial electrophysiology (iEEG) studies using cognitive tasks have provided important novel contributions as well as corroborations in understanding the link between human cognition and neural activity. For language, this has occurred across multiple levels of linguistic study such as sub-lexical phonetics [1,2] and orthography[3,4], lexico-semantic processing [5–7], and syntax [8]. However, though iEEG during clinical treatment is recorded 24 hours-a-day for ~7 days for each patient, due to patient and clinical considerations task time is often severely limited. For language, this can mean research projects can stretch over many years to collect enough data to investigate a single linguistic question. Despite this enormous effort on the part of the patients, researchers, and clinical team this dataset may not be useful again for additional questions. To demonstrate a natural language approach to increase the usefulness of iEEG recordings for language study, we provided patients with a tablet pre-loaded with digital media containing an abundance of natural language (movies, podcasts, etc.) which wirelessly synchronizes media presentation and iEEG data with high temporal precision. Once collected, the language presented can be characterized in a multitude of ways to characterize language comprehension at every level of linguistic study.

Here we validate this approach by reporting a vertical slice of what a fully scaled-up effort would look like. First we detail the unobtrusive, wireless syncing system between the media a patient experiences while using our tablet and the recorded clinical iEEG data. Modern tablet computers are powerful enough to record with the temporal precision needed for iEEG studies, portable enough to remain with patients for days, and simple enough to encourage enjoyable patient use. When the patient chooses to watch a video, listen to a podcast or audiobook, or play a game the synchronization system will facilitate later neural data analysis. Second, we describe the approach used to label the natural language stimuli being presented. Third, we report traditional stimulus-locked analyses to verify that stimuli are accurately tagged and that our synchronization method works. Finally, we illustrate how potential approaches for making use of these datasets in a post-hoc manner would proceed, focusing in our example on contextual probability. We approximated contextual probability of verbs by using a probabilistic model [9]. Specifically, we used a smoothed trigram language model trained on a movie dialog corpus that estimated the probability of each word given the preceding two words.

Together, these aims highlight the approach advocated herein. First, the collection of electrophysiology collected intracranially, time-locked with high temporal precision to natural language presentation. Second, the usefulness of this data for later efforts to answer nuanced and complex linguistic questions.

Methods

Syncing Equipment

Figure 1A is a schematic of the synchronizing triggers which are wirelessly sent from the tablet to the clinical recording equipment. To remain unobtrusive in the clinical environment, we designed a temporal synchronization scheme for the tablet that was wireless and had sub-millisecond precision. The wireless feature was vital for ease-of-use in the clinical environment where patient care has absolute priority. The tablet had both BlueTooth and WiFi wireless technologies embedded, but neither could reach sub-millisecond precision in their timing, so we turned to the ZigBee (IEEE 802.15.4) wireless protocol designed for the Internet of Things and specifically including remote control of devices where latency is intolerable. ZigBee is not currently built into commercially available tablets, but it is implemented in a small off-the-shelf USB dongle made by Digi International (XStick XU-A11) that is fully compatible with the tablet. To feed information into the clinical amplifiers, we used an Arduino Fio V3 (SparkFun DEV-11520) that easily integrates a Digi International XBee Series 1 module (XB24-API-001). The Fio V3 has an Atmega 32U4 microcontroller that is compatible with the Arduino programming environment. The digital out pins on the Fio were connected to pins 2-9 on a DB25 connector compatible with the clinical amplifiers.

On the software side, the ZigBee appeared as a standard serial port, e.g. COM4, and was easily accessed from the tablet, including by NeuroBehavioral Systems Presentation software and Python. We used these interfaces to directly measure the latency of the wireless connection between the XStick dongle (on the tablet) and the XBee Series 1 module (connected to the clinical amplifier). As a reference we used another Arduino board (Teensy 3.1) with a wired connection to the tablet that was previously verified to have negligible latency. To measure the latency, we programmed the tablet to send simultaneous signals to both the wired reference board and the wireless ZigBee connection. The reference board also listened for a pulse from the DB25 output of the wireless receiver. The difference between these times was the latency of the system at 9.8(+/- 0.1) ms (variability reported for this and the following section is standard error). This is well within the required 1ms precision, and the consistent latency can easily be subtracted.

Given this latency, we are then in a position to align the tablet's clock with the clock in the neural recording. We do this with a random interval scheme. A short python script always runs in the background whenever the participant is logged into the tablet. Every few seconds the script sends a pulse to the neural recording amplifier and records the pulse-time with respect to the tablet's own high precision clock. The time between pulses is randomly selected from 1, 2, 3, 4, or 5 seconds. The random sequence has maximum entropy of all possible sequences which makes it the most robust to random drop out or the occasional pulse that might be delayed. The pulses from the two clocks are aligned offline using robust fitting techniques. This whole process adds less than a millisecond of variability.

Media Presentation

Movies, TV shows, podcasts, audiobooks, and games were pre-loaded on the Surface tablet computer supplied to the patients. To play movies on the tablet and synchronize the participant's experience with their neural recording, we modified the open source VLC media player (VLC 2.2, original source available at https://www.videolan.org/ and modified source at https://github.com/oldstylejoe/vlc-timed2/tree/timing_mod). Internally, VLC uses time stamps to align its video and audio streams. Each of the streams are rendered by separate processes that tend to drift over time. As audio drifts ahead (behind) of the video frame, the markers of the two streams deviate and video frames are skipped or repeated. This makes for a good viewing experience, but can cause problems with alignment of the patient's audiovisual experience with the electrophysiology since a video frame comes about every 40ms (24Hz). To compensate for this, we modified the rendering code at the level of the Microsoft direct3d driver to record which frame is being displayed and when the frame was presented. The frame number is the time (in microseconds) since the beginning of the movie that the audio or video frame was recorded. The presentation time is recorded using the tablet's internal high precision clock. A limited interface allowed the participant to open movies, play/pause them, and seek locations, while we could still record exactly what was on the screen and playing on the speakers at each instant.

The timing of the A/V was thoroughly tested using previously developed techniques [10]. The most important quantities are the A/V latency: the time from when an event (sound or video) is requested to when it is rendered. For the audio, we first measured the latency of the tablet's microphone by playing a beep at a precisely known time, and we found a latency of 10.01(+/- 0.1)ms. This was as expected since audio recordings require very precise temporal alignment. We then programmed the tablet to play a loud sound at regular intervals so we could record the time between when the sound was requested and when the speakers made noise: 69(+/- 0.7)ms. To characterize the video, we used a sub-millisecond latency wired Arduino that could flash an LED at specific times. We then programmed the tablet to simultaneously flash the LED and change the screen. To measure the interval between these two, we used a high speed camera (420Hz) and recorded 100 repetitions. The screen had about a 16ms on/off time, i.e. it completely turned from black to white within 1 frame, and a clearly visible double buffering with 1 frame of no response (the back buffer populating), 1 frame of updating the screen, and then the image is fully updated.

Language Timing Annotation

To move from data collection to analysis of stimulus-locked neural data we obtained the timing of relevant stimuli and their identity, such as words and phonemes during their media experience. We used a freely available tool to semi-automate temporal tagging, FAVE-align from the University of Pennsylvania Linguistics Lab [11]. Figure 1B at the top demonstrates how words and phonemes are extracted from the movie audio file. FAVE-align takes both audio file and transcript as input to determine stimulus beginning and ending times. For movies, the transcript is available in the form of the closed captions, which can be extracted from the movie file and fed into FAVE-align. Transcripts are also available for audiobooks, which by nature have transcripts, and podcasts, some of which have transcripts available, providing the necessary ground truth input. With FAVE-align, it was necessary to go through and confirm the onset times were accurate. As voice recognition and annotation is an area of great progress over the recent past and foreseeable future, more powerful tools will become available to ensure even less work is necessary for the temporal annotation of audio media.

Patients

Data from two patients who had both watched the same movie, *Zoolander,* were selected for analyses. These patients had long-standing pharmaco-resistant seizures and participated after fully informed consent monitored by institutional review boards. WADA tests determined that both patients were left-hemisphere language dominant and both patients were judged to have average general intellectual function. Patient A (seizure onset age: 2; surgery age: 31) had bilateral electrode strips and Patient B (seizure onset age: 21; surgery age: 33) had a right-sided electrode grid and strips.

Electrophysiological Data Pre-Processing

Data were preprocessed using MATLAB (MathWorks), the Fieldtrip toolbox [12], and custom scripts. We used an average subtraction reference for each patient, followed by a bandstop around line-noise and its harmonics (60,120,180Hz) to reduce noise. Analysis focused on power in the high-gamma frequency range (here defined as 70-170Hz) as it correlates with local neuronal population activity [13] and performs well in mapping neuronal activity in both sensory [14], motor[15], and language [1,3,16] cortex with excellent spatial and temporal precision. To obtain high-gamma power, epochs were transformed from the time domain to the time-frequency domain using the complex Morlet wavelet transform from 70-170Hz in 10Hz increments. Constant temporal and frequency resolution across target frequencies were obtained by adjusting the wavelet widths according to the target frequency. The wavelet widths increase linearly from 14 to 38 as frequency increased from 70 to 170Hz, resulting in a constant temporal resolution with a standard deviation of 16ms and frequency resolution of 10 Hz. For each epoch, spectral power was calculated from the wavelet spectra, normalized by the inverse square frequency to adjust for the rapid drop-off in the EEG power spectrum with frequency, and averaged from 70 to 170 Hz, excluding line noise harmonics. This data was smoothed by a moving window exactly matching the temporal characteristics of the wavelet. Data were then high-passed at 0.5 Hz to remove any offset and long slow drifts over the course of the several hours a movie takes.

Data Analysis: Stimulus-Locked Averages

The first analysis approach uses standard event-related average analyses to validate our ability to time-lock to language events perceived while listening to various forms of language-rich media. First, we compared the auditory words with a separate class of visual events. The visual events, referred to as “shot-changes”, were defined as when the proportion of displayed pixels which changed between frames were above a threshold. To show electrode preference for either auditory or visual stimuli, epochs were created for all perceived auditory word and visual shot-change events. The epochs were taken from 500ms prior to stimulus onset to 1500ms post stimulus onset, with the onset of the stimulus, either visual or auditory, as the 0ms point. Epochs judged to contain artifacts were identified by outlier values in amplitude and variance, visually inspected, and removed from further analysis. Significant differences between visual and auditory stimuli were identified using a two-stage statistical procedure.

The first stage was to determine if the auditory and/or visual stimuli evoked a significant increase in high-gamma power at each electrode. This was accomplished with a 1-sample t-test, separately comparing auditory trials and visual trials timepoint-by-timepoint to a population mean of 0, corrected for temporal false-discovery rate at $p<.05$ [17].

The second stage was a 1-way ANOVA, corrected using a bootstrapped shuffling method [18], run timepoint-by-timepoint for high-gamma power between aligned language and shot-change epochs to characterize electrode preference. For Patient A, 5159 auditory word-epochs were created and 2115 visual shot-change epochs were created. For Patient B, 5163 auditory word-epochs were created and 2227 visual shot-change epochs were created. The slight differences in trial numbers were caused by watching slightly different amounts of the movie. An electrode was judged to be responding preferentially to shot-changes if that electrode both responded above baseline to visual stimuli and if shot-change epochs were significantly greater than language epochs during a period of 100-to-400ms post stimulus onset. An electrode was judged to be preferentially responding to language if that electrode both responded above baseline to language stimuli and if language epochs were significantly greater than shot-change epochs during the period of 100-to-400ms post-stimulus onset.

Next, we sought to show that the electrodes with an auditory preference were sensitive to linguistic phenomenon instead of just representing a non-specific auditory sensory response. For this we broke the auditory epochs into content and function words to see if we could replicate the well-known phenomenon of differential neural processing based on broad syntactic class [7,19]. For Patient A there were 2642 Content-word epochs and 2517 Function-word epochs. For Patient B there were 2637 Content-word epochs and 2526 Function-word epochs. An electrode was judged to be syntactically selective if it fulfilled the two criteria establishing a language-preferring electrode and if it additionally showed a significant difference between function and content words during the period of 100-to-400ms post-stimulus onset using the same 1-way ANOVA and shuffling method from above.

Data Analysis: Example of Post-Hoc Language Characterizations using Contextual Probability

There is a long history of electrophysiological work on predictability in language comprehension, most notably focusing on the ease or difficulty of integrating a word's lexico-semantic identity into the ongoing larger cognitive context [20]. This often takes the form of contrasting unexpected words such as "dog" in contexts such as "I take my coffee with cream and dog" which elicit an increased negativity relative to more expected words, such as "sugar" in the same context [21]. Here we use a measure of the word contextual probability (i.e. word predictability) in ongoing naturalistic language processing, instead of experimenter-created stimulus sets. We trained a trigram language model with modified Kneser-Ney smoothing [22] on

Cornell Movie-Dialogs Corpus [23] using the SRI Language Modeling toolkit [24]. This type of language model has previously been shown to be a good model for predictability effects in behavioral and neural language comprehension data [25] and using language models has been used for N400-like responses in the past [26]. Using this language model, we estimated contextual probability as the log probability of each word given the preceding two words.

To examine the sensitivity of our neural data to contextual probability, we regressed high-gamma power on the logs of these frequencies for the verbs. We included various covariates which were intended to disentangle various types of predictive processing. Some of these were manually coded, such as whether the word was a function word (e.g., auxiliaries such as “be”) or a content word (e.g., “copying”). For others, we used data from a norming task in which we asked 60 participants to write the first sentence that came to mind when presented with each unique verb in the movie. Based on these norming data, we calculated and included the following values as covariates in the model: the log of the number of distinct syntactic frames associated with each verb, the log of the frequency with which each verb appeared as intransitive; the log of the frequency with which each verb appeared as transitive; the log of the frequency with which each verb appeared with a direct object; and the log of the frequency with which each verb appeared with an indirect object. We also included interaction terms between these last three covariates. In total 10 covariates were used: Function/Content, Log number of syntactic frames, log frequency of intransitivity, log frequency of transitivity, log frequency of direct object, log frequency indirect object, along with the three-way interaction and all 2-way interactions of the latter three covariates.

We performed 4256 linear regressions (28 time windows by 99 electrodes for Patient A and 28 time windows by 53 electrodes for Patient B) of the average HGP data in 25ms windows starting 200ms before word onset and ending 500ms after word onset for all electrodes. Each regression included 893 verb “trials.” We performed FDR-corrections on the p-values of the F-statistics (11 and 875 degrees of freedom) of each linear regression. Below, we only report findings when the corrected model p-value was less than .05 and when the uncorrected p-value associated with contextual probability in that model was less than .05. To even more stringently avoid the possibility of reporting false positives, we also exclude results from electrodes which do not show significant activity in more than two of the 25ms time windows.

Results

Stimulus-Locked Averages

Figure 2 displays locations and example average waveforms of electrodes displaying stimulus-locked effects between auditory words and visual shot-changes. We wanted to establish that electrodes displayed differentiable activity between two stimulus modalities, visual shot changes and auditory words, using traditional stimulus-locked averages. Of the 118 electrodes measured, 12 were found to preferentially respond to auditory stimuli (~10%) and 38 were found to preferentially respond to visual stimuli (~32%). The language responsive electrodes were all clustered in perisylvian areas (e.g. 7 in the STG, 3 in Rolandic cortex, 2 in supramarginal cortex). The shot-change responsive electrodes were mainly clustered in ventral visual areas (e.g. 12 in the fusiform, 6 in ventral prefrontal, 7 in lateral temporal areas, 6 in medial temporal areas). Of all these selective electrodes, only a single electrode in the caudal STG was found to be both visual and auditory preferential; it first preferred auditory words and later preferred visual shot changes.

Figure 3A displays locations and example average waveforms of electrodes displaying stimulus-locked effects between function and content words. We wanted to establish that the auditory responses found were sensitive to language characteristics and did not just reflect non-specific auditory sensory responses. To do this we compared content and function words. We found 7 of the 12 language selective electrodes exhibited a distinction between content and function words in the first 400ms after word occurrence. Content-word-preferring electrodes were found in posterior perisylvian areas (caudal STG with 3 electrodes and supramarginal with 2 electrodes) and function-word-preferring electrodes were slightly more distributed (caudal

STG, middle STG, and inferior postcentral all with 1 electrode). Each patient had at least one content-preferring electrode and one function-preferring electrode, representing a double-dissociation between broad syntactic class for both patients. Figure 3A in the top right displays one electrode from each subject from the same area in the right hemisphere (caudal STG) which both show a preference for content words over function words, demonstrating the reproducibility across patients of these findings.

Language Probabilities and Verb Transitivity

Figure 3B displays results from our regression model between high-gamma power and contextual probability. In Patient A, we found significant activity associated with contextual probability measures in left middle STG beginning at 125ms after word onset and persisting until 225ms. Later, between 325 and 350ms as well as between 475 and 500ms, we found significant activity associated with contextual probability in left caudal STG. In Patient B, for whom we had only right hemisphere coverage, we found no activity associated with contextual probability. Since both Patient A & Patient B had electrodes responding preferentially in the right perisylvian areas this suggests, very tenuously since the results come from only two patients and only one movie, contextual probability effects may be localized to the left (language-dominant) hemisphere.

Discussion

Here we demonstrated from beginning-to-end how a comprehensive effort using iEEG to study natural language heard during an audiovisual media experience would progress. First, we described the physical and software platform that was created to allow for a patient to unobtrusively experience natural media which was precisely synchronized with recorded clinical neural data. Second, we identified exact timing of words in a movie, tagged broad syntactic properties, and found word contextual probabilities. Third, we reported event-related analyses which confirmed we were able to accurately time-lock to words heard during the continuous media experience. Finally, we showed with an analysis of contextual probability effects on the neural data how experimenters could in a post-hoc manner take the identified sequence of heard language and characterize this language based on questions of scientific interest. At a most basic level, perisylvian electrodes were responsive to spoken dialogue and ventral-temporal electrodes were responsive to shot changes, identifying separable networks during processing of a movie, with the language network revealing sensitivity to broad syntactic class and contextual probability.

The power of this method for post-hoc analysis is suggested by our example focused on linguistic prediction as indexed by contextual probability. The results from this analysis revealed significant activity associated with contextual probability in the left STG. Of interest were the differing time courses of this relationship in the middle-STG, which began at ~125ms, versus the caudal STG, which began at ~325ms. Understanding the relationship of language comprehension and word predictability, particularly how the bottom-up sensory encoding experience interacts with top-down predictions [27], is important in understanding how we can understand speech heard at ~5 words a second. As an example, in visual language it has been demonstrated that whether a function word predicts the following word will be a function word or a content word causes differentiable activity as early as ~60ms [7]. A more thorough study of this question with more patients, more words, and with additional electrode coverage would allow for in depth characterization of the interaction of predictability and language comprehension across the cortex. Examining the time course of early responses, which in this example were modulated by the contextual probability of an incoming word, are possible only with the temporal precision of electrophysiology.

The introductory analyses presented here are of course just one part of the larger context of natural language. The annotations were performed with a mix of freely available software and custom built modeling. As the data accumulated in the manner we describe grows, because of the tight time-locking between media and neural data it will remain viable to approach it with novel and more complex annotation approaches as advances in computing, modeling, and analysis improve. Indeed, as the data accumulates and analyses are performed, the opportunities presented to link neural data and linguistic phenomenon may drive analyses in media annotation to answer questions that are not possible with current approaches. As the media experienced by the patient remains available for additional annotation, characterizing that media in new ways and extracting new variables for analysis is limited only by hypothesis generation.

The number of possible linguistic questions regarding the auditory media patients will hear is vast. However, we envision a fully scaled-up effort not just as an increase in the number of patients enrolled and the amount of language heard, but also in a more thorough characterization of the visual context in which that language is experienced. For example, how does the visual context affect language processing, such as the presence or absence onscreen an object or person being discussed? How about an understanding of different word expectation probabilities based on the physical appearance of the speaker? Also of importance is the related questions regarding whether video cues for their speech, i.e. lip movements, are present or absent.

The study of in-depth hypotheses regarding the full visual semantic context will require automated tools for dense labeling of the semantic entities and contexts that appear in each movie frame. An image can be annotated with the names of objects that appear in it as well as with the category of the scene that it represents. For example, an image that could be labeled as an “outdoors city” scene might also be correctly described as containing ‘pedestrians’, ‘buildings’ and ‘cars’. The ability of computer vision algorithms to identify objects in an image has improved substantially in the recent years. Deep learning methods using convolutional neural networks [28] have shown a remarkable performance on classification [29] of a wide range of object classes. Today, it is possible to classify images with respect to vocabularies of thousands of objects using off the shelf software [30]. There have been recent advances in the problems of object localization and scene classification [31–33]. Combining this dense labeling with eye-tacking software would allow for examinations of the interrelation of visual attention and language processing.

The last potentiality we mention is to move beyond just labeling media experienced, which emulates natural language, into labeling the truly natural language of conversation which the patient engages in during their stay. This would be an increase in necessary coordination with the patient and the clinical team to ensure patient comfort and experimenter conformance with patient privacy guidelines. But even if only with a subset of patients, the possibility of obtaining conversational natural language with iEEG would be an important corroboration and extension of the natural language findings from the experienced media. This would be accomplished using the tablet's recording capabilities to capture the conversations in which the patient takes part. Another possibility is to use clinically recorded audio and video, which is increasingly high-definition, in patient rooms. Algorithms exist which automatically de-identify video by detecting and obscuring faces and auditory recordings of conversations can have word times tagged and identifying nouns removed so that only the time-stamp and word and phoneme identity are uploaded to a publicly-available database. Likely, there will be patients who are fine with engaging with the tablet but not with being recorded, which is why having an adaptable and modular set-up will ensure that the most data is collected while keeping the experience for the patient and clinical team seamless and safe.

With 'Big Data' becoming less of a buzzword and more of a reality, we imagine multi-site collaborations together building an 'intracranial neurolinguistic corpus' of millions of words presented in a natural context and aligned to hundreds of channels of iEEG for each patient. Big databases of sub-lexical and lexical stimulus characteristics [34,35], stimulus meaning [36], behavior [37,38], and extracranial electrophysiological data [39] have revealed nuances and precision in findings which would be impossible for traditional smaller studies. Indeed, large-scale multi-site studies using iEEG and cognitive tasks are already underway for neural prosthetics [40,41]. By bringing a natural language approach in an unobtrusive, patient- and clinical-friendly way, researchers can collaboratively bring the same scalable benefits to iEEG language research.

Chapter 5, in part, has been submitted for publication of the material as it may appear in Language, Cognition and Neuroscience. The dissertation/thesis author was the primary investigator and author of this material. Eric Halgren will be senior author. Additional co-authors include Adam Morgan, Joseph Snider, Meilin Zhan, Xi Jiang, Victor Ferreira, Roger Levy, and Thomas Thesen.

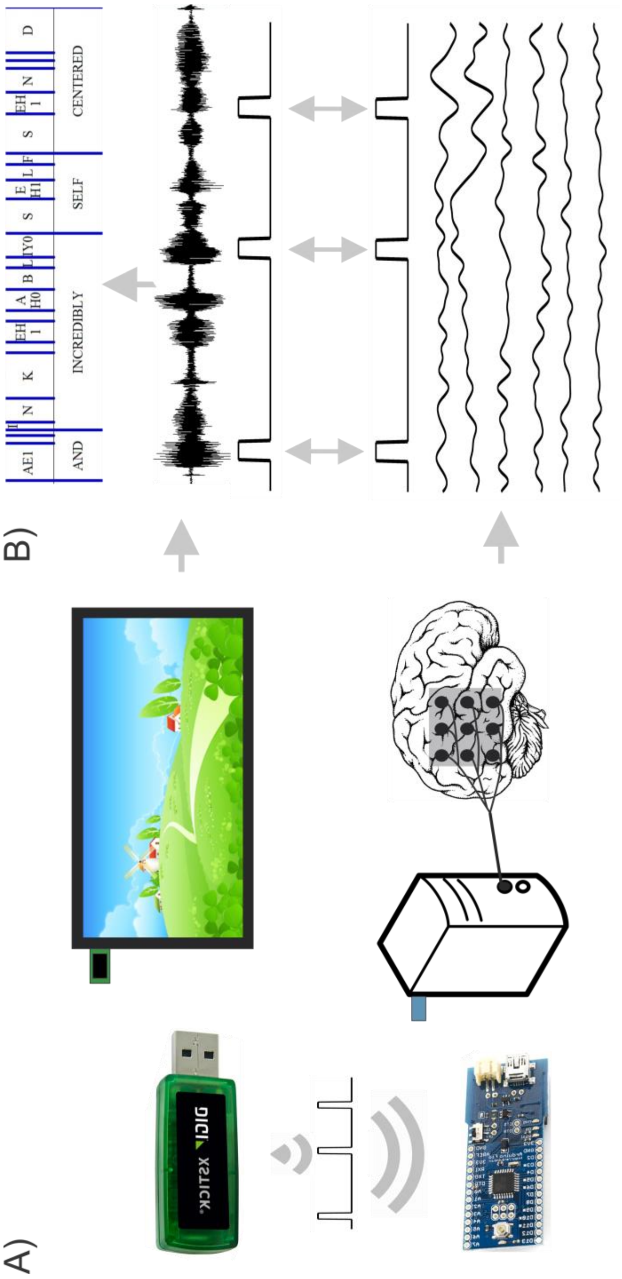


Figure 5.1: Unobtrusive Media Presentation, Synchronization with Intrancranial Electrophysiology, and Language Annotation. A) The tablet (top) is pre-loaded with natural media language (movies, TV shows, audiobooks, and podcasts) and given to the patient for use throughout their stay. Media presented on the tablet is synchronized with wirelessly-sent synchronizing pulses to the recording computer (bottom) which is recording the clinical electrophysiology. The pulses are sent with an XStick (green USB) to the receiving Arduino Fio V3 (blue Arduino) which is plugged into a spare channel in the recording system. B) The audio file of the movie is extracted (middle) and aligned precisely with the electrophysiological data (bottom) by the shared synchronzation pulses in both data. The audio file is then annotated for language, here done by FAVE-align (top), so that the annotated words and phonemes are then time-locked with respect to the electrophysiological data.

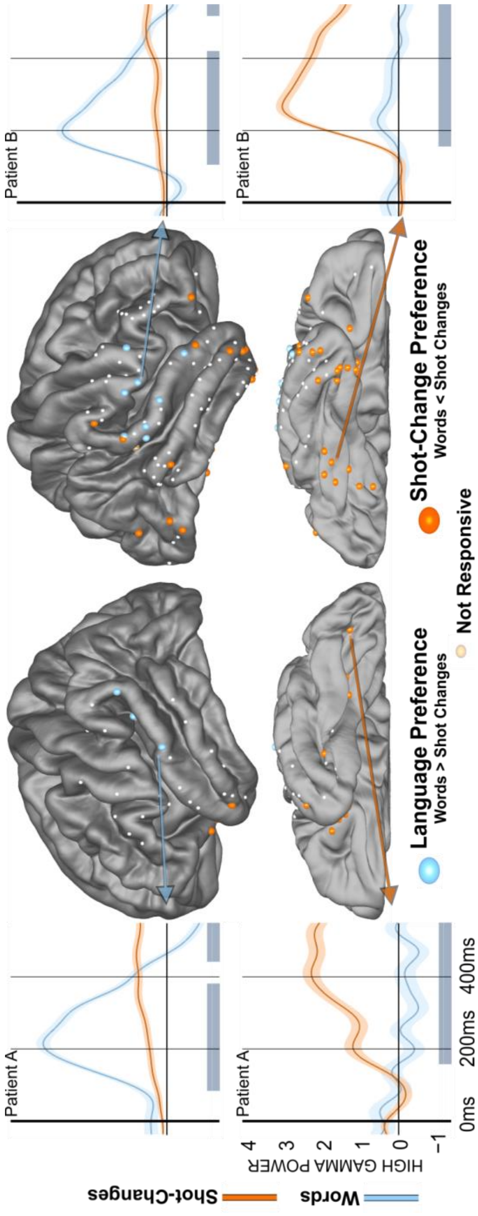
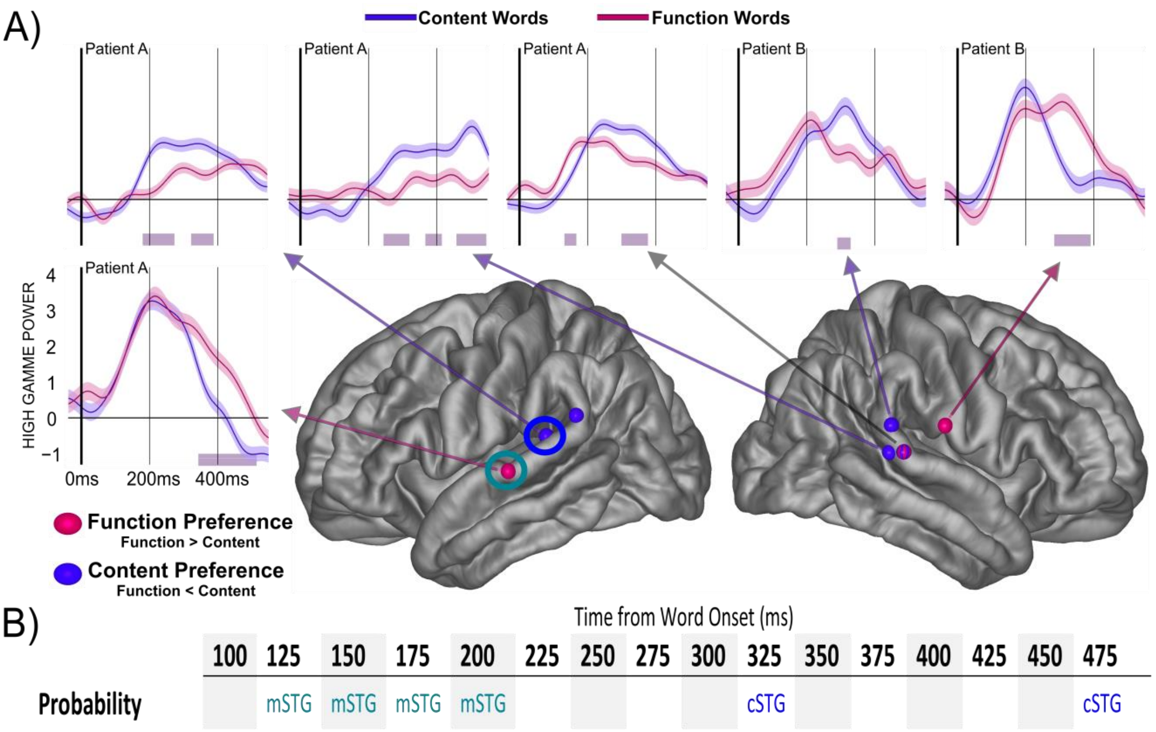


Figure 5.2: Stimulus-Locked Averages from 2 Patients Distinguish Auditory Language from Visual Shot-Change Responses. Displayed on the average brain are electrodes from two patients which demonstrated a stimulus-specific response to either words (light blue), shot-changes (orange), or were not-responsive to either stimulus type (white). The shot-change specific electrodes are found in typically visual areas such as the ventral and inferior occipito-temporal areas. The language-specific electrodes are found in expected perisylvian areas. The four example wave-forms show the differences between language and shot-change high-gamma power averages, with two electrodes from each patient displayed. The three vertical black bars on each plot signify 0, 200, and 400ms and the horizontal black bar signifies a high-gamma power of 0. The blue bar at the bottom of each plot displays periods of significant difference between language and shot-change stimuli, corrected for false-discovery rate.



Time from Word Onset (ms)

	100	125	150	175	200	225	250	275	300	325	350	375	400	425	450	475
Probability		mSTG	mSTG	mSTG	mSTG					cSTG						cSTG

Figure 5.3: Language-Responsive Electrodes Display Sensitivity to Broad Syntactic Class and Contextual Probability. A) Displayed on the average brain are electrodes from two patients which displayed a preference for either function words (red violet) or content words (purple). The six example waveforms show that within the language-specific electrodes from Figure 2, many (7 out of 12) demonstrated significant differences based on broad syntactic class. For each plot the three vertical black bars signify 0, 200, and 400ms from word onset and the horizontal black bar signifies a high-gamma power of 0. The purple bar at the bottom of each plot displays periods of significant difference between function and content words, corrected for false-discovery rate. B) Two electrodes, circled in the top plot, showed significant activity associated with contextual probability. The electrode in the middle STG (blue-green circle) was significantly associated starting at ~125ms while the electrode in the caudal STG (blue circle) was significantly associated starting at ~325ms.

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