

Connectivity in Cortical Networks During Word Reading

by

NICOLAS BEDO

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Abstract

The neural processes underlying word reading remain much of a mystery. In particular, the flow of information within and between language networks during word reading has not been adequately explored. The present study investigated local spectral power changes and functional and effective (causal) connectivity at each stage of word reading. EEG was used to record brain activity from healthy volunteers ($n = 15$), during a reading task. Independent component analysis yielded multiple sources of activation previously identified with fMRI and PET as being crucial to word reading. A combination of event-related spectral perturbation and phase synchrony analyses was performed on these independent components. Additionally, analyses of transfer entropy were conducted to investigate the possible causal information flow between sites of interest. Results confirm the VWFA as a central hub for word reading, showing a progression of theta band phase synchrony with early visual areas and then later with high-level language processing areas. Transfer entropy analyses largely converged with the theta synchrony results, again emphasizing the VWFA as a crucial node in the reading network, initially receiving information from early visual cortex, and then sending information to high-level areas. These results highlight the interplay between local and long-distance neural dynamics involved at each stage of processing during reading. Additionally, these measures of functional and causal connectivity may be used as a benchmark for comparison with clinical populations (e.g. individuals with certain kinds of dyslexia), such that disturbances in connectivity may provide insight as to underlying neurological problems.

Preface

Portions of this research have been presented previously under the citations:

Bedo, N., Ribary, U., & Ward, L.M. (April 2012). *Functional and Effective Connectivity During Letter- and Word-Reading*. Poster presented at Cognitive Neuroscience Society, Chicago, IL .

Bedo, N., Ribary, U., & Ward, L.M. (February 2012). *Connectivity in Cortical Networks During Word Reading*. Poster presented at AAAS, Vancouver, BC

Bedo, N., Ribary, U., & Ward, L.M. (November 2011). *Spatio-temporal Dynamics and Interregional Synchronization During Letter- and Word-Reading*. Slide session presented at the 52nd Annual Meeting of the Psychonomic Society, Seattle.

LW, UR, and NB designed the study. NB ran the participants, analyzed the data, and wrote the produced the posters. The UBC Behavioral Research Ethics Board (BREB) approved the study under Ethics Certificate # H00-80505. All participants provided written informed consent.

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1 Introduction

The ability to read is a curious faculty to possess. Somehow, we are able to take shapes and symbols in the environment and process them as language, complete with nuanced systems of semantics, pronunciation, grammar, and syntax. Word reading is a multi-stage process that involves the extraction of information from orthographic symbols, and requires the engagement of multiple visual, auditory, and language networks. However, reading is not simply the breakdown of orthographic symbols, but rather a conversion of symbols into sound and meaning (although not necessarily in that order).

What is perhaps even more fascinating is that reading was developed by humans only recently in the timeline of human existence, yet our brains adjust very early in development to accommodate such a task and can do so with relative ease. As reading skill develops, established neural real estate is recycled and networks are formed to support the task (Dehaene and Cohen, 2011). Although much has been discovered with regard to mapping reading functions on to brain locations, the communication within and across these networks remains unclear.

1.1 Reading in the Brain

Researchers have proposed two distinct routes in the brain for word reading (Dehaene, 2009; Jobard et al., 2003). The ‘indirect’ route converts the visual words into their auditory counterparts by using grapheme-to-phoneme strategies (i.e. ‘sounding it out’). Once pronunciation is assessed, one may access the word’s meaning. This route is used for uncommon or novel words that do not have an established template in memory with which to compare (e.g., “LUKORO”). In contrast, the ‘direct’ route identifies the word form and automatically accesses semantic information which may then lead to phonological access. The direct route is used for

common, yet irregularly spelled words (e.g., “YACHT”). Regardless of the disparity of ordering and timing of cognitive processes in the two routes, there nevertheless exists a substantial amount of overlap between them regarding the brain areas recruited for word reading. Figure 1.1 illustrates a modern view of the cortical regions involved in reading, showing clearly that reading recruits wide-spread and diffuse networks, predominantly in the left hemisphere.

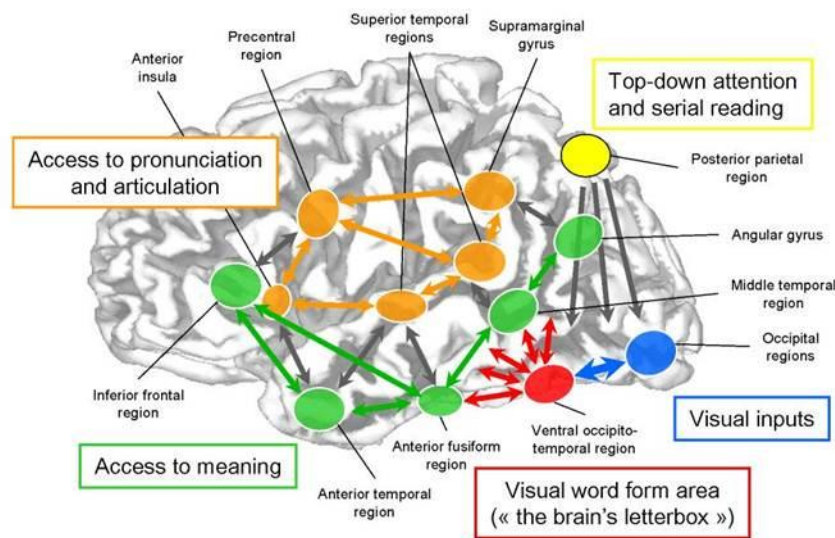


Figure 1.1. A contemporary view of the cortical networks involved in reading. The arrows in this model indicate inferred inter- and intra-network relations. Adapted from “Reading in the brain: the science and evolution of a human invention,” by S. Dehaene, 2009, p. 4. Copyright 2008 by Viking. Adapted with permission.

Over the past few decades, cognitive neuroscience research has focused on identifying these individual regions of interest in the brain that correspond to the many stages of word reading. Although many regions have been uncovered, however, one region in particular seems especially suited for the task of processing orthographic stimuli.

1.2 The Visual Word Form Area

Numerous studies have identified a region in left ventral occipito-temporal cortex, specifically in the posterior fusiform gyrus, that is crucial to orthographic processing (for a review, see Price 2012). Dehaene and Cohen (2011) have championed the existence and specialization of this region, termed the visual word form area (VWFA). The VWFA seems to be optimally nested between basic visual and high-level language processing centers in the brain, affording it efficient access to these regions. Indeed, a meta-analysis of 35 neuroimaging (fMRI and PET) studies confirms the VWFA as a central hub, crucial for processing orthographically-legal stimuli, that also relays visual word information to higher-level sites for further processing (Jobard et al., 2003).

The VWFA has been shown to respond preferentially to orthographic stimuli in specific ways. Neuroimaging studies have shown that consonant strings elicit activity in the VWFA, while checkerboards do not (Cohen et al., 2000). Additionally, it has been shown that the VWFA responds to written, but not spoken, words (Dehaene et al., 2002). Similarly, this region shows greater activation for words and word-like stimuli than for equally complex non-word-like stimuli (Liu et al., 2008). Importantly, this activity is not dependent on the visual hemifield in which the word is presented (Cohen et al., 2000). That is, regardless of the location of the word in space, the information is routed to the VWFA in the left hemisphere for processing. Neuropsychological lesion studies show that damage to the VWFA may lead to deficits in reading performance, and perhaps even alexia, the inability to read (Gaillard et al., 2006).

Event-related potential (ERP) studies have identified a reproducible negative peak in the ERP localized to the VWFA approximately 170 milliseconds (N170) exclusively after the presentation of a word (Tarkiainen et al., 2002). The unilateral N170 ERP component generated by the VWFA is considered the standard measure of word form processing, and is essentially used as a benchmark for ERP studies on the subject.

The VWFA shows a number of invariances, activating for both lower and uppercase words (Dehaene et al., 2004) and for both print and handwritten words (Qiao et al., 2010). Interestingly, VWFA differentiates words and their mirrored counterparts, but shows no differentiation for mirrored faces or objects (Pegado et al., 2011), similar to the face-inversion effect of the fusiform face area (Farah et al., 1995, Kanwisher et al., 1998), providing evidence for VWFA specialization (although some controversy exists regarding that point; Price, 2012; Price and Devlin, 2003).

1.3 Beyond VWFA

In their meta-analysis, Jobard and colleagues (2003) identified higher-level brain areas responsible for processing beyond the pre-lexical orthographic processing presumed to be accomplished by the VWFA. After basic word form processing, several cortical sites allow for semantic access, including left anterior (Price, 2012) and posterior middle temporal gyrus (MTG; Jobard et al., 2003; Vandenberghe et al., 1996), left basal temporal areas (Jobard et al., 2003), angular gyrus (Price, 2012; Vandenberghe et al., 1996) and left inferior frontal gyrus (IFG, pars triangularis; McCandliss et al., 2003; Jobard et al., 2003; Price, 2012). At the stage of graphophonological conversion—converting the word forms into sounds—left MTG and STG, left IFG (pars opercularis), and left supramarginal gyrus are engaged (Jobard, 2003).

The localization of these functions in the brain has been made possible by modern hemodynamic neuroimaging techniques. However, certain aspects of reading in the brain remain impenetrable to these techniques, namely, those processes that occur on the scale of milliseconds and are too subtle to be seen by averaged evoked waveforms in the ERP. In particular the oscillatory activity of the neurons involved in processing the reading stimuli is hidden from these techniques. As reading is a distinctive cognitive activity, it is highly likely that neural oscillations play a significant role in both local processing and in communication between various brain regions in its implementation in the brain. Although little is at present known about the role such neural oscillations might play, there is a considerable amount of information available about their role in other perceptual and cognitive processes.

1.4 The Role of Neural Oscillations

Beyond hemodynamic neuroimaging and standard ERP methods in the investigation of functional brain activity, EEG and MEG offer the promise of being able to analyze neural oscillatory activity at specific frequencies. However, very few studies have analyzed neural oscillations with regard to word reading. When analyzing oscillatory dynamics, a few parameters are considered at any given time point: the signal's frequency, amplitude, and (instantaneous) phase.

Frequency refers to the number of cycles per second in the sinusoidal or narrow band signal, measured in Hertz (Hz), while phase refers to a given position in a cycle. For example, a 5 Hz signal contains five 200 millisecond cycles per second. From start to finish, a cycle starts with a phase angle of 0 degrees and is complete at 360 degrees, where it begins anew.

A raw EEG signal may be decomposed to further examine the component frequencies embedded within it. Based on almost a century of EEG research, a family of frequency bands has been classified, with each band pertaining to a facet of cognitive processing. EEG and MEG have revealed relevant cognitive processing within the frequency range of 1-100 Hz, although more invasive intracranial electrodes have shown activity upwards of ~200 Hz (Fries, 2009).

Whether observing a raw, broadband signal or the signal at an individual frequency, the amplitude is the power of those oscillations and is the result of the compounded, synchronous activity of millions of neurons. This activity is not produced by the action potentials of those neurons, but rather by the excitatory and inhibitory post-synaptic potentials at the neuronal dendrites. When discussing ‘local’ or ‘intra-regional’ fluctuations in spectral power, these synchronous post synaptic potentials are precisely the neural processes at play. In the case of EEG, which is known to have poor spatial resolution, ‘local’ generally refers to a cortical patch approximately 2 centimeters in diameter, although modern source localization techniques greatly aid in specifying more narrow regions. ‘Inter-regional’ or ‘long-distance’ synchronous activity refers to interactions between regions more than 2 centimeters apart, often when discussing functional connectivity between two brain areas of interest, as in the case of phase synchrony.

Phase synchrony (also referred to as phase locking or phase coherence) has repeatedly been suggested to be the mechanism by which transient functional networks emerge and dissolve as needed to accomplish elementary cognitive processes (Fries, 2005; Varela et al., 2001). According to this framework, local neural assemblies may oscillate in such a way that capitalizes on the time window in which messages may be sent and received. Doesburg et al. (2009) elaborate: “...synchronization enables transient functional integration between specific neural groups as bursts of action potentials are consistently exchanged during the depolarized phase of

the receiving neurons' ongoing membrane potential fluctuations, thereby enhancing communication between populations oscillating in synchrony.”

Communication through synchrony is specific and short-lived, lasting just long enough for one site to exchange information with another. In fact, the constraining of synchrony prevents the global phase-locking found in epilepsy, in which the cascading of neural communication is left unregulated and is in direct conflict with normal cognitive processing.

The recent explosion of research investigating oscillatory dynamics in the brain has revealed patterns of local activity and long-distance connectivity at specific frequency bands, each of which pertain to fundamental aspects of cognitive and neural processes.

1.4.1 Theta

The theta (3-7 Hz) frequency band, whose source has been attributed primarily to the hippocampus, among other subcortical structures, has been shown to play a role in memory processes. For example, theta phase in the rat hippocampus influences the coding of place, in addition to affecting neural plasticity and long-term potentiation (Kahana et al., 2001). In humans, theta power increases have been observed in a variety of memory tasks, such as encoding (Sederberg et al, 2003), episodic memory processing (Klimesch et al., 2001), and holding items in working memory (Ward, 2003). Theta power also plays a large part in perception, as much of perception involves identification and categorization processes, which require interfacing with memory networks. For example, theta power increases in the left temporal lobe when accessing lexico-semantic information in response to written words (Bastiaansen et al., 2005). In a MEG study, monolingual English and bilingual English/Chinese (Mandarin) readers showed theta bursts in right STG between 100-300 ms after reading words

written in their native language. Theta activity was seen in the left STG, but occurred between 0-450 ms after word presentation for native English speakers, and 0-200 ms for native Chinese speakers.

This perceptual theta response is not, however, restricted to the visual modality. In a study of haptic object identification, theta power in participants' temporo-parietal cortex increased as a function of time spent identifying the object (Grunwald et al., 2000).

Long distance phase synchrony in the theta band shows similar patterns, independent of local theta power. Sauseng and colleagues (2005) found that during a visual working memory task, phase locking between anterior and posterior cortices increased as executive function demands increased in a working memory task, while local theta power showed no differentiation.

1.4.2 Alpha

Until recently, alpha band activity (8-13 Hz) was thought to reflect a cortical 'idling' (Palva and Palva, 2007; Ward, 2003), an idea stemming from the early recordings by Hans Berger in the 1930s in which alpha power was largest when participants were in a relaxed state, and waned in times of increased task demands. However, there is now growing evidence that alpha activity actually represents selective inhibition or constraining of activity, particularly with regard to attentional processing (Klimesch, 1999; Palva and Palva, 2007). Doesburg et al. (2009) detail an additional dimension to this position, reporting that alpha oscillations may serve an inhibitory role at the local level, but inter-regional alpha synchrony actually acts to facilitate visuo-spatial attentional processing.

1.4.3 Gamma

The gamma frequency band (30+ Hz) has received much attention since the pioneering work by Singer, Gray, and colleagues on the cat visual cortex (Sauseng and Klimesch, 2008). The role of gamma rhythms in the brain is still a controversial and uncertain topic, however. Gamma oscillations have been extensively associated with visual awareness (Ward, 2003), perceptual binding (Tallon-Baudry et al., 1996), and consciousness (Dehaene and Nachacche, 2000), Doesburg et al., 2009). Fries (2009) has hypothesized that gamma synchrony acts as a general process in the integration of information in the cortex, and does not necessarily subserve any particular cognitive agenda. As such, it is unclear how to interpret the few results found in studies of word reading and gamma band activity.

A recent study using intracranial EEG revealed a pattern of increased gamma band activity in a posterior-anterior direction in the left hemisphere (Mainy et al., 2007) during word reading. According to these results, a burst of gamma activity occurs in the VWFA at ~150 ms, followed by increased gamma power at semantic and phonological areas at ~400 ms. The spatiotemporal evolution of gamma power following the presentation of visual word forms suggests an important role for gamma oscillations in the propagation of the reading signal.

1.5 Reading network connectivity

Despite the growing popularity of the study of neural oscillations, both local and long-distant, in the investigation of cognitive processes, their role in word reading has been desperately understudied. The current understanding of how information is transmitted among brain regions during reading is minimal and comes primarily from the inferences made by examining patterns of activation of localized sources rather than objective measures of

connectivity. For example, using MEG, Marinkovic et al. (2003) show a clear pattern of activation starting in early visual cortex in the occipital lobe, which rapidly sweeps across the left hemisphere through the temporal lobe and ultimately to language centers in the inferior frontal lobe. From results like these, it is clear that the signal is propagated from region to region, however, it remains unknown just *how* these transitions occur, and how these areas are sharing information.

Equipped with an understanding of where these activations are occurring, it is paramount that we investigate how they interact and share information as doing so could not only elucidate the underpinnings of how the reading signal is propagated over time, but could also clarify how reading disorders (e.g. certain types of dyslexia) occur and potentially how to treat them.

The present study used high-density EEG to examine oscillatory dynamics, including functional and effective connectivity, during a word reading task. A series of hypotheses was tested. First, we tested the viability of independent component analysis and dipole fitting to locate neural sources that have been previously identified by fMRI and PET studies. Then, phase synchrony was employed to calculate the degree of functional connectivity between pairs of cortical sites during word reading. We hypothesized that connectivity would follow established patterns of activation (Marinkovic et al., 2003), and would occur in the theta and gamma frequency bands, beginning in the posterior sensory cortices and gradually progressing to more anterior, high-level language centers. Additionally, it was expected that the VWFA would play a crucial role as a central hub, linking low-level visual systems to high-level language areas. Lastly, in order to assess the causal influence of one brain site on another, transfer entropy analysis was used. Our hypothesis again was that the flow of information would originate from early sensory areas, and propagate to more anterior regions.

2 Methods

2.1 Participants

Fifteen right-handed volunteers (10 male) attending UBC, aged 18-35 years (mean age 22, SD 4.26 years), were paid to participate. The experiment was approved by the Behavioural Research Ethics Board of the University of British Columbia, and all participants provided written consent. All participants indicated English as their first and primary language, and no histories of neurological, learning, or reading disorders or dysfunctions were reported during a prescreening interview. All participants had normal or corrected-to-normal vision. Additionally, all participants indicated hand preference with the Edinburgh Handedness Inventory (Oldfield, 1971).

2.2 Stimuli and Procedure

Participants were instructed to observe a sequence of three individual letters, followed by a three-letter word. The participants' task was to respond on a keyboard as to whether or not the word that appeared match the sequence that came before it. All letter sequences and words were three letters long, and were sourced from a pool of 456 possible words. Each trial had a 50% chance to be either a match or non-match trial. Figure 2.1 shows a schematic of the task. The font used was 65-point Times New Roman and the font color was white on a black background. In addition to the standard task instructions, participants were urged to read the entire word that appeared after the sequence, as some of the letters would occasionally appear in both the sequence and the word, but would still be a non-match (e.g. C-A-R and CAN). These instructions were given to deter participants from simply comparing the forms of the shapes on the screen instead of actually reading the words. Participants went through a practice session of ten trials prior to the real task and were offered extra practice trials if needed (no one needed

extra practice). Trials began with a fixation cross for 1000 ms, followed by each of three letters being presented for 100 ms, with a 900 ms inter-stimulus interval. Finally a three letter word appeared, at which point the participant was required to respond. The word remained on the screen for 1500 ms. Trials were separated by a 900 ms inter-trial interval and a 30 s break was given after each 50-trial block.

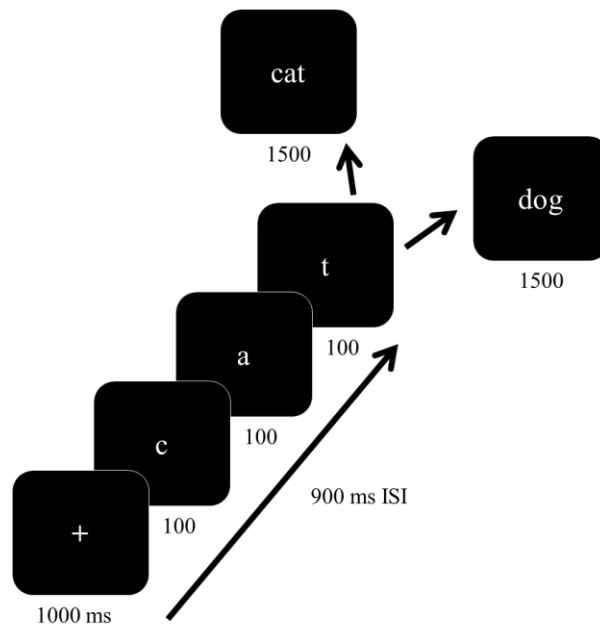


Figure 2.1. A schematic of the stimulus presentation and task. After a three letter sequence is presented, volunteers must respond as quickly as possible as to whether or not the word that appears matches the sequence that came before it.

2.3 EEG Acquisition

EEGs were recorded from 60 passive electrodes in a standard electrode cap (Electro-cap, Inc., Eaton, OH, USA) at equidistantly-spaced locations based on the International 10–10 System, referenced to the mastoids with the ground at AFz. Data were sampled at 500 Hz through an analog pass band of 0.01–100 Hz (SA Instrumentation, San Diego, CA, USA). Eye

muscle activity was recorded by electrooculogram (EOG) from four periocular electrodes. All electrode impedances were kept below 10 k Ω .

2.4 EEG Data Analysis

Prior to analysis, all signals were re-referenced to an average reference, resampled to 250 Hz, and digitally high-pass filtered at 1 Hz using EEGLAB software (Delorme and Makeig, 2004), an open source MATLAB toolkit (MathWorks, Natick, USA), and custom scripts. First, the continuous data were epoched into 6 second bins time-locked to the presentation of the word. The epochs capture 4 seconds before, and 2 seconds after, word presentation. Epoching was performed in order to contain only the relevant processing associated with the task (letter and word processing), and not the inter-trial activity, or the activity occurring during breaks between blocks so as not to introduce extraneous noise into the Independent Component Analysis.

2.4.1 Independent Component Analysis

Independent Component Analysis (ICA) was then performed on these epochs using EEGLab's *runica* function. ICA is a method of blind source separation which takes into account the information from all channels, and then produces an equal number of statistically maximally-independent signals, termed independent components (ICs), free of the volume conduction that convolutes the raw scalp EEG. These new 'virtual channels' are essentially information sources that, when mixed (via volume conduction), produce the original scalp data. The brain sources of the ICs were then localized using EEGLab dipole fitting algorithms.

2.4.2 Dipole Fitting (Source Localization)

The sources of the ICs were found using the *Dipfit* algorithms in EEGLab. Electrode sites were co-registered to the Montreal Neurological Institute (MNI) average brain, allowing for Talairach

coordinates to be produced for the IC dipoles. Dipoles sourced outside of the brain were rejected as artifacts, and only dipoles with less than 15% residual variance were considered for further analysis. Importantly, the subsequent spectral power and connectivity analyses were performed on the ICs themselves, and not on dipole activations. The dipoles only serve as a tool for interpretation of the IC activity, but have no bearing on the other analyses.

2.4.3 Dipole Clustering

Cluster analysis was conducted to identify common brain sources across subjects on all subjects' dipoles based on Talairach locations in the brain, such that each cluster contained potentially multiple dipoles across subjects depending on their proximity to each other. Twenty-five clusters were fitted composed from a total of 442 dipoles using EEGLab's *k*-means clustering algorithm. Essentially this method places *k* (in this case $k=25$) random seeds as cluster centroids. Each IC is then assigned to the nearest centroid. The centroids are then recalculated. Again, the IC's are assigned to the nearest centroid, and this loop is repeated until the centroids no longer shift. This method is meant to minimize the intra-cluster distances while maximizing the inter-cluster distances. Once clusters were established, they were pruned to contain only the most representative IC from each participant. Pruning generally consisted of choosing the IC in closest proximity to the centroid and with the lowest residual variance, although more ambiguous cases warranted examination of scalp maps and ERPs to determine inclusion of one IC over another.

Wavelet analysis was performed on the ICs, decomposing the broadband signals into their component frequencies. Specifically, a Morlet wavelet analysis on each IC time series yielded wavelet coefficients of the sinusoidal oscillation between 1 and 50 Hz, from which amplitude (power) and phase at each time point were computed to be used in computing event-related spectral perturbation and phase synchrony analyses.

2.4.4 Event related spectral perturbation

Measures of event-related spectral perturbation (ERSP) were computed by performing a time-frequency decomposition on the retained ICs of the clusters of interest. ERSPs indicate the level of intra-regional synchrony over the span of the epoch, allowing us to observe fluctuations in oscillatory power, between 2-50 Hz, over time, relative to a baseline (-250 to -50 ms before the presentation of the first letter of a trial). All ERSPs were computed at a significance threshold of $p < .01$ by EEGLab's permutation test.

2.4.5 Phase Synchrony

Phase synchrony analyses were conducted in order to assess inter-regional functional connectivity, or the degree to which two brain areas are sharing information. This is done by computing the phase-locking values (PLVs) between channels of data, each corresponding to an IC, and thus, to a brain region. PLV's are computed using the following formula from Delorme and Makeig (2004):

$$CC_{1,2}(f, t) = 1/N \sum_{k=1}^N \frac{W_{1,k}(f, t)W_{2,k}^*(f, t)}{|W_{1,k}(f, t)W_{2,k}(f, t)|}$$

where $W_{i,k}(f,t)$ are the wavelet coefficients for each time point, t , and frequency point, f , for each IC, i , and $k=1$ to N is the index of trials. The PLVs produced by these computations are indicators of the degree of constancy of the phase differences between signals. PLVs range from 0 to 1, where 0 indicates the absence of any phase locking, and 1 indicates perfect phase locking, such that the phase difference between two channels at a given time point remains constant

across all trials. Figure 2.2 graphically illustrates the conceptual basis of phase synchrony and PLVs.

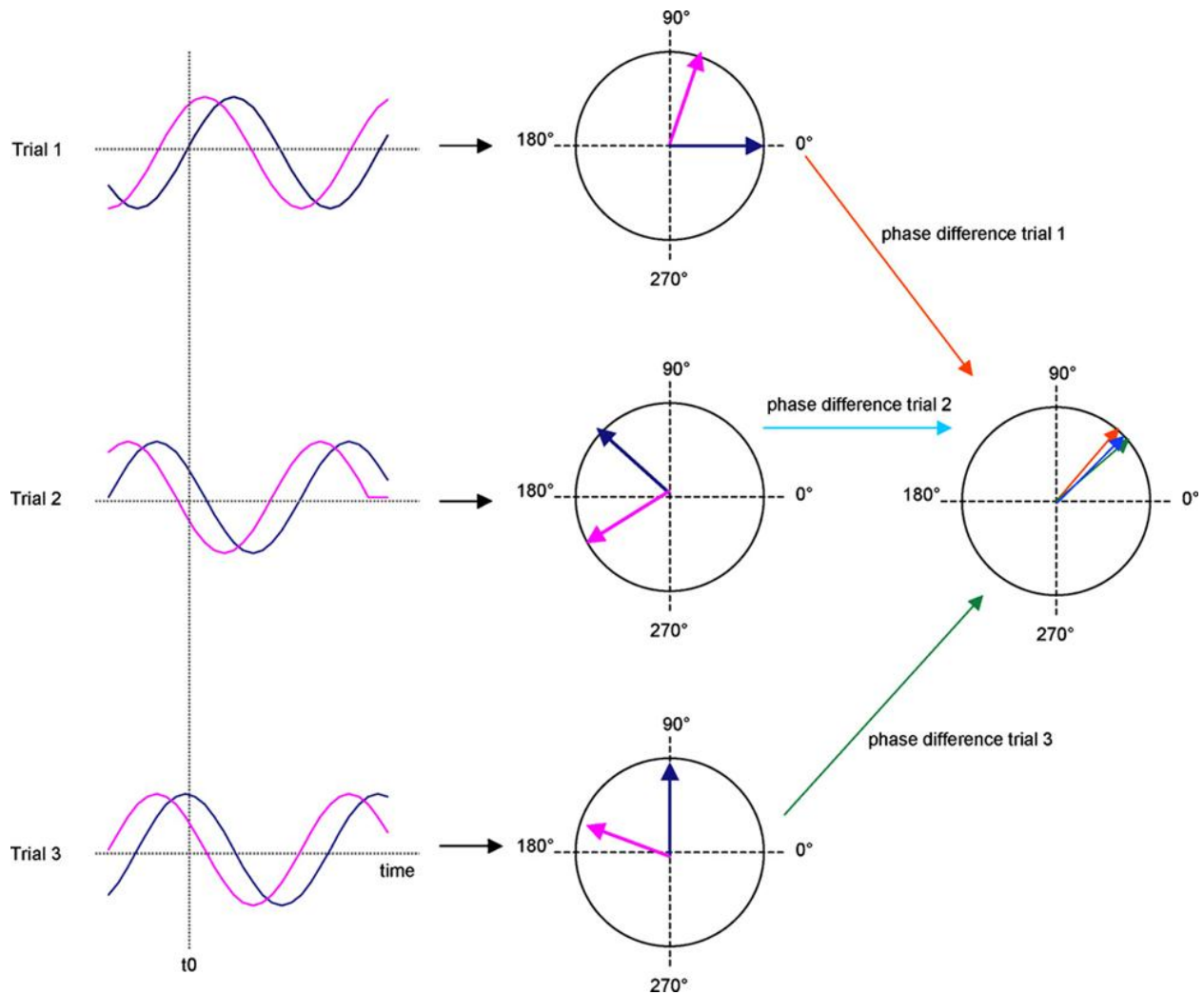


Figure 2.2. Constancy of phase difference and PLVs. The phase lag between the two channels (from two brain regions) in this time window remains essentially the same across all trials. This will produce a larger phase locking value, which has been shown to indicate a functional relationship between the sources of those two channels. Adapted from “What does phase information of oscillatory brain activity tell us about cognitive processes?,” by Sauseng and

Klimesch, 2008, *Neuroscience & Biobehavioral Reviews*, 32(5), 1001-13. Copyright 2008 Elsevier Ltd. Adapted with permission.

PLVs were computed on each pair of component clusters by identifying the ICs from subjects common to both clusters. Permutation statistics (Maris and Oostenveld, 2007) were used, constructing a surrogate distribution (N=200 permutations) from which to compare the obtained PLVs. Only PLVs significant at $p < .005$ were considered valid. This was performed for each subject in each component cluster. The PLVs from each cluster were then averaged across subjects to obtain the final measures.

2.4.6 Transfer Entropy

While measures of functional connectivity show which brain areas are engaged and sharing information, these measures do not indicate a causal flow of the information. That is, a measure such as phase synchrony cannot show us which site is *sending* the information, and which site is *receiving* the information, or if a bi-directional relationship exists. In order to understand such relationships, effective (causal) connectivity analyses must be employed. One such analysis that is commonly used is Granger causality, or variants thereof. However, a disadvantage of this method is that it assumes, *a priori*, a linear model of the interaction between neural sources (Wibral et al., 2011). A linear model may become problematic when trying to determine causal relations in a highly non-linear system such as the brain. For this reason, we have adopted a recent technique called transfer entropy, as it can determine causal interactions without needing to specify a model *a priori* (Schreiber, 2000; Vicente et al., 2011).

3 Results

3.1 Behavioral Performance

Volunteers were required to respond as to whether or not the word matched the letter sequence that preceded it. Subjects completed the task with a mean accuracy of 96.0%. Of the correct trials, participants showed no significant difference in reaction times between the match ($M = 532$, $SD = 140$) and non-match ($M = 546$, $SD = 161$) trials, $t(14) = -1.04$, $p = .32$. Match and non-match trials were then collapsed for all analyses of brain activity.

3.2 Localization of Active Brain Regions

ICA and dipole fitting were used to identify neural sources of activity within subjects. Cluster analysis was then used to group valid ICs in order to identify which active brain regions were common across subjects. Table 3.1 summarizes the details of each cluster. Figure 3.1 illustrates the scalp maps for each component cluster at a site relevant to word reading, while Figure 3.2 shows selected dipoles in three-dimensional Talairach space.

Table 3.1 Dipole cluster properties (reading ROIs in bold)

Cluster Brain Region*	Talairach Coordinates			BA	RV%	No. of Subjects Contributing
	x	y	z			
Wernicke's/AG	-39 ± 9	-52 ± 12	22 ± 8	39/22	4.4	12/15
Ventral ACC	8 ± 10	6 ± 7	33 ± 11	24	5.54	9/15
Right Inf. Occ-Temp	62 ± 7	-52 ± 9	-2 ± 10	37/21	5.02	11/15
Dorsal PCC	1 ± 7	-39 ± 8	27 ± 9	31	5.77	11/15
Right STG/MTG	56 ± 6	-17 ± 5	-3 ± 6	22/21	1.82	8/15
Left V3	-37 ± 9	-78 ± 10	4 ± 11	19	3.62	11/15
Left IFG	-57 ± 5	25 ± 10	-7 ± 10	47	4.69	7/15
Right IFG	45 ± 13	36 ± 5	-16 ± 10	47/11	5.09	7/15
Somatosensory Cortex	6 ± 8	-62 ± 7	41 ± 7	7	4.48	8/15
Broca's Area	-57 ± 11	10 ± 6	23 ± 11	45/44/9	4.5	9/15
Right Dorsal PCC	23 ± 6	-47 ± 10	22 ± 12	31	3.43	10/15
Right V2	30 ± 6	-82 ± 13	3 ± 8	18	3.95	10/15
VWFA	-62 ± 12	-50 ± 11	-5 ± 8	21/37	6.43	9/15
Left STG/A1	-71 ± 3	-22 ± 9	8 ± 10	22/42	5.03	11/15

BA Brodmann Area; **RV** residual variance (percent not accounted for by dipole); **AG** angular gyrus; **ACC** anterior cingulate cortex; **PCC** posterior cingulate cortex; **STG** superior temporal gyrus; **MTG** middle temporal gyrus; **V3** extrastriate visual cortex; **IFG** inferior frontal gyrus; **V2** extrastriate visual cortex; **VWFA** visual word form area; **A1** primary auditory cortex. *Regional locations based on centroid mean, not all ICs within a cluster fall within a region.

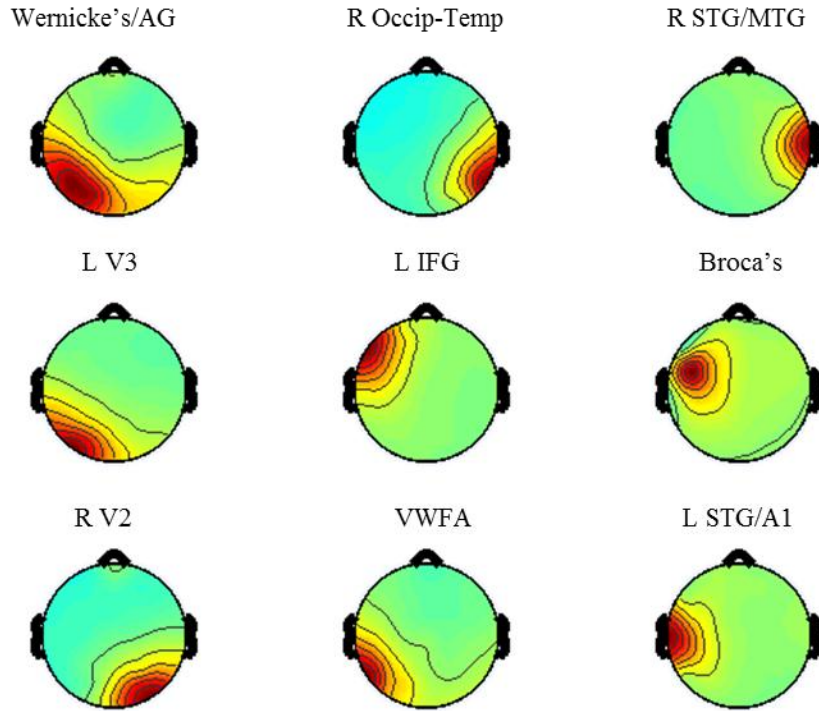


Figure 3.1. Averaged scalp maps for component clusters. Importantly, these scalp maps clearly depict single dipole sources, as expected from ICA (Delorme et al., 2012), affording us the interpretation that these locations represent compact cortical generators of activity. These single dipole maps are apparent at the subject level as well. The ERP localized to the VWFA dipole cluster showed a negative peak at ~170 ms (N170), considered a trademark electrophysiological response to categorical processing, such as word and face processing. This result lends credence to the localization techniques used here.

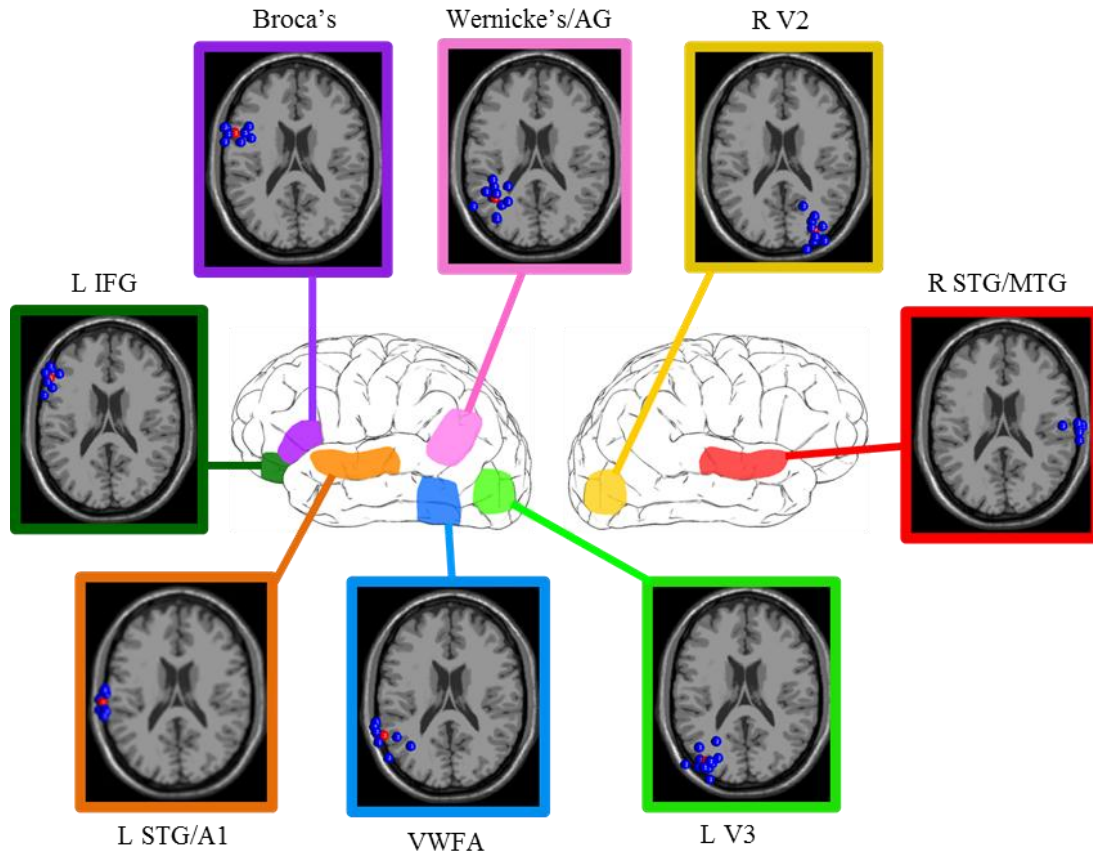


Figure 3.2. Selected dipole clusters in three-dimensional Talairach space. Individual subjects are represented by blue dots; red dots are the cluster centroids.

3.3 ERP from VWFA

Figure 3.3 shows the ERP generated by the centroid of the VWFA cluster. As does the fusiform face area for faces (Kanwisher and Yovel, 2006), the VWFA generates an ERP component called the N170 when a reader is exposed visually to a standard word. As can be seen from the figure, a standard N170 (Tarkiainen, et al., 2002) is generated by the centroid IC of the VWFA dipole cluster, verifying that this is indeed the VWFA prominent in fMRI and PET studies.

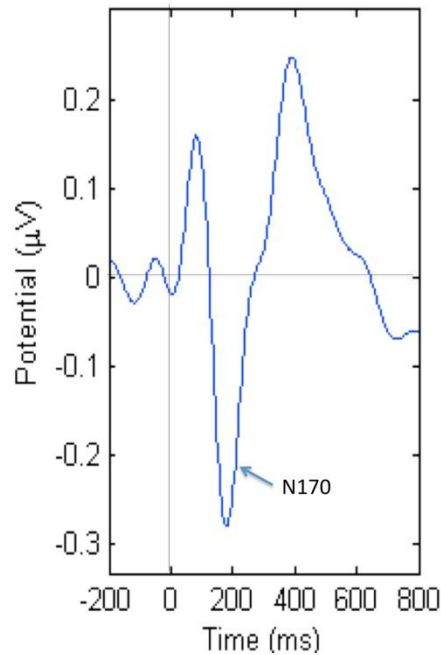


Figure 3.3. N170 generated by the centroid IC of the VWFA dipole cluster.

3.4 ERSP

Figure 3.4 shows the results of the ERSP analysis for the VWFA. This is representative of all of the brain regions, although the precise details vary. It can be seen that most of the power changes occur in the theta band (3-7 Hz) of frequencies. There is a “theta burst” shortly after the presentation of each letter, and after the presentation of the comparison word, as predicted. Gamma activity occurs also around the presentation of each letter and the word. Alpha (8-13 Hz) depression is also observed after each letter and more strikingly after the word presentation. Finally, there is a burst of beta activity around the time of the response. All of these activities are consistent with expectations based on previous studies.

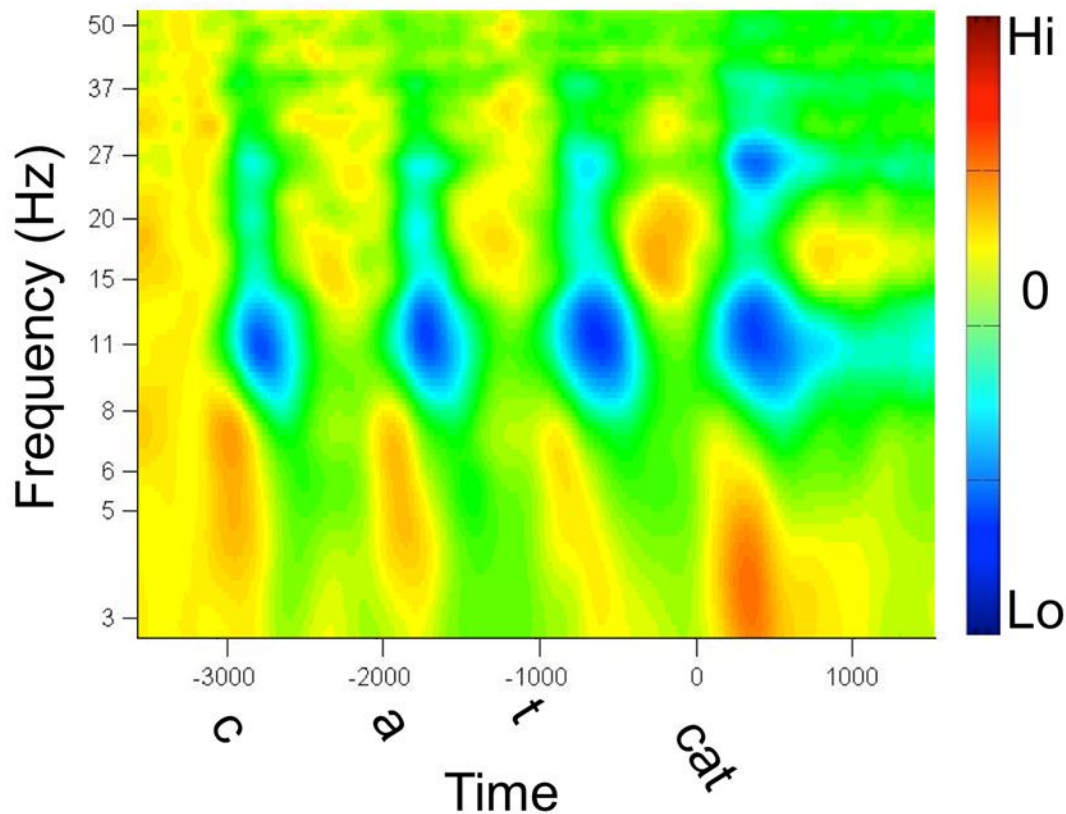


Figure 3.4. Average ERSP for the VWFA in dB with respect to a baseline from -250 to -50 before the presentation of the first letter.

3.5 Phase Synchrony

Measures of phase synchrony were computed on pairs of IC clusters to determine the degree of functional connectivity between them at specified frequency bands. Analyses reveal diffuse global connectivity in the theta band, showing extensive inter-hemispheric engagement as well as connectivity within the left hemisphere. Inspection of VWFA theta band connectivity over time shows widespread connectivity across the entire left hemisphere and with key regions in the right hemisphere. Figure 3.5 illustrates the temporal evolution of VWFA theta band phase synchronization with other areas. Noteworthy theta connectivity involving the right STG was

observed beginning immediately (<50 ms) following stimulus presentation, engaging with additional left-hemispheric regions, and then abruptly dropping after 550 ms post-stimulus, as pictured in Figure 3.6.

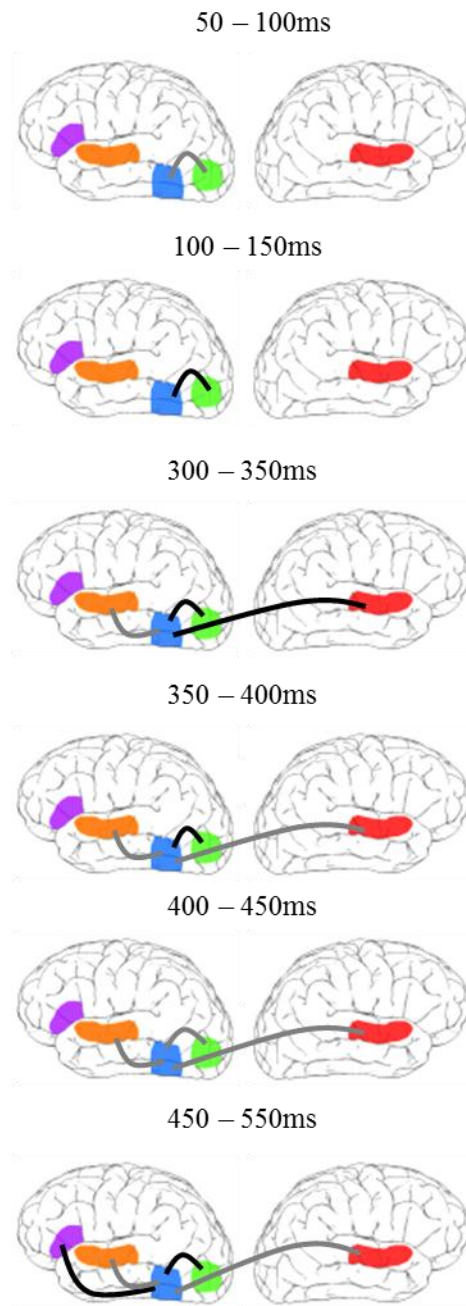


Figure 3.5. Theta band synchrony (lines) involving the VWFA evolving over the course of viewing a word. All raw PLVs were significant at $p < .005$ by permutation test. The results

shown here are either 2 (gray lines) or 3 (black lines) standard deviations above the pre-stimulus baseline. Each line represents a cluster pair containing at least 7 participants.

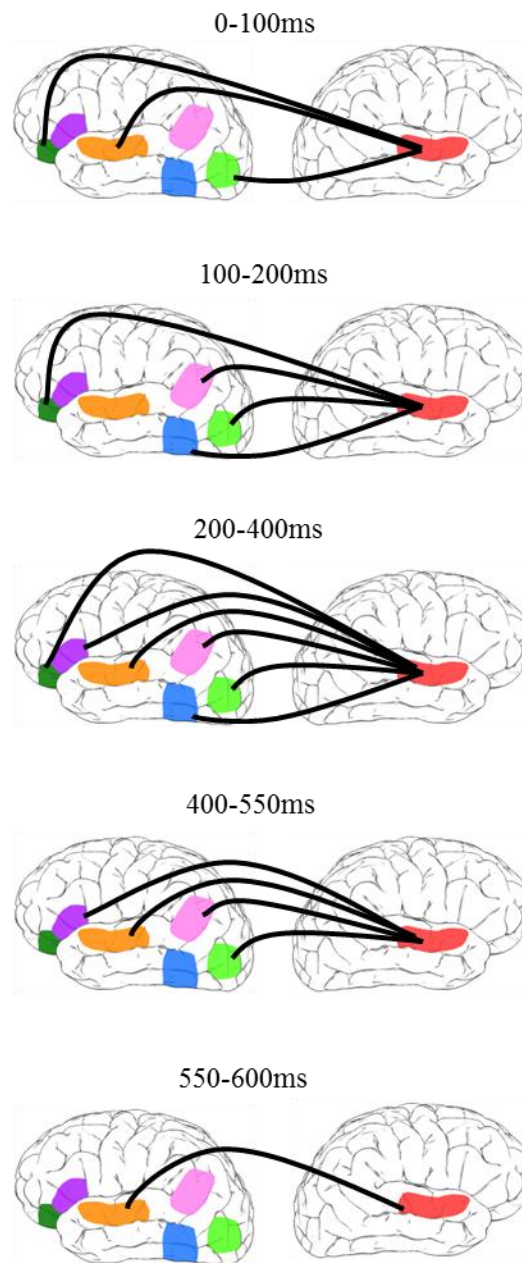


Figure 3.6. Right STG theta synchrony (black lines) with the reading network over the course of viewing a word. All raw PLVs were significant at $p < .005$ by permutation test. The results shown here are 3 standard deviations above the pre-stimulus baseline. Each line represents a cluster pair containing at least 7 participants.

Gamma-band synchrony was distributed predominantly throughout the left hemisphere, save for the occasional inter-hemispheric engagement involving right occipital cortex (see Figure 3.7).

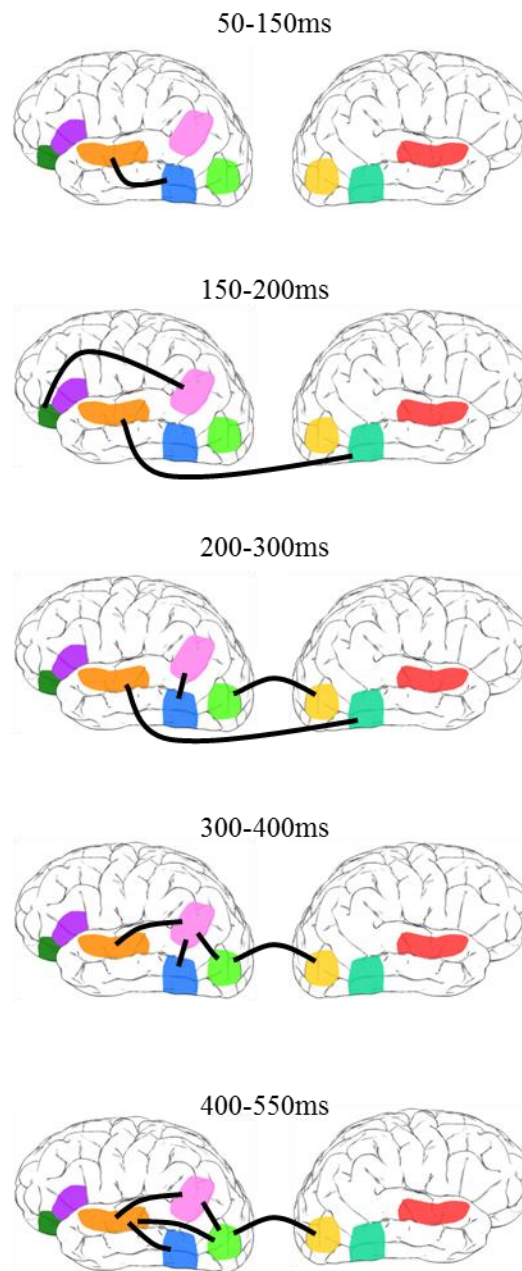


Figure 3.7. Gamma phase synchrony in response to word reading. Whereas results show clear gamma synchrony between many cortical sites in the reading network, the temporal evolution of the connectivity appears less uniform and regular than, for example, the theta band activity reported above. All raw PLVs were significant at $p < .005$ by permutation test.

3.6 Transfer Entropy

In order to understand the causal relationships between cortical sites in response to viewing a word, transfer entropy algorithms were employed, allowing us to determine the directionality of the connectivity, adding a layer understanding to the network dynamics. Transfer entropy measures were computed between the VWFA and other relevant regions in the left hemisphere, including early visual cortex, left STG and Broca's area, in addition to the right STG. Results show the VWFA as being a source of information transfer, as well as receiving information from other sites (see Figure 3.8). Widespread bidirectional connectivity involving the VWFA is seen shortly after word presentation, notably with both high-level language centers, and low-level perceptual areas. At ~300 ms, the VWFA is engaged in bidirectional information flow with early visual cortex and left and right STG. Soon after, at ~350 ms, the VWFA begins to send information to Broca's area, and at ~400 ms, the VWFA and left STG cease to exchange information. At ~450 ms, the VWFA ceases to send information to right STG, while still receiving feedback from the site. At this time, the VWFA is no longer receiving information from early visual cortex, though the VWFA is still sending feedback to lower level visual areas.

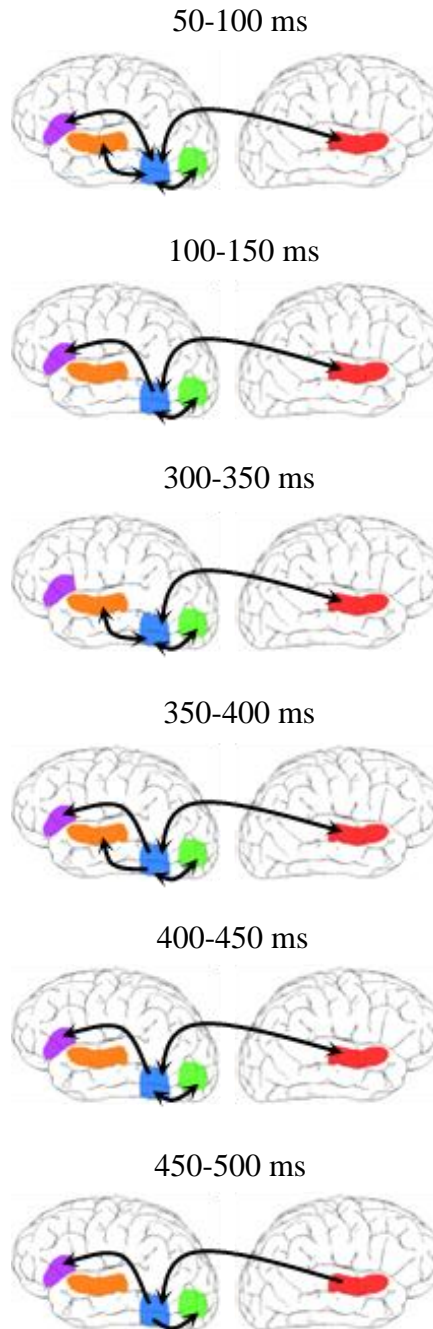


Figure 3.8. Effective (causal) brain connectivity in word reading. Transfer entropy shows the causal information flow (black arrows) among selected sites during word reading. Results indicate a feed-forward sweep, with feedback following each propagation of the signal, consistent with a re-entrant processing account. Results reflect a group average. Each participant's result was significant at $p < .01$ by permutation test.

4 Discussion

In the present study, the cortical networks underlying word reading were examined. In particular, emphasis was placed on the role of oscillatory dynamics in network processes. With the aid of EEG source localization, a series of hypotheses was tested. First, we tested the viability of ICA and dipole fitting to locate neural sources that have been identified by neuroimaging studies. If the resulting locations converged on regions discussed in the literature, then connectivity analyses were conducted on the activity at those locations in the brain. Specifically, phase synchrony analysis was employed to calculate the degree of functional connectivity between pairs of cortical sites during word reading. Our hypothesis regarding theta synchrony was confirmed, while gamma synchrony also seemed to play a part in word form processing. The role of the VWFA as a focal point of the reading network was confirmed, as it engaged both with low-level sensory areas and with high-level language areas. Lastly, transfer entropy analysis was used in order to assess the causal influence of one brain site on another. Our hypothesis was partly confirmed, as the results show the flow of information originating from early sensory areas and propagating to more anterior regions. However, an additional element of top-down influence was also observed very early after stimulus presentation.

4.1 Source Localization

As expected, ICA and dipole fitting revealed neural sources that converge remarkably well with existing evidence (Jobard, 2003). Notably, the dipole fitting was able to identify a region in inferior temporo-occipital cortex, best represented as VWFA, which has consistently been shown to respond to orthographic stimuli (Dehaene, 2009). Additionally, semantic processing areas such as the right STG/MTG and a region composed of Wernicke's area and the

angular gyrus were found. With regard to grapho-phonological processing, the left STG, including primary auditory cortex, and Broca's area were established as neural sources. With these regions verified, we then conducted connectivity analyses.

4.2 Phase Synchrony

Our hypotheses concerning the temporal evolution of theta phase synchrony was confirmed. Indeed, theta synchrony emerged in posterior visual cortex, and cascaded to higher level areas over time. Synchrony at such low frequencies reflects the patterns of activation seen in ERPs, which is expected since low frequencies tend to dominate the ERP waveforms produced in the brain. As previously mentioned, theta oscillations have strong ties to memory systems, and so it makes sense that theta activity is present in a task that automatically retrieves semantic information from memory stores.

Gamma synchrony, while showing a less defined spatio-temporal pattern of emergence, still seems to play a role in word reading. In fact, phase synchrony between the angular gyrus and the VWFA occurred exclusively in the gamma band, perhaps indicating a role independent of the standard progression of activity.

Somewhat unexpected was the level of involvement from the right STG/MTG region, which showed widespread theta synchrony with almost all of the regions found in the left hemisphere at some point during word reading. The inclusion of the right STG/MTG area was expected to a certain extent for retrieval of semantic information. However, these results show functional connectivity to both sensory and language areas immediately after stimulus presentation (<100 ms). The exact role of this region beyond high-level language processing remains unclear.

4.3 Transfer Entropy

After functional relationships were established between brain areas using phase synchrony, transfer entropy was used to determine the causal flow of information in those relationships. So, rather than two areas simply engaging in the sharing of information, we aimed to determine the directionality of that information flow.

As expected, the VWFA was intricately involved in information transfer during word reading, reflecting the theta phase synchrony results. Interestingly, the transfer entropy results from ~300 ms onward show an initial bidirectional flow of information from each region to the next, followed by feedback signals being sent to lower areas, a phenomenon that has been termed ‘re-entrant processing,’ which indicates a sort of reverberation of perceptual processing (Di Lollo et al., 2000).

An unexpected result was the early (<200 ms) wide-spread causal connectivity, particularly between the VWFA and higher-level language areas such as left and right STG and Broca’s area. This makes sense, however, as participants may come to expect and anticipate features of the word they are asked to process, based on the sequence of letters they have just experienced. This anticipation and expectation can influence and constrain the processing at lower level areas.

4.4 Limitations and Future Research

A potential limitation of the study is that the task being used is not a ‘pure’ reading task, as it involves a fairly significant working memory component. Participants are required to hold up to three letters in mind and then make a comparison using those three letters. While this task

allows for the analysis of individual letter processing in addition to words, it simultaneously introduces potential concerns. It is highly unlikely that the observed local and long distance interactions are solely generated by attentional and executive processes. Rather, it is more likely the case that the observed interactions are in fact representative of reading processes, and the attentional and working memory aspects of the task serve to modulate the strength of those interactions. A simple remedy would be to use a standard lexical decision task, in which a letter string is presented—either a real or pseudo word—and ask participants to indicate whether or not the string is a real word. This type of task obviously involves reading, but also forgoes the need to maintain items in short-term storage.

Another potential limitation in this study concerns the number of letters in each word. Being that all of the words were three letter strings, it is possible that the stimuli were too simple to reveal neural activity that would otherwise be prominent as a result of complex words. As an exploratory study, it was paramount that the task be as simple and accessible as possible, with the possibility of using it for developmental populations, as well. Now, with a better understanding of network connectivity at the current 3-letter implementation, it would certainly be interesting and informative to see how the network interactions evolve as a function of word complexity.

4.5 Conclusion

Results presented here clearly confirm a number of propositions. First, EEG and source localization techniques can yield neural sources for word reading that converge with existing neuroimaging results. Additionally, phase synchrony and transfer entropy analyses confirm a diffuse network of regions that transiently interact and share information at cognitively relevant

time points. This study has documented the functional and causal connectivity one should find in a normal control subject. This catalog of connectivity may be used to compare against populations with specific learning or reading disorders or dysfunctions to uncover specific differences in connectivity between regions rather than broad differences in activity within a certain region.

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