Comprehending Comprehension: Insights from Neuronal Oscillations on the Neuronal Basis of Language Nietzsche H. L. Lam

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Nietzsche H. L. Lam

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The research presented in this thesis was performed at
the Donders Institute for Brain, Cognition and Behaviour, Donders Centre for Cognitive Neuroimaging, Radboud University Nijmegen, Netherlands.

Financial support for this research was provided by
the International Max Planck Research School (IMPRS) for Language Science - The IMPRS Fellowship - to Nietzsche H. L. Lam, and the Netherlands Organization for Scientific Research - the Spinoza Prize Award for the Language in Interaction Gravitation grant - to prof. dr. Peter Hagoort.

ISBN
978-90-76203-80-5

Cover Artwork
Design adapted by Nietzsche H. L. Lam,
Original design *Network Avatar series. Composition of human heads, lights and grids on the subject of science, artificial intelligence and technology*
Andrew Ostrovsky, https://www.shutterstock.com/g/agsandrew

Illustrations
The MOUS Series, Nietzsche H. L. Lam

Print
Ipskamp Printing, https://www.proefschriften.net/

Comprehending Comprehension: Insights from neuronal oscillations on the neuronal basis of language

Proefschrift

ter verkrijging van de graad van doctor
aan de Radboud Universiteit Nijmegen
op gezag van de rector magnificus prof. dr. J. H. J. M. van Krieken
volgens besluit van het college van decanen
in het openbaar te verdedigen op vrijdag 10 Februari 2017
om 10:30 uur precies

door

Nietzsche Ho Lok Lam
geboren op 31 Augustus 1989
te Hong Kong

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Prof. dr. Peter Hagoort

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GENERAL INTRODUCTION

The brain is estimated to be composed of 86 billion neurons (Azevedo et al., 2009), and together they orchestrate our thoughts, perception and behaviour. In particular, language is a remarkable and unique capacity that humans possess, an ability that showcases the impressive functions and capabilities of the brain. When it comes to comprehending language, the complexity of this process is often overshadowed by the apparent ease with which we read or listen. Consider how quickly and effortlessly you are able to derive meaning from a new sentence – words arranged in a combination that you have not previously seen or heard. Just how does your brain allow you to go from seeing scribbles on a page or listening to the vibrations of another person’s vocal chords to understanding the phrase “It is raining outside”?

1.1 Neuronal oscillations as a means to study brain function in the context of language processing

The study of neuronal oscillatory activity (also referred to as oscillations) has been useful in studying the properties and functions of the brain, and how the brain underlies behaviour. Over two decades of research has shown that the modulation of oscillatory activity relates to a wide range of processes such as attention, memory, motor preparation and awareness (e.g., Jensen, Kaiser, & Lachaux, 2007; Klimesch, Freunberger, & Sauseng, 2010; Klimesch, 2012; Lega, Jacobs, & Kahana, 2012; Schoffelen, Oostenveld, & Fries, 2005; Schoffelen, Poort, Oostenveld, & Fries, 2011; Schoffelen, Oostenveld, & Fries, 2008; Staudigl & Hanslmayr, 2013; van Ede, de Lange, Jensen, & Maris, 2011). Language processing is a higher order cognitive domain which draws on many other (lower level) domains such as vision, audition, attention and memory. As such, it involves a neural network distributed across the brain, consisting of multiple regions involved in supporting these specialized subprocesses. Yet, the precise nature of these individual neural regions and how they interact together are still not well understood. One way to study this would be to investigate the dynamics in neural oscillatory activity, which reflects local changes in ongoing brain activity. As there are but few studies on oscillations in the context of language, this thesis embodies the endeavour to use neuronal oscillations to illuminate the neurobiological mechanisms involved in sentence processing, as a small window into how the brain works.

Language processing at the sentence level

Language processing occurs at multiple levels, and a common division is made between the single word level and the sentence level. The abundance of language research focuses on processing below the sentence level (Hagoort & Indefrey, 2014), as evidenced by many models on, and research performed at, the lexical and sublexical level (Gaskell & Marslen-Wilson, 1997; Hickok & Poeppel, 2007; Kujala, Vartiainen, Laaksonen, & Salmelin, 2011; McQueen, Cutler, & Norris, 2006; Norris, 1994; Papoutsi, Stamatakis, Griffiths, Marslen-Wilson, & Tyler, 2011; Tyler & Cutler, 2009). With most research focusing on the processing of individual words, in order to obtain the full picture on language processing, we need to further our efforts in understanding how words are processed at the sentence level. The goal of this thesis is to use neuronal oscillations as an indicator of brain activity during sentence processing, and to address 4 diverse aspects of sentence processing, one in each of the content chapters:

1. Is low frequency oscillatory-speech entrainment a robust and reliable process in speech (in the form of sentences) perception?
2. Do oscillations really underlie entrainment, or might it be evoked-activity?
3. When reading, how does the sentence context influence the processing of individual words?
4. Can the *CNTNAP2* gene account for individual differences in reading sentences?

Largest data set on sentence processing

The data collected for this thesis, belongs to the largest multimodal imaging study on language processing – which we refer to as the Mother of all Unification Studies (MOUS). This study encompasses 204 participants who participated in two scanning sessions – one with Magnetoencephalography (MEG), and the other with functional Magnetic Resonance Imaging (fMRI) – while reading or listening to strings of words. In addition, a behavioural session was done to assess memory capacity and intelligence, and saliva was collected for genetic analysis. This thesis describes analysis results obtained from the MEG data that I acquired over a period of 32 months, with a focus on oscillatory activity in both the auditory and visual modalities.

Overview

To set the background for the experimental questions in this thesis, I will begin with an introduction to neuronal oscillations – how they arise and act as an index of neuronal activity. Then, I will elaborate on the characteristics of oscillations, their importance in helping us to understand the brain, and how they are measured. Subsequently, I will provide a brief background on the current state of our knowledge on the neurobiological infrastructure of language processing, as well as an overview of the methods used in the thesis to quantify neuronal oscillatory activity. The last section will outline how each subsequent chapter was designed to answer one of the 4 questions of this thesis.

1.2 Brief introduction to oscillatory neural activity

At the core of all brain processes is ‘communication’ – the coding and transmission of information between neurons. Neuronal oscillatory activity, measured at the level of the whole brain using Magnetoencephalography (MEG), provides a macroscopic, non-invasive perspective on neuronal activity and communication between groups of neurons (Hämäläinen, Hari, Ilmoniemi, Knuutila, & Lounasmaa, 1993)[1]. Oscillatory activity is present at various different frequencies and commonly divided into the following frequency bands: delta (1 – 3 Hz), theta (4 – 7 Hz), alpha (8 – 12 Hz), beta (13 – 30 Hz) and gamma (30 Hz and higher). These frequencies can occur in parallel, which suggests that neuronal groups which are active at different rates can occur simultaneously. Together, these dynamic patterns of interaction between neuronal groups are thought to provide a flexible manner for processing information (Fries, 2005, 2015; Varela, Lachaux, Rodriguez, & Martinerie, 2001).

Origins of oscillations

Oscillations, as picked up in the MEG (see next section for details), reflect rhythmic, synchronized synaptic input received by groups of pyramidal neurons. I will explain this briefly, and begin by introducing that at the core of neural information transmission is the electrochemical gradient that exists across the cell membrane of the neuron. This gradient produces a *membrane potential* i.e. a difference in voltage between the inside and outside of the cell.

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[1] The MEG signal can also be quantified in terms of event-related fields. These are averaged responses in the time domain that are strictly time-locked to events (Makeig, Debener, Onton, & Delorme, 2004; Tallon-baudry & Bertrand, 1999).

When the membrane potential of a neuron *depolarizes* (goes from a resting value of -70mV to -55mV) the neuron produces an *action potential* (taking the membrane potential to 40 mV) which is propagated along its axon (Fig. 1). At the end of the axon, this electric signal results in the release of neurotransmitters into the synaptic cleft. These neurotransmitters then bind to the receptors at the dendrites of the postsynaptic neuron, which causes a change in the membrane potential, producing a postsynaptic potential (PSP) (Fig. 1).

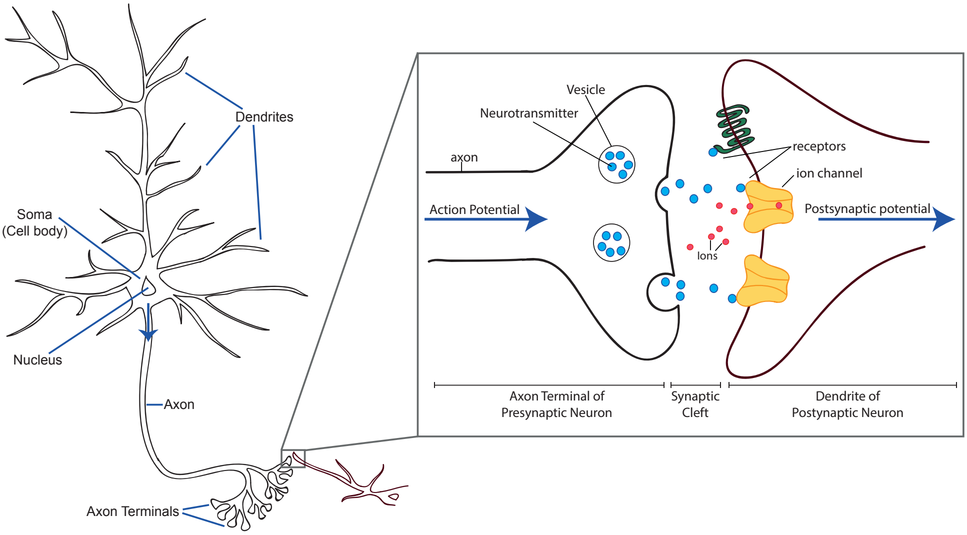

Fig. 1. *Left*, Pyramidal neuron. These neurons are found throughout the cerebral cortex and are the source of brain activity measured by MEG. Postsynaptic potentials are received at the dendrites. If a sufficient number of excitatory postsynaptic potentials are received, the neuron depolarizes and an action potential (nerve impulse) is propagate along the axon (in the direction indicate by the blue arrow) to the axon terminals. *Right*, Synaptic Cleft - signal (information) transmission between neurons. In the presynaptic neuron the action potential arrives at the axon terminal and leads to a vesicular release of neurotransmitters across the synaptic cleft. Neurotransmitters diffuse across the cleft and bind to the receptors on the dendrite of the postsynaptic neuron. This causes the opening of ion channels to allow an influx of (positive or negative) ions which leads to a postsynaptic potential.

PSPs can be inhibitory (IPSP), which lower the membrane potential, or excitatory (EPSP), which raise the membrane potential. Furthermore, PSPs are graded potentials, and can be combined spatially (if two PSPs occur close to each other) or temporally (close in time, one after another). If a sufficient amount of EPSPs are received (relative to IPSPs) this will lead to an action potential. When input arrives in a rhythmic pattern to a neuron, this causes a rhythmic sequence of PSPs. This rhythmic fluctuation in the membrane potential which indicates the neuron’s excitability – its likelihood to produce an action potential – is what the oscillatory signal reflects. Thus, oscillations measure the rhythmic input in groups of pyramidal neurons, which is an outcome of a series of excitatory and inhibitory signals between the interaction of pyramidal neurons and interneurons[2].

Aside from the cortex, the thalamus also plays a role in the generation, sustention, and adaptation of neuronal oscillations (Pulvermüller, 1996; Sherman, 2005, 2007; Steriade, 1999, 2006; Wang, 2010). This is possible via the afferent neurons connecting the thalamus and the cortex, known as the thalamo-cortico-thalamic loop. Early sleep studies on oscillations suggested that slow oscillations (< 1 Hz) are generated intracortically, but fast oscillations (20 – 60 Hz) are governed by corticothalamic interactions (Steriade, 1999, 2006). More recently, several mechanisms have been proposed on how alpha, theta and beta oscillations are generated via corticothalamic interactions (Hindriks & Putten, 2013; Ketz, Jensen, & Reilly, 2015; Rennie, Robinson, & Wright, 2002; Robinson et al., 2006), while other suggest that beta and gamma oscillations are generated intracortically, and only thereafter supported by thalamic input (Steriade, 2006).

In sum, MEG-derived oscillations provide a whole brain perspective on the emergent rhythmic patterns of activity, that result from local and long-range connections between neurons that are generated by the cortex and thalamus together. As oscillations capture how the firing activity of one group of neurons affects another, oscillations are argued to index the high degree of temporal control in brain activity. In turn, this had led to the proposal that information is encoded, transferred and integrated as function of neuronal firing patterns (Engel, Fries, & Singer, 2001; Fries, 2005, 2015; Varela et al., 2001). In support, oscillations have been implicated in various cognitive processes like perception, motor preparation and control, memory, and attention (Bonnefond & Jensen, 2012; Hoogenboom, Schoffelen, Oostenveld, Parkes, & Fries, 2006; Laaksonen, Kujala, Hultén, Liljeström, & Salmelin, 2012; Sauseng, Griesmayr, Freunberger, & Klimesch, 2010; Schoffelen et al., 2005, 2011).

Measuring oscillations with Magnetoencephalography (MEG)

Magnetoencephalography (MEG) is a safe and non-invasive technique that measures the activity of synchronized neuronal populations. Using a set of analysis procedures the characteristics of oscillatory activity (frequency, power and phase) from the signal can be extracted.This technique picks up the magnetic fields generated from the postsynaptic potential (PSP) of pyramidal neurons (Hämäläinen et al., 1993). When a PSP occurs at the apical dendrites, this causes a current to flow from the apical dendrites to the soma of the neuron, also known as the primary current. Due to charge conservation, to complete the current loop, there is a volume (secondary) current that goes from the apical dendrites to the soma, outside the cell (Gloor, 1985). According to Faraday's law each of these currents produces a magnetic field which is perpendicular to its current.

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[2] In the neocortex about 70 – 80% of the neurons are pyramidal neurons while 20 – 30% are interneurons. Most interneurons are inhibitory – they inhibit pyramidal neurons – and they come in variety of structure and configurations. The small amount of interneurons which are excitatory bare a resemblance to pyramidal neurons. For more details see Markram et al., 2004.

MEG is predominantly sensitive to the current from pyramidal neurons in the sulci because their dendrites are spatially aligned and perpendicular (tangentially orientated) to the cortical surface. With this orientation, the magnetic fields caused by the primary and volume currents do not cancel out, and can therefore be measured (Nunez & Silberstein, 2000; Nunez, 1986). In comparison the MEG is less sensitive to neurons in the gyri which are parallel (have a radial orientation) to the cortical surface (Cuffin & Cohen, 1979; Hämäläinen et al., 1993).

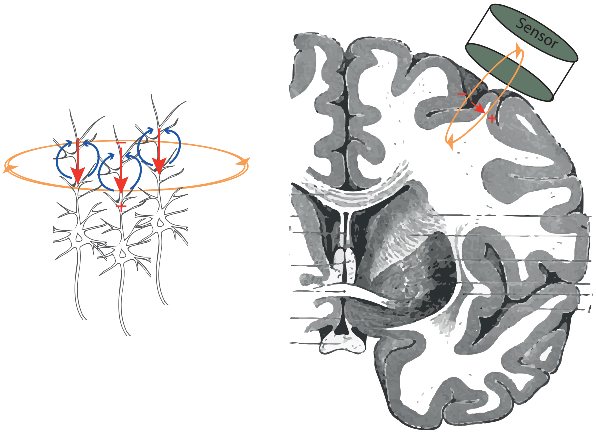


Fig 2. Schematic diagram of the generation of a brain signal. *Left,* Synchronized postsynaptic potentials from aligned pyramidal neurons will generate an electric current (red = primary, blue = volume) that can be measured extracranially. *Right,*These electric currents generate a magnetic field that can be measured with MEG.

The PSP of a single pyramidal neuron is very small. When 80,000 to 100,000 neurons synchronously receive input and produce PSPs, this cumulative signal is strong enough to be measured. As the magnetic fields from the brain are very small (around 10^{-12} Tesla, the earth's magnetic field is 10^{-5}), to be sensitive to these fields, the MEG system contains sensors (known as superconducting quantum interferences devices) that operate under very low temperatures (about -269 °C). These sensors are assembled in an array to form a helmet, which allows the magnetic signals to be sampled across surface of the brain. Furthermore, to prevent interference from other stronger magnetic fields, the MEG system is situated within a magnetically shielded room (Cohen, 1972; Hämäläinen et al., 1993).

Fig 3. MEG system. Participant sits in (adjustable) chair. Visual stimuli is presented on the screen and auditory stimuli via ear tubes (not shown in figure).

Characterizing oscillations

To study how the brain responds and processes information, we make use of the three characteristics of oscillations (Fig. 2). First, the *frequency* defines the number of oscillatory cycles per second; the higher the number of cycles, the higher the frequency. Second, the *amplitude*, or more commonly *power* (amplitude squared), describes the amount of energy in the oscillation, how strongly it is expressed. The third is *phase,* which describes the momentary location in an oscillatory cycle in degrees (or radians), relative to the origin of the oscillation.

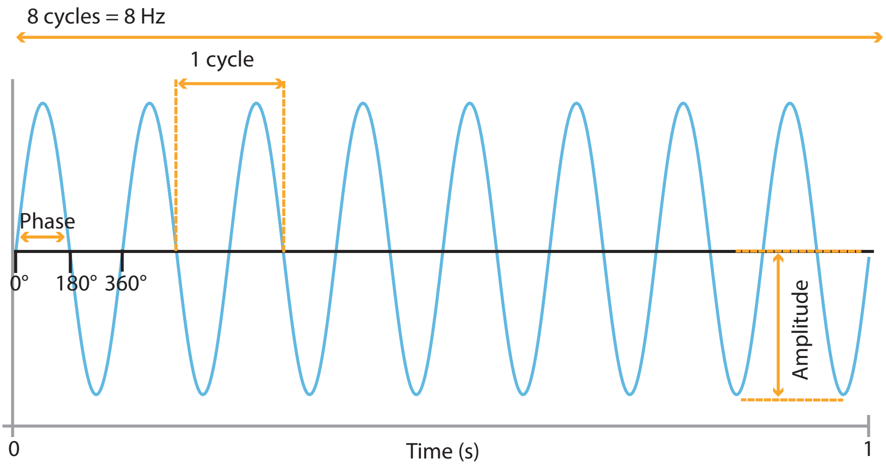


Fig 4. Features of an oscillation. Frequency, measured in Hertz, is the number of cycles per second in an oscillation. Amplitude is the fluctuation of the oscillation relative to its zero point, and describes the amount of energy in an oscillation. Phase is the momentary location in the oscillation, relative to its origin (0°).

Power is used to quantify synchronous activity of neurons within a local area (a defined patch of cortex of about 1 cm). Relative to an event (such as pressing a button or reading a word) a change in the strength of synchronicity can be observed. These changes are referred to as event-related desynchronization (ERD; Pfurtscheller & Aranibar, 1977) which is a relative decrease in a power, or an event-related synchronization (ERS; Pfurtscheller, 1992) which is a relative increase in power. In general, an ERS in the alpha and beta band are associated with a decrease in neural activity of a brain region, whereas in the gamma band it is associated with an increase in neural activity (Jensen & Mazaheri, 2010; Klimesch, Doppelmayr, Pachinger, & Russegger, 1997; Osipova et al., 2006). For the theta band, the relationship between the event-related synchronicity of neurons and overall local neural activity remains equivocal. For certain frequency band, specific proposals on the role of (de)synchronization have also been made. For instance, alpha oscillations (around 8 – 13 Hz) are proposed to inhibit neural regions not necessary for the task at hand in order to decrease distraction and allow for optimal task performance. Beta oscillations (around 13 – 30 Hz), most commonly observed in tasks involving motion (preparation) or attention, have been proposed to reflect whether the current cognitive or sensorimotor state is (expected to be) maintained or changed (Engel & Fries, 2010). These theories help to consolidate the many findings on oscillations, but they do not imply a one-to-one relationship between a particular frequency band and a cognitive process. Rather, the temporal nature of oscillatory changes relative to the task, the location(s) of the oscillation, and the presence of other frequencies, are all factors that contribute to understanding the function of oscillations. In chapters 3 and 4 of this thesis, I focus on measures of oscillatory power to understand how sentences are processed and whether oscillations can capture individual differences in this process.

Phase is used to quantify the relationship between two rhythmic signals, and in the context of brain function, phase can be used for two purposes. One is to quantify the coherence (degree of synchronization) in neural activity between two, distinct (distal) neuronal populations, whereby coherence is proposed to reflect the communication between regions (Fries, 2005, 2015). The other purpose is to determine whether neuronal oscillatory activity entrains (adapts its rhythm by synchronizing) to the rhythmic input in the environment, and in turn how this supports perception. Chapter 1 and 2 focus on measures of entrainment to investigate the perception of speech in the form of sentences, and in Chapter 6 I propose the potential of using coherence between neural regions to further the research in this thesis.

1.3 Neurobiology of language processing

Speech perception

Speech is a continuous stream of sounds, *whereovertimethewordsarejoinedtogetherlikethis.* In order to understand speech, listeners first need to identify and segment individual words. Children and adults alike make use of various cues in speech for segmentation such as the (rhythmic) stress information in syllables (e.g., Cutler, Mehler, Norris, & Seguí, 1992; Goyet, Schonen, & Nazzi, 2010; Roncaglia-denissen, Schmidt-Kassow, & Kotz, 2013; Sebastián-Gallés, Dupoux, Seguí, & Mehler, 1992; Vroomen, Tuomainen, & de Gelder, 1998), phonotactics (e.g., McQueen, 1998), and the transitional probability between syllables (e.g., Johnson & Tyler, 2010; Thompson & Newport, 2007). To understand how the brain supports speech perception, neuroimaging studies have shown the involvement of left inferior and middle frontal gyri and bilateral temporal lobes during perceptual and segmentation tasks (e.g., Hickok & Poeppel, 2007; Hickok, 2001; McNealy, Mazziotta, & Dapretto, 2006, 2010). Together, these studies provide ample evidence that syllables and phonemes are important tools for segmentation, but it is unclear how units of speech are identified and tracked.

The last decade has seen the rise of a popular proposal that neuronal oscillations are suited to support the early stages of auditory speech processing. As oscillations reflect the fluctuation in the excitability of neuronal populations, the synchronization of neural activity to external stimuli has been propose to allow for optimal processing of external input. This process is referred to as entrainment of neural rhythms (Ding & Simon, 2014; Giraud & Poeppel, 2012; Gross et al., 2013; Luo & Poeppel, 2007; Peelle & Davis, 2012; Poeppel, 2003).

The popularity of this idea is based on two premises. First, from an evolutionary perspective, the motor (articulatory) and auditory perception systems should have evolved in a way such that the rhythms produced can also be perceived (Giraud & Poeppel, 2012; Liberman & Mattingly, 1985; Liberman & Whalen, 2000). Second, speech is quasi-rhythmic, whereby prosodic, syllabic and phonemic patterns occur in a relatively predictable manner. From these premises, oscillations are proposed to synchronize with the rhythm of the speech envelope to make sure that important information e.g., the boundaries between syllables and phonemes, are tracked and sampled accurately, and within a time frame when neuronal populations are most suited (excited) for receiving information.

Although the cortical entrainment hypothesis is appealing, many aspects remain controversial. One concern is whether entrainment is driven predominantly by the acoustic cues e.g., the onset of a syllable or is it also modulated by top-down cognitive functions such as prediction and attention. Another question is the functional role of entrainment: Does it detect temporal features like speech edges (e.g., word onsets), discretize speech into syllables, or does it perhaps recombine already parsed speech features into meaningful segments (Ding & Simon, 2014)? Moreover, what are the neurobiological processes that give rise to entrainment? Are neuronal oscillations involved in the actual segmentation, or do they simply reflect the underlying process of doing so? And, of course, to challenge the core of the proposal, are we looking at true oscillatory activity, or are we merely observing a frequency domain representation of a tight temporal summation of evoked potentials in response to edges in the speech signal? In chapters 2 and 3, I further investigated the nature of neural entrainment to speech.

Sentence processing

When reading or listening to a sentence (in the visual or auditory domain), we perceive words one at a time. To understand a sentence, we need to retrieve our knowledge of each word from long term memory, maintain the perceived words in short term memory while we perceive the following ones, and to assemble the words into a meaningful whole (Hagoort, 2003, 2005, 2013). In parallel are other processes like attention and prediction to ensure that words are correctly perceived, retrieved, and that based on the context (earlier words in a sentence) we can apply certain constraints on what we expect the next word to be.

The majority of our knowledge on the neurobiological infrastructure of processing and combining words into a sentence comes from studies on functional Magnetic Resonance Imaging (fMRI) and event-related potentials. From the fMRI literature, there is a general agreement that left frontal, left temporal, and left inferior parietal regions are important for sentence processing (Friederici, 2012; Hagoort & Indefrey, 2014; Hagoort, 2013; Menenti, Petersson, Scheeringa, & Hagoort, 2009; Price, 2010; Snijders, 2010; Snijders et al., 2009; Tyler & Marslen-Wilson, 2008). In particular, sentence processing consistently involves left inferior frontal regions, and left superior and middle temporal regions, and the transfer of information between these regions likely involves one or more of the ventral and dorsal tracts that connect them (Friederici, 2012; Hagoort & Indefrey, 2014; Hagoort, 2013; Hickok & Poeppel, 2007). Less is known about the role of the right hemisphere and language processing. There is some evidence that right inferior frontal gyrus plays a role in integrating semantic information in discourse (Menenti et al., 2009), and more generally, across various language tasks, right (and left) frontal and parietal regions are associated with executive functions during language such as executive control and attention (Corbetta & Shulman, 2002; Duncan, 2010; Fedorenko, Duncan, & Kanwisher, 2013; Niendam et al., 2012; Vigneau et al., 2011). Importantly, the role and contribution of each region during sentence processing depends on the type of sentence, and the conditions being compared; for instance, whether it is a simple sentence compared to a complex sentence or a baseline with no language stimuli (Fedorenko & Thompson-Schill, 2014). Furthermore, the contribution of each region during sentence processing is determined by its interaction with other regions that form part of the network (Hagoort, 2013). Thus, the current challenge lies in characterizing the activity in each region, and how it relates to activity in other regions, during sentence processing.

The language studies that use event-related potentials (or their MEG counterpart: event-related fields) have captured many time-locked aspects of the neural activity involved in sentence processing. When reading a single word, about 100 ms after word onset, processing begins with the analysis of visual word features (Tarkiainen, Helenius, Hansen, Cornelissen, & Salmelin, 1999) Subsequently, lexico-semantic processing begins around 250 ms, and is known to produce an event-related response that peaks around 400 ms (Kutas & Federmeier, 2011). This peak is known as the N400 in electroencephalography (EEG) and N400m in MEG, and has been instrumental in demonstrating that the brain is sensitive to the (semantic) context of a word.

Not all neural activity is characterized by time-locked changes to an event (e.g., a word). Furthermore, as sentence processing occurs over time, dynamic changes to neural activity over time cannot be captured with event-related potentials/fields. Rather, the nature of oscillations is better suited to reflect these types of modulation in neural activity. Although there are many studies on oscillations most have not been on language processes; rather, they focused on sensorimotor, visual and memory processes. For instance, theta and gamma oscillations have been consistently associated with memory processing (for a review, see Nyhus & Curran, 2010). Amongst the studies done on sentence processing using oscillations there is no consensus on the functional roles of these oscillations. Some have suggest that syntactic processing involves beta and alpha oscillations (Bastiaansen, Magyari, & Hagoort, 2010; Davidson & Indefrey, 2007; Kielar, Panamsky, Links, Kira, & Meltzer, Jed, 2015), while semantic processing involves gamma oscillations (Bastiaansen & Hagoort, 2015; Bastiaansen, Magyari, & Hagoort, 2010; Hald, Bastiaansen, & Hagoort, 2006). However, these interpretations are too specific – they pertain only to language processing, and do not attempt to relate how oscillations, like those in the beta and gamma oscillations, are robustly observed during sensorimotor and visual processing (Ede & Maris, 2013; Engel & Fries, 2010; Gross et al., 2013; Muthukumaraswamy & Singh, 2013; Tan, Gross, & Uhlhaas, 2016). In part, the specificity of these interpretations could have been because most of these studies only looked at a few frequency bands. In sum, results on the oscillatory dynamics on sentence processing are in their early days. More investigations on a wider range of oscillatory frequencies during language processing are required, and it may well be necessary to perform these studies in mind of, and related the oscillatory findings to those in other domains of cognition for a coherent, meaningful and parsimonious explanation of the functional role of oscillations. The role of oscillations in sentence processing is addressed in chapters 3 and 4 of this thesis.

1.4 Individual differences in the language system

Our genome is a sequence of over 3 billion nucleotide base pairs (adenine with thymine and cytosine with guanine), and together with the environment influences all of human biology. In particular, in the context of this thesis, genetics co-determines the structure and function of the brain, and thus eventually thought and behavior. Humans and chimpanzees evolved from the same ancestor, and share about 98% of their DNA (The Chimpanzee Sequencing and Analysis Consortium, 2005) making us alike in many ways. Yet, some portion of the genetic difference between us and chimps accounts for the human ability to communicate and use language. Our ability to learn thousands of words, map their sounds and symbols to distinct meanings, as well as perceive and create complex messages is unparalleled.

Researchers in molecular biology have begun to unravel the mysteries of the human genetic sequence and determine which genes influence language and communication (for an introduction to language and genetics see Dediu, 2015; for a review on language and genetics see Fisher & Vernes, 2015). Seminal work by Lai, Fisher, Hurst, Vargha-khadem, & Monaco (2001) discovered the first piece of evidence for a genetic basis to language – disruption in the *FOXP2* (Forkhead box P2) gene resulted in a severe developmental disorder with a strong disruption in speech and language (developmental verbal dyspraxia). Subsequently, other genes have been implicated in language and communication, which include but are not limited to *CNTNAP2, DCDC2, ROBO1, KIAA0319/THEM/TTRAP* (e.g., Bates et al., 2011; Carrion-Castillo, Franke, & Fisher, 2013; Fisher & Scharff, 2009; Hannula-jouppi et al., 2005; Marino et al., 2013; Meng et al., 2005; Rice, Smith, & Gayán, 2009).

Within the field of molecular genetics, discoveries were initially made by searching for an association between molecular mutations and disrupted social, communicative or language behavior i.e. observable traits, also referred to as phenotypes. More recently, there has been a growing interest in using indirectly observable traits, referred to as endophenotypes or biological markers, depending on whether heritability criteria are fulfilled (Gottesman & Gould, 2003). This includes measure of cognitive processes like memory and reading (e.g., nonword repetition tasks) as well as measures of neural activity. Neural measures are considered as a path that bridges genes with behavior; they are the consequence of genetic factors which are biologically closer than phenotypes (Gottesman & Gould, 2003).

The influence of genes on neural structure is visible, as evidenced by a higher degree of similarity in neuroanatomy between individuals with a higher genetic affinity (Peper, Brouwer, Boomsma, Kahn, & Pol, 2007; Thompson et al., 2001). However, given the complex genetic network and dynamic neural network involved in language and communication, much work remains to demonstrate reliable, observable functional differences in the brain that can be explained by genetic variance. In chapter 4, I use oscillations to study variance in the language system.

1.5 Methods used in this thesis

Spectral analysis

The MEG signal is recorded in the time domain, i.e. it is stored as a set of amplitude values evolving over time. In order to quantify oscillatory activity, which is conveniently done in the frequency domain, a Fourier transform is applied to the MEG signal. This signal processing technique is known as *Spectral Analysis*. The Fourier transform of the time domain signal produces a signal as a function of frequency. The frequencies are defined as a finite set of sine and cosine waves each with their respective phase and amplitude (Fourier coefficients).

The result of the Fourier transform serves as a basis to derive frequency specific power (energy) and is taken to reflect the strength of the synchronous activity within a local group of neurons. For each segment of data a power estimate is calculated and power estimates are then averaged across trials to improve the signal to noise ratio; this is known as a time-frequency analysis. Coherence, which makes use of the phase information, quantifies the degree to which two signals are in a consistent phase relationship over a defined period of time. Coherence is a normalized value that falls between 0 (no phase relationship, i.e. the phase difference between two signals are random) and 1 (a stable phase relationship). The presence of coherence is taken to reflect a functional relationship between signals.

Source Reconstruction

The MEG signal measured at the scalp reflects a superposition of the magnetic fields caused by electric activity of multiple sources in the brain, and source reconstruction techniques need to be applied to deduce the sources of the measured signal.

In this thesis, I used the source reconstruction method known as Dynamic Imaging of Coherent Sources (DICS) (Gross et al., 2001), a beamforming approach that makes use of adaptive spatial filtering to identify the neural generators of the MEG effects measured at the scalp. This method assumes that there is no correlation (i.e. orthogonality) between the time courses of source activity, but unlike other methods makes no assumptions on the number of sources or their spatial distribution. Rather, the main feature of beamforming is to independently estimate the activity of each source.

In practice, beamforming divides the brain into an equal spaced 3 dimensional grid (I used 5798 grid points which were 8mm apart), or vertices (a set of points) that describe the cortical sheet (I used 8196 vertices). Each grid point or vertex marks a source in the brain or a location on the cortical surface. For each of these locations, a spatial filter is constructed, and used to estimate the activity of a source at that location. The activity at each source is a weighted, linear combination of all sensor signals, following the unit-gain constraint which seeks to reduce the variance of the activity at each location (Gross et al., 2001).

1.6 Outline of this thesis

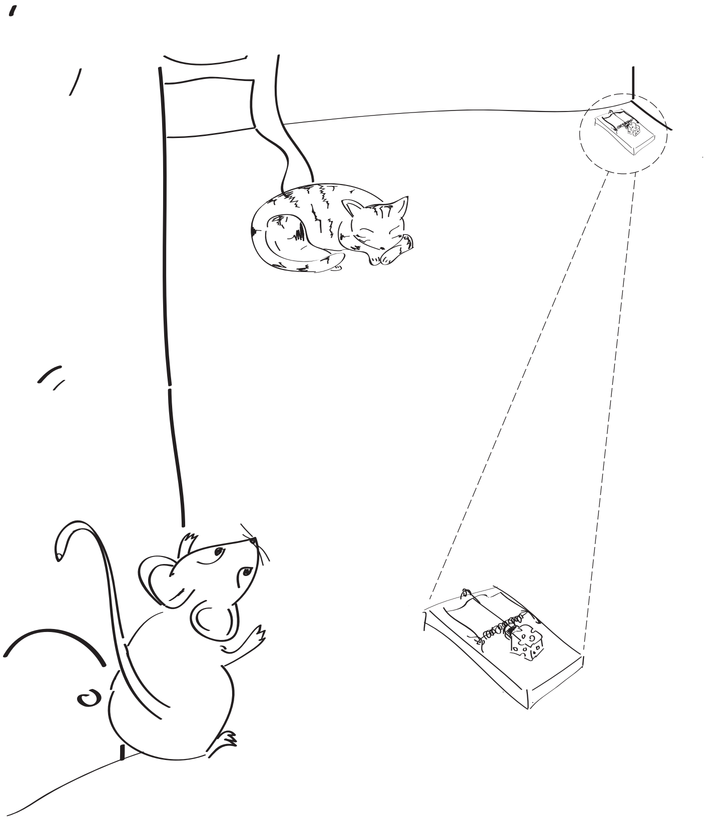
Neuronal oscillations are considered to support brain function and cognition. The perception and comprehension of sentences is a complex process, and our knowledge on this matter could benefit from further investigation using oscillations as a measure of dynamic changes in brain activity. Thus, the main goal of this thesis is to use oscillations to investigate how different aspects of sentence processing are orchestrated in the brain. These aspects can be divided into two stages of sentence processing: perception of speech or orthographic input and comprehension of sentences.

So how do neural regions support the perception of speech in the form of sentences? Neural entrainment is considered as a manner for tracking and segmenting speech. In **Chapter 2** I asked whether cortical entrainment to speech is a robust and reliable phenomenon at both low frequencies (delta and theta) and high frequencies (gamma). Individual differences have been observed in various aspects of language processing and proven to be insightful in understanding the brain and the language system (Dubois & Adolphs, 2016; Mahowald & Fedorenko, 2016; Woodard, Pozzan, & Trueswell, 2016). Therefore, in this chapter I also investigated individual differences in cortical entrainment. In **Chapter 3**, I tested the basic assumption behind cortical entrainment, on whether it reflects true oscillations or whether it is the frequency domain representation of a summation of evoked potentials in response to speech edges. To address this question, I sought for empirical evidence for both possibilities, and discussed future investigations along this line of work.

Within the topic of sentence comprehension I explored 2 processes: how individual words are processed in a sentence (as opposed to individually, in the absence of a meaningful context), and how this process is affected by an incremental context as the sentence unfolds. In **Chapter 4,** to address these questions, I first focused on the modulation of oscillations in the theta, alpha, beta and gamma band in response to the reading of words (one-by-one) in a sentence. Then, I examined whether this modulation depended on the degree to which the sentence context was informative by comparing words early in a sentence to those late in a sentence. In **Chapter 5**, I extended these findings and investigate whether the individual variability in oscillations during sentence processing can be explained by genetic variation in the common variant rs7794745 of the *CNTNAP2* gene. Finally, in **Chapter 6**, I discussed the broader implications of the findings in this thesis, speculate on the direction and potential of neuronal oscillations for our understanding of the brain, and propose future investigations on the neurobiology of language.

2

LOW FREQUENCY OSCILLATORY SPEECH ENTRAINMENT: A REPLICATION AND DEMONSTRATION OF INDIVIDUAL DIFFERENCES IN ENTRAINMENT



2.1 Abstract

Cortical oscillations have been considered to be instrumental for the tracking and segmentation of continuous speech. Earlier work has suggested that delta, theta and gamma oscillations can entrain to the phase of the speech rhythm. Here, we used magnetoencephalography, and employed a large sample of 102 participants together with a broad set of stimuli to investigate entrainment of neuronal oscillations to speech. In replication of previous studies we observed entrainment of delta and theta oscillatory activity by the speech envelope, but in contrast to previous work we did not observe gamma entrainment. For the first time in speech entrainment studies, we demonstrate individual differences for (i) the peak frequency of entrainment, and (ii) for hemispheric lateralization of the low frequency entrainment. We argue that the former supports the involvement of intrinsic oscillations in entrainment, and that the latter is evidence against the Asymmetric Sampling Time Theory of a default right-hemispheric bias for processing signals on a slow time scale. We conclude that even though low frequency entrainment to speech is a robust phenomenon, the characteristics of the entrainment vary across individuals, and this variation is important for understanding the underlying neural mechanisms of entrainment, as well as, its functional significance.

2.2 Introduction

Human speech represents one of the most complex auditory signals that are perceived, containing information at multiple temporal scales that needs to be processed for comprehension. The difficulty in speech perception also lies in its continuous and incremental nature which requires the listener to integrate current input with previous, partially processed input. And yet, we listen to speech with great ease. How is the brain able to keep up with this task? Focusing on the early stages of auditory processing, the brain is required to parse the input into relevant temporal segments, which can then be further processed by the neural system for language, and integrated into context. Ultimately, this cascade of processing operations results in comprehension. A popular perspective on early neural auditory processing is that neuronal oscillations play a mechanistic role in the processing and prediction of temporally structured perceptual information.

Entrainment to low-level visual and auditory stimuli

Neuronal oscillations reflect cyclic fluctuations in the excitability of neuronal populations, and certain phases within each cycle are considered optimal for processing input from the environment (Buzsáki & Draguhn, 2004; Schroeder & Lakatos, 2009; Schroeder, Wilson, Radman, Scharfman, & Lakatos, 2010; Van Rullen & Koch, 2003). Upon presentation of a periodic external signal, alignment of a neuronal oscillation to the signals' rhythm allows for periodic occurrence of high levels of neuronal excitability to correspond with the events in the signal. This synchronization of rhythms is referred to as entrainment, and facilitates optimal sampling in discrete time windows. It allows the information in the signal to be divided into meaningful chunks, which can then be processed and understood. Subsequently, this information can be used to predict the upcoming signal, whereby higher order regions provide top-down feedback to facilitate or inhibit entrainment of oscillations to the signal. Direct evidence for these entrainment mechanisms have been shown in both monkeys and humans whereby the entrainment of oscillations with basic, rhythmic auditory or visual stimuli can shape perception (Busch, Dubois, & VanRullen, 2009; de Graaf et al., 2013; Lakatos et al., 2005; Lakatos, Chen, O'Connell, Mills, & Schroeder, 2007; Lakatos, Karmos, Mehta, Ulbert, & Schroeder, 2008; Romei, Gross, & Thut, 2010; Spaak, de Lange, & Jensen, 2014).

Entrainment to speech

Evidence for an instrumental role of oscillatory entrainment to speech processing is more tentative. This is partially because speech is complex, and difficult to manipulate in comparison to the basic stimuli in the aforementioned studies (e.g., circular sine-wave gratings presented at a specific frequency, flashes of light, or Gaussian noise bursts). Another reason is that speech rhythmicity is quasi-periodic (i.e. less regular than strictly periodic signals), which makes entrainment more difficult. To rise to the challenge of understanding speech perception, several theories have been proposed on the role of neuronal oscillations in speech perception (e.g., Ghitza & Greenberg, 2009; Ghitza, 2011; Giraud & Poeppel, 2012; Howard & Poeppel, 2010; Peelle, 2012; Poeppel, 2003; Shamma, Elhilali, & Micheyl, 2011). For instance, Giraud & Poeppel (2012) proposed that the spike train input to auditory cortex (which captures the energy fluctuations of the speech signal) influences neuronal excitability: the neurons in primary auditory cortex adjust (reset) the phase of their excitability rhythm which allows them to entrain to the rhythmic regularities of the speech signal.

As the linguistic information in speech occurs at different rates in a quasi-regular manner, these theories assume that neuronal oscillations at frequencies that roughly correspond to these rates are suited for parsing and decoding speech. On average, prosody occurs at a rate of about 1 – 3 Hz, syllables at about 4 – 7 Hz, and phonemes at about 30 – 50 Hz. Accordingly, slow oscillations, delta and theta sample speech at the prosodic and syllabic rate, respectively, while fast oscillations in the gamma band (around 30 Hz and beyond) facilitate the sampling of phonemic information. In addition, it has been suggested that sampling rates are thought to be hierarchically embedded, with theta as the dominant sampling rhythm, and with coordinated sampling at the delta and gamma frequencies (Giraud & Poeppel, 2012; Gross et al., 2013). A related issue to sampling speech at multiple time scales is whether it is supported by a division of labour between the hemispheres as proposed in the Asymmetric Sampling Time Model by Poeppel (2003) and further elaborated by Giraud & Poeppel (2012). In this model, the left auditory cortex is biased towards sampling signals at fast time scales, while the right auditory cortex is biased to sample at slower time scales (for support see Boemio et al., 2005; Giraud et al., 2007; Morillon et al., 2010; Shtyrov, Kujala, Palva, Ilmoniemi, & Näätänen, 2000; for a counter argument see Mcgettigan & Scott, 2012).

Delta, theta and gamma entrainment?

Empirical studies have provided support for the role of delta and theta bands in entrainment (e.g., Abrams, Nicol, Zecker, & Kraus, 2008; Bourguignon, De Tiège, de Beeck, et al., 2013; Cogan & Poeppel, 2011; Gross et al., 2013; Luo, Liu, & Poeppel, 2010; Luo & Poeppel, 2007; Molinaro, Barraza, & Carreiras, 2013; Peelle, Gross, & Davis, 2013), and mainly theta entrainment has been associated with speech intelligibility (Ahissar et al., 2001; Luo & Poeppel, 2007; Peelle et al., 2013). To date, only one study has demonstrated involvement of the gamma band (Gross et al., 2013). These authors used a 7 minute story to study entrainment of oscillatory activity to speech and found gamma phase-amplitude coupling to the speech envelope, alongside with phase-phase coupling of delta and theta oscillations to speech. In addition, they showed that ‘edges’ in the speech signal (corresponding to word and syllable onsets) were associated with oscillatory phase resetting in the theta band, a mechanism thought to support/maintain entrainment. They further demonstrated that directly following a speech edge there was an increase in intra-cortical oscillatory cross-frequency coupling between delta, theta and gamma frequencies.

However, there have been some limitations in previous studies. First, most had a relatively small sample size (ranging from 10 to 22 participants). Second, most used simple language stimuli in small quantities (1,3,4, or 10 short sentences, Abrams et al., 2008; Ahissar et al., 2001; Cogan & Poeppel, 2011; Luo & Poeppel, 2007), with a few using a wider variety of sentence structures in the form of a continuous text (Bourguignon, De Tiège, de Beeck, et al., 2013; Gross et al., 2013; Molinaro et al., 2013). These previous studies found support for the involvement of delta, theta, and/or gamma are involved in entrainment. Moreover, some studies showed that entrainment was stronger for the regular (forward) speech condition than a control or contrast condition (e.g., reversed speech, noise-vocoded speech). These studies thus speculated that entrainment not only reflects a bottom-up, passive process fully determined by the temporal characteristics and cues in the speech signal, but also involves a top-down component that predicts the upcoming word (Gross et al., 2013; Peelle et al., 2013). The conclusions and predictions from these earlier empirical studies have strong implications for speech perception mechanisms.

Current study

To provide further empirical evidence for, and to advance our understanding of, entrainment to speech an independent replication of these earlier findings with a larger sample and a larger variation in the stimuli set is necessary. In the current study, we sought to replicate the previous findings of entrainment whilst addressing the aforementioned shortcomings. In the current study, we used data from an unprecedented sample of 102 participants to address neural oscillatory entrainment to the speech envelope. We measured brain activity with magnetoencephalography (MEG) while participants listened to sentences. We quantified the relationship between neuronal oscillations and the envelope of the speech signal using coherence. Participants were presented with 120 sentences. We ensured the use of a diverse set of sentences which varied in complexity and structure. Sentences had an average length of 4.2 s. Based on previous studies, we analyzed entrainment between 0.5 to 50 Hz to include the delta (0.5 – 3.5 Hz), theta (4 – 7 Hz), alpha (8 – 12 Hz), beta (13 – 30 Hz), and gamma (30 – 50 Hz) bands.

The study of variation allows for (i) the identification of whether the general effect at the group level is a true effect, or just a result of averaging, (ii) an explanation for differences in speech perception, and (iii) testing and revision of theories. Importantly, in addition to replicating previous work, a second goal of our study was to seize the opportunity to quantify individual differences in neural oscillatory entrainment of speech, given our large sample size.

We found support for entrainment at low but not high frequencies. Moreover, we were able to quantify and observe a rather large individual variability in entrainment, both in terms of strength and in terms of lateralization.

2.3 Methods

Participants

A total of 102 native Dutch speakers (51 males), with an age range of 18 to 33 years (mean of 22 years), participated in the experiment. These participants formed part of the MOUS study (Mother of all Unification Studies; *N* = 204), and all participated in an fMRI and a MEG session. Half of these participants completed both sessions where they read the stimuli, and the other half listened to recordings of the stimuli. The current study pertains to participants from the MEG session in the auditory modality. All participants were right-handed, had normal hearing, normal or corrected-to-normal vision, and reported no history of neurological, developmental or language deficits. The study was approved by the local ethics committee (CMO – the local “Committee on

Research Involving Human Participants” in the Arnhem-Nijmegen region) and followed the guidelines of the Helsinki declaration.

Language stimuli

The stimuli consisted of 360 sentences and their word list counterparts. The sentences varied between 9 and 15 words in length, of which half contained an embedded clause and half did not. The stimulus material was recorded by a native female Dutch speaker in a sound-proof recording booth. The speaker read the stimuli in a natural manner: the sentences were read at a regular pace with an average duration of 4.2 s (min: 2.8 s, max: 6.0 s), and the word lists were read with a brief pause between words, averaging 7.7 s (min: 5.5 s, max: 11.1 s). Subsequently, all stimuli were equalized to the same amplitude, and an onset and offset ramp of 10 ms was applied.

The current study is only concerned with the sentences (see table 1 for an example). The word lists were not a suitable control condition because there was a temporal gap between each word, in contrast to the sentences which consisted of continuous speech. These low-level differences in the temporal properties and rhythmic structure (clearer speech edges in word lists than in sentences) meant that any differences in entrainment between the sentences and word lists would be severely confounded by a difference in duration between words.

Sentence
Bij de opening van de nieuwe sporthal kregen de talrijke bezoekers een consumptie
At the opening of the new sports hall received the many visitors a (free) drink

Table 1. Exemplar sentence in Dutch, and literal English translation.

Task and Procedure

Experimental Design

We divided the sentences into 6 groups of 60 sentences. Using a Latin square design we created 6 sets of stimuli, each consisting of 2 groups (i.e. 120 sentences). Participants were exposed to one of the 6 sets. Participants assigned the same set had sentences presented in a different (randomized) order. In the experiment, the stimuli were presented in a mini block design, and alternated between a sentence block (containing 5 sentences) and a word list block (containing 5 word lists), for a total of 24 blocks. The first mini block (sentences or word lists) was randomized across participants.

At the beginning of each block, the block type was announced for 1500 ms: *zinnen* (sentences) or *woorden* (words), followed by a 2000 ms blank screen. At the beginning of each trial a fixation cross was presented for a jittered duration between 1200 – 2200 ms. Subsequently, the auditory signal was presented for each trial (sentence or word list), and the fixation cross remained on the screen until the auditory signal was completed. Within each block, the inter-trial interval was a blank screen with a jittered duration between 1200 – 2200 ms.

In order to check for compliance, 10% of the trials were randomly followed by a yes/no question about the content of the previous sentence/word list. Half of the questions on the sentences addressed sentence comprehension (e.g. *Did grandma eat a pancake?).* The other half of the sentences, and the questions following the word lists addressed a content word (e.g. *Was a music instrument named?*). Participants answered the question by pressing a button for 'Yes'/ 'No' with their left index and middle fingers, respectively. For both question types, half of the trials had a yes-response as the correct answer.

All stimuli were presented using Presentation software Version 16.0, Neurobehavioral Systems, Inc). Speech stimuli were presented binaurally via MEG-compatible tubes. The questions were presented in black mono-spaced font, on a gray background. To reduce eye movements during listening, subjects were instructed to focus on a fixation cross. These visual stimuli were presented with an LCD projector (with a vertical refresh rate of 60 Hz) situated outside the MEG, and projected via mirrors onto the center of the screen inside the MEG room, within a visual angle of 4 degrees.

Prior to performing the sentence listening task, we adjusted the hearing level for each subject. To ensure a sufficient cortical auditory response, the minimal auditory threshold was determined, and subsequently all auditory stimuli were presented at 50 dB above the minimum threshold. For task familiarization purposes participants completed a practice task (using a separate set of stimuli from the actual task).

MEG data acquisition

MEG data were collected with a 275 axial gradiometer system (CTF). The signals were digitized at a sampling frequency of 1200 Hz (the cutoff frequency of the analog anti-aliasing low pass filter was 300 Hz). Three coils were attached to the participant's head (nasion, left and right ear canals) to determine the position of the head relative to the MEG-sensors. Throughout the measurement the head position was continuously monitored using custom software (Stolk, Todorovic, Schoffelen, & Oostenveld, 2013). During breaks the participant was allowed to reposition if needed. Participants were able to maintain a head position within 5 mm of their original position. Three bipolar Ag/AgCl electrode pairs were used to measure the horizontal and vertical electro-oculogram, and the electro-cardiogram.

Data processing

All analyses were done with custom written Matlab scripts and FieldTrip (Oostenveld, Fries, Maris, & Schoffelen, 2011).

Artifact detection

Physiological artifacts (eye movements and muscle contractions) and superconducting quantum interference device (SQUID) jumps were identified using a semi-automatic artifact identification procedure (http://www.fieldtriptoolbox.org/tutorial/automatic_artifact_rejection), followed by visual inspection. Data segments that contained artifacts were not subjected to further analysis. Across subjects, an average 80% of trials were retained after rejection.

Preprocessing

The envelope of each speech signal was constructed as the sum of the Hilbert envelopes of 10 distinct bandpass filtered frequency bands of the original auditory signal (as per Gross et al. 2013). Subsequently, each envelope signal was downsampled to 1200 Hz, and temporally aligned to the corresponding MEG data. The MEG signal was initially epoched into the individual sentences, demeaned, and the power line interference was removed using a band stop filter (finite impulse response window sinc filter) between 49 to 51 Hz. Subsequently, the MEG signal and speech signal were downsampled to 300 Hz, and cut into 2 s long epochs (with a 50% overlap to reduce bias in the coherence estimate) which produced a frequency resolution of 0.5 Hz. To facilitate the combination of MEG topographies across subjects, the data was transformed to a synthetic horizontal and vertical planar gradient representation using interpolation.

Sensor level coherence was computed between low frequency oscillations (delta, theta, alpha and beta) and the speech envelope, as well as, the phase of the gamma band envelope and the speech envelope. The latter involved two additional processing steps prior to the spectral analysis: the application of a band pass filter to the MEG data to extract the gamma band activity between 30 to 50 Hz which was followed by the absolute of the Hilbert transform to obtain the amplitude envelope. This was done separately for each planar gradient.

Sensor level Coherence

Spectral analysis

To quantify entrainment of the MEG signal to the speech envelope we calculated coherence. To do this, we first computed the power spectra for each signal, and the cross-spectra between the speech signal and brain signal, for each frequency. To do this, each epoch was tapered (using multiple tapered versions of the epoch) to achieve a spectral smoothing of ± 2 Hz. Subsequently each tapered epoch was Fourier-transformed and the cross- and power-spectra were calculated.

$$S_{ab}(f) = F_a(f) \times F_b(f)^* \qquad (1)$$

F_a denotes the Fourier-transformed of the signal a (a particular MEG channel or the speech envelope) at frequency f, while * represents the complex conjugate. The cross spectrum was obtained by multiplying the Fourier-spectra of one signal (e.g., from an MEG channel) with the conjugate of the Fourier-spectra of another signal (e.g., speech).

When a = b, then the Fourier-spectra of one signal is multiplied with its own conjugate which produces the power spectrum. Coherence Coh_{ab} was then calculated as follows:

$$Coh_{ab} = \left| \frac{S_{ab}}{\sqrt{S_{aa} \times S_{bb}}} \right| \qquad (2)$$

In this formula, the power spectra and cross spectrum are averaged across trials. Coherence values range from 0 to 1, with 0 indicating no consistent phase relationship between signals, and 1 indicates a fully consistent phase difference between signals. Finally, the coherence values of the horizontal and vertical gradients were recombined by taking the average of the two gradients.

Peak frequency selection

Visual inspection of the sensor level data indicated that there was considerable variability across participants for the frequencies at which coherence peaked, see Fig. 1. To optimize the sensitivity of our analysis, we identified individual peak frequencies for each participant at the sensor level. These individually selected peaks were subsequently used for source level analysis. For the gamma band, as effects in this range are usually broadband, we did not select a peak frequency but instead opted for a broad bandwidth between 30 – 50 Hz. This range was motivated by previous entrainment studies (Giraud & Poeppel, 2012; Gross et al., 2013; Luo & Poeppel, 2007; Poeppel, 2003).

For each participant the peak detection process was as follows: a peak detection algorithm was used to identify, for each channel, the frequency bins that showed a distinct peak in the coherence spectrum with a coherence value larger than 0.02. This yielded a binary vector (as a function of frequency), with a 1 indicating a peak, for each channel. Next, these binary vectors were summed across channels yielding a spectrum of

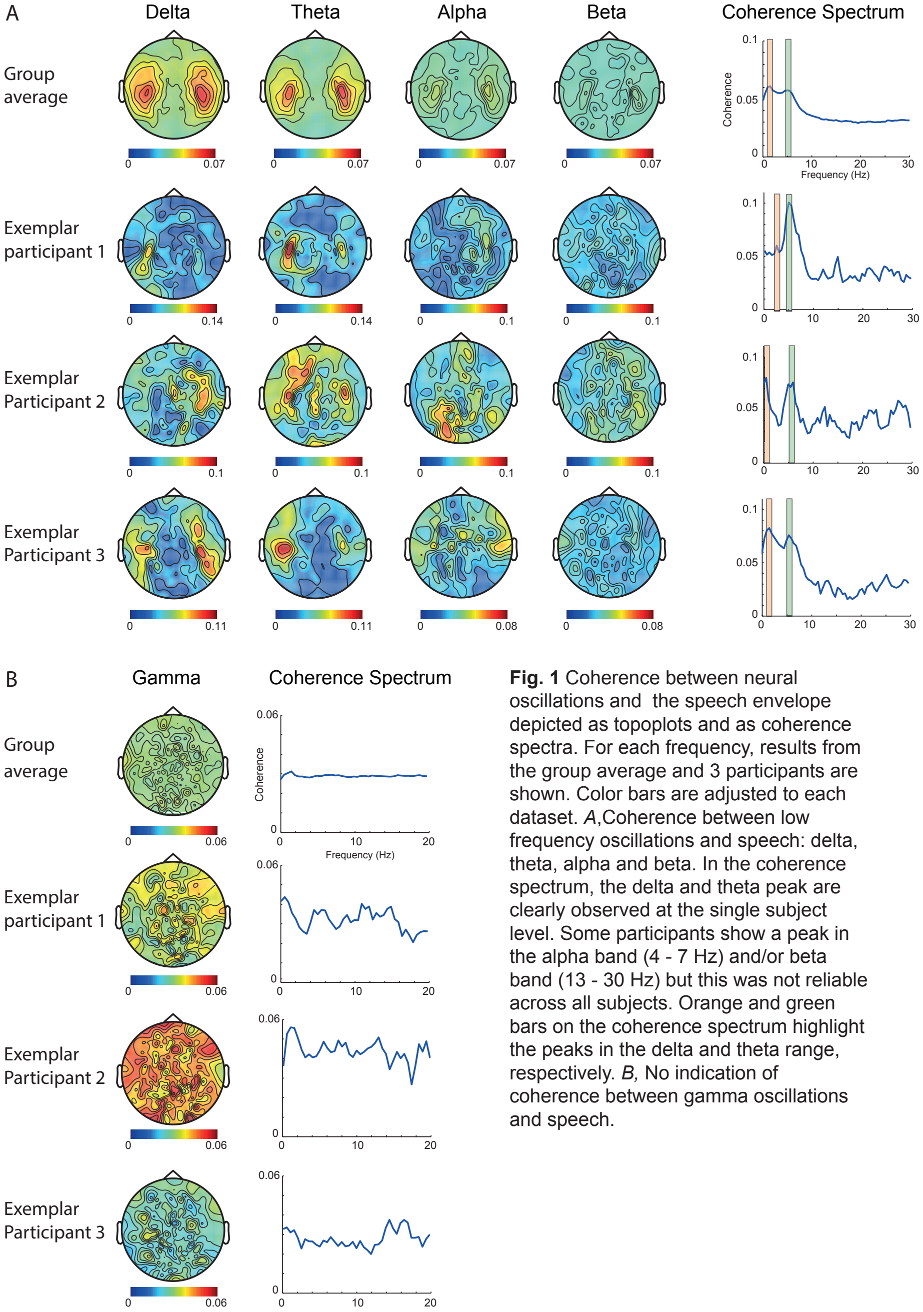


Fig. 1 Coherence between neural oscillations and the speech envelope depicted as topoplots and as coherence spectra. For each frequency, results from the group average and 3 participants are shown. Color bars are adjusted to each dataset. *A*, Coherence between low frequency oscillations and speech: delta, theta, alpha and beta. In the coherence spectrum, the delta and theta peak are clearly observed at the single subject level. Some participants show a peak in the alpha band (4 - 7 Hz) and/or beta band (13 - 30 Hz) but this was not reliable across all subjects. Orange and green bars on the coherence spectrum highlight the peaks in the delta and theta range, respectively. *B,* No indication of coherence between gamma oscillations and speech.

peak counts across channels. The assumption here was the higher the peak count, the more reliable the peak. This vector was then multiplied to a second vector containing the standardized coherence across frequencies. This accounted for variance in coherence strength. The weighted vector was then smoothed (boxcar of 2 samples) and a second peak detection with a threshold of 2 was performed to identify the peak frequencies across the sensor array. Comparison of the estimated peak frequency with visual identification of the peak frequency for 10 subjects determined this peak detection process to be adequate.

Processing of the anatomical MRI and digitized headshape for MEG source reconstruction

For source reconstruction purposes, we coregistered the anatomical MRI to the MEG-sensors. This was achieved by manual alignment of two reconstructions of the head surface. A digitized head shape, consisting of approximately 500 points across the scalp, was obtained with a Polhemus device (a 3D digitizer from Fastrak, Polhemus Inc. Colchester, VA, USA). The second head shape (at the brain-skull boundary) was obtained by segmenting the participant's T1-weighted anatomical MRI image.

Subsequently, the aligned anatomical image was used to create a volume conduction model based on a single shell description (Nolte, 2003) of the inner surface of the skull, using the segmentation function in SPM8. Source reconstruction was performed on a set of 8196 dipole locations distributed across the cortical sheet. Freesurfer 5.1 (Dale, Fischl, & Sereno, 1999) was used to create a high-resolution description of the cortical surface. Next, these cortical surfaces was surface-registered to a template mesh using the Caret Software package (Van Essen et al., 2001), and subsequently downsampled from 168,342 dipoles per hemisphere to 4098 dipoles. The surface registration procedure resulted in individual cortical sheets that are topologically equivalent across participants (i.e. a particular topological point in the cortical sheet of one participant correspond to the same particular point in all other participants). In addition, all topological points could be related to a cortical atlas (the Conte 69 atlas,Van Essen, Glasser, Dierker, Harwell, & Coalson, 2012) and thus were labeled and assigned to an anatomical region e.g., left inferior frontal and left superior parietal regions. The benefits of using this cortical surface were that it is (a) comparable across participants, (b) contains an equal number of vertices on each hemisphere, and (c) that each vertex has a contralateral homolog which facilitated the subsequent comparison of activity between hemispheres in the lateralization analysis.

Source localization of the coherence between the phase of low frequency oscillations (theta–beta) and the speech envelope

We computed coherence at the source level using a frequency domain beamformer (DICS; Gross et al., 2001). The sensor level cross-spectrum in combination with the forward solution was used to compute a set of spatial filters, one filter for each dipole location on the cortical sheet. The sensor level Fourier-transformed tapered data were then projected through the filters to produce source level Fourier coefficients. In the next step, the coherence between the speech envelope and the estimated activity at the dipole locations was computed in a manner similar to that at the sensor level. As a result, the MEG signal is denoted by dipole activity estimated at a particular grid point instead of activity at a particular channel.

Source localization of the coherence between the phase of the gamma band envelope and the speech envelope

We were interested in whether the phase of the gamma band envelope entrained to the phase of the speech envelope. We computed the data covariance-matrix (at the sensor level) which was used to obtain a time domain spatial filter (LCMV beamformer, Van Veen, Van Drongelen, Yuchtman, & Suzuki, 1997). We then projected the bandpass filtered Fourier-data through the spatial filter, applied a Hilbert transform and took the absolute value. This produced estimates of the gamma band envelope at each dipole location. Finally, we computed coherence between the gamma band envelope and the speech signal, in a manner similar to that shown in the source analysis for coherence in low frequencies.

Statistical Inference

Coherence

We did not statistically assess the level of coherence between oscillations and sentences because we did not have a suitable control condition. As explained in the methods section, our word list condition had fundamentally different acoustic properties than the continuous speech in the sentences, which would render any statistical differences uninterpretable due to this confound. As this study formed part of a larger study, with predefined conditions it was not possible to provide participants with a third condition such as reverse or vocoded speech. Nevertheless, we are confident that our coherence results reflect entrainment because the effects are localized to auditory cortex, and because we see clear peak frequencies in the single subject level data (see results).

Lateralization of coherence

For the theta and delta bands, we determined whether coherence was stronger in one hemisphere than the other by performing statistical inference using a non-parametric permutation test together with a clustering method to address multiple comparisons (Maris & Oostenveld, 2007). We used the dependent samples *t*-statistic to quantify each sample (frequency by space data point): the difference in entrainment between each left hemisphere dipole location and its right-sided homologue. Samples that exceeded the uncorrected significance level of 1% were clustered according to adjacency (in space). For each cluster, the cluster-level *t*-statistic was calculated by summing the *t*-statistics across the individual elements. Next, to test the observed *t*-statistic, a reference distribution was computed. This distribution was created by permuting (randomly exchanging) data between dipoles in the left and right hemisphere and then calculating the maximal positive and negative cluster-level *t*-statistic for each permuted data set. Finally, the observed *t*-statistic was tested against the reference distribution. The observed *t*-statistic was considered significant if it was located beyond the determined threshold, on the negative or positive end of the reference distribution. The statistical threshold is specified in the section of each analysis below.

2.4 Results

Question performance

The mean percentage of correct answers for the questions that proceeded a sentence was 86.8% (*SD* = 9.9%). This suggested that all participants were attentive and listened to the materials properly.

Speech entrainment using coherence

Sensor level phase coupling

We computed coherence between neuronal oscillations and speech for four different frequency bands: delta (0.5 – 3 Hz), theta (4 – 7 Hz), alpha (8 – 12 Hz) and beta (13 – 30 Hz). Phase coupling between the neuronal oscillations and speech envelope was observed in the delta and theta bands in temporal-parietal sensors, a spatial distribution that is characteristic of a response in auditory regions. This topography is evident at both the group level and single subject level results (see Fig. 1). Phase coupling was not observed in the alpha or beta band.

Within each frequency band, we were also interested in the variability of the frequency showing the strongest coherence (peak frequency). Using a peak detection algorithm we found individual differences in peak frequency for each frequency band, as displayed in Fig. 2. We exploited this individual difference in the source analysis by only including participants with a peak frequency in the sensor analysis, and only using their peak frequency for source estimation. For the delta and theta bands we did not detect a peak for all 102 participants, 88 participants had a peak in the delta band and 91 participants had a peak in the theta band. The main reason our algorithm did not detect a peak in a small number of the participants was because there were too few channels (under 10%) with a clear peak in the theta band (see Peak frequency selection under Methods). This led to extremely low standardized peak values that did not surpass the peak detection threshold. Lowering the threshold revealed a peak for 3 out of 10 participants. Importantly, the lack of peaks was not because the peak fell on boundary of the defined theta window (4 – 7 Hz), since relaxing the boundaries to 3.5 – 7.5 Hz did not lead to the detection of peaks.

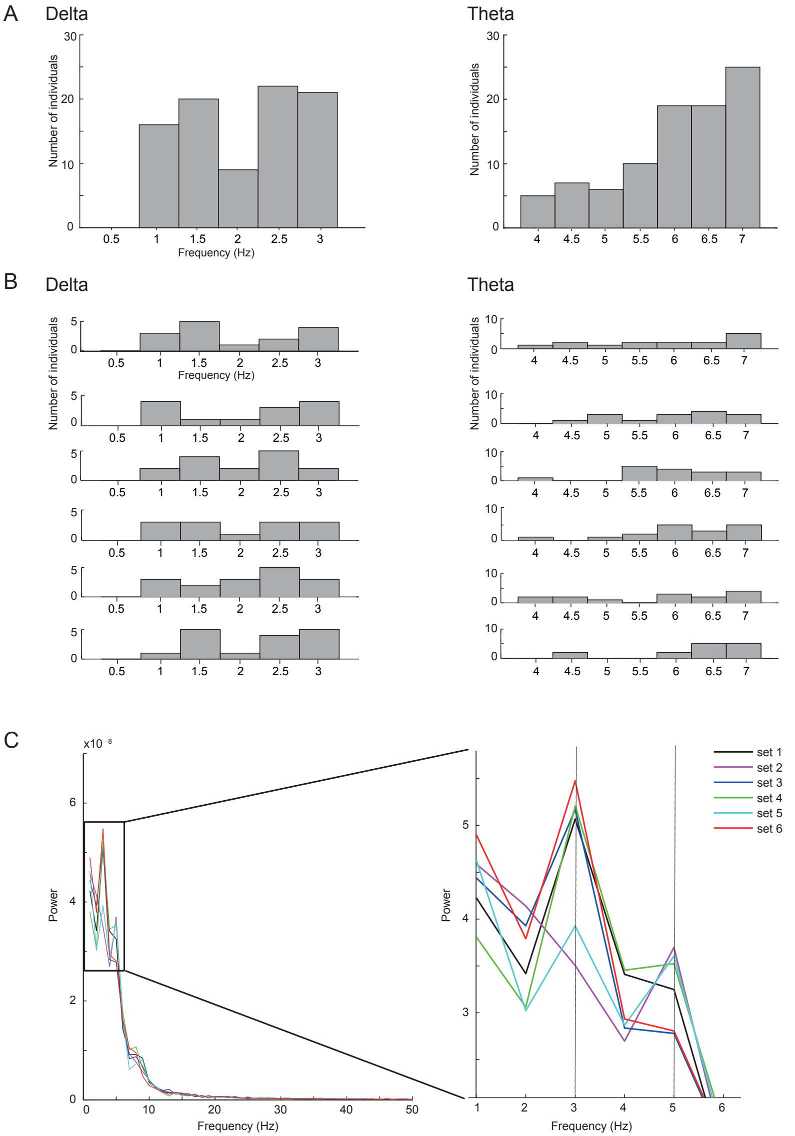


Fig. 2. *A, B,* Distribution of coherence peak frequency for delta and theta entrainment. Participants were exposed to different stimulus sets. Only participants with a peak frequency are included in the historgrams. 88 individuals had a clear delta peak in the coherence spectrum, while 91 individuals had a clear theta peak in the coherence. *A,* Distribution of peak frequencies across all subjects *B,* Distribution of peak frequency for subjects of each stimulus set. All sets demonstrate a wide distribution in peak frequency, even though all sets contain the same averaged power spectra (i.e. speech envelope). *C,* Average power spectra for each stimulus set. Dotted lines mark the peak in the power spectra at 3 Hz for delta and 5 Hz for theta.

Sensor level phase-amplitude coupling

There is some empirical evidence that the envelope of gamma oscillations entrains to the low-frequency phase of the speech envelope. To verify this in our data, we computed coherence from between the phase of the gamma envelope (30 – 50 Hz) of the neural signals and the phase of the speech envelope. We found no meaningful spatial pattern of coherence between the phase of the gamma envelope and phase of the speech envelope (Fig. 1B).

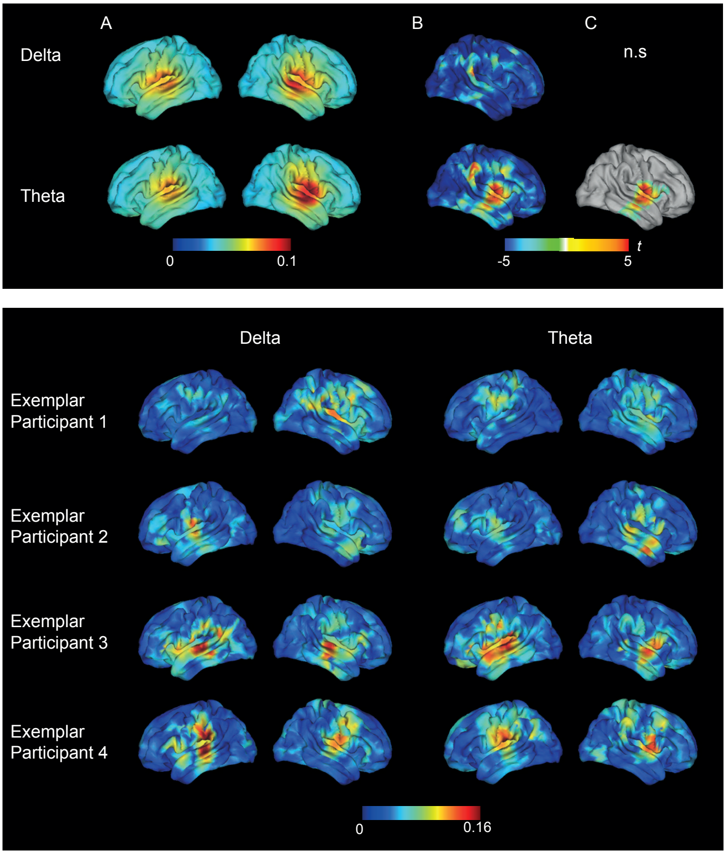


Fig. 3 *Top,* Brain maps depict the surface representation of beamformed coherence. *A,* Coherence values between the speech envelope and neural oscillations for the left and right hemisphere. *B,* Statistical maps of lateralized coherence (Left – Right) in t-values, cold colors represent stronger coherence on the right. *C,*Statistical maps masked for significance (p < 0.025). *Bottom,* Brain maps depict the surface representation of beamformed coherence in 4 representative subjects for the delta band and theta band.

Source level low frequency phase-phase coupling

We also computed the coherence between the neuronal sources of oscillations and the speech signal. Fig. 3 (top) depicts the group level source coherence estimates and statistical inference for delta and theta. We did not source localize the alpha and beta band because there was no clear topography or peaks in the coherence spectrum at the sensor level. Coherence between speech and the delta and theta oscillations localized to superior temporal cortex (the activity in inferior motor cortex is due to spatial blur). This location is in line with primary auditory cortex. The spatial maps suggest that the peak location for delta oscillations is more posterior in bilateral temporal cortex, whereas it is more anterior for theta oscillations. This analysis demonstrated that the phase of low frequency delta and theta neuronal oscillations entrain to the phase of the speech envelope in primary auditory cortex.

Lateralization of speech entrainment

It has been suggested that (the auditory cortex in) each hemisphere has a bias in tracking a specific speech rhythm (Giraud & Poeppel, 2012; Poeppel, 2003), with a preferential role for the right hemisphere in the theta and delta frequencies. We performed a statistical comparison between the coherence values of the left and right homologous cortical regions, separately for the delta and theta band because they showed clear, strong entrainment. Our results at the group-level showed that even though both delta and theta oscillations entrain to speech in both hemispheres, only theta oscillations showed stronger entrainment on the right than left auditory cortex ($p = 0.0035$) (Fig. 3). We also quantified individual variation in lateralization, and found a similar number of left- and right-lateralized individuals for entrainment in both the delta and theta band (Fig. 4). For the delta band, 55% (48/88) of the individuals were right-lateralized, and the standardized mean right-, and left lateralized values were 0.36 and 0.36, respectively. For the theta band, a slightly higher percentage of individuals were right-lateralized (56%; 51/91) and there was a larger difference between the normalized mean right-lateralized value (0.50) and left-lateralized value (0.32) which explains why only the theta but not delta band showed a significant bias for right hemisphere entrainment at the group level.

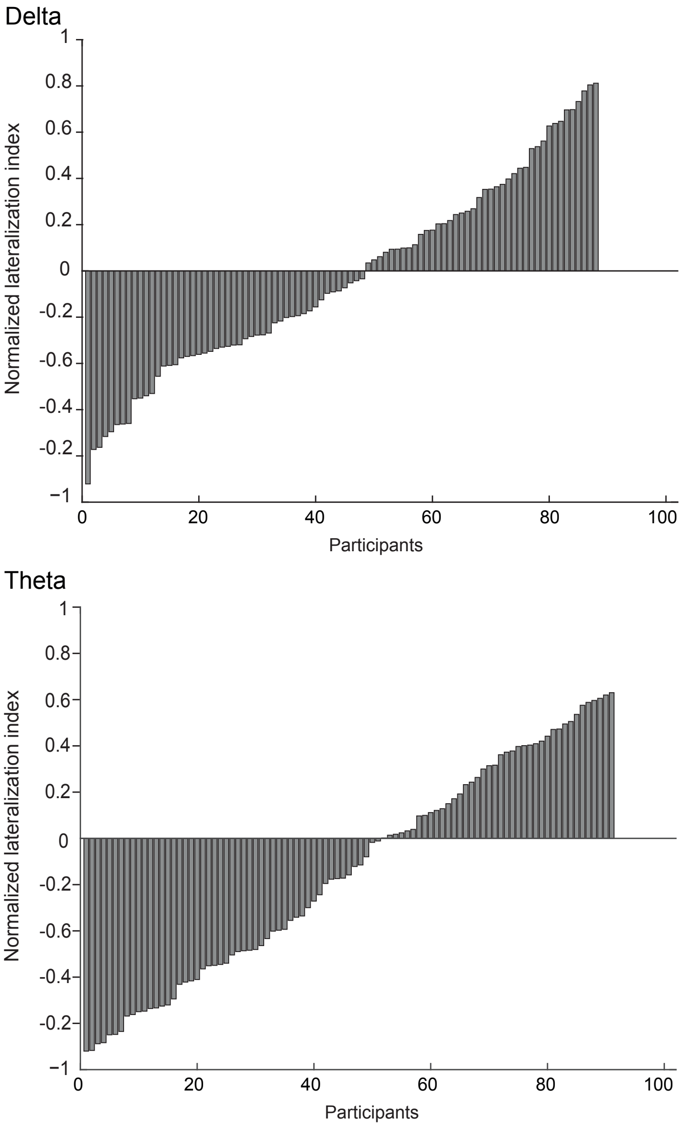


Fig. 4 Bar graph of individual lateralization indices in superior temporal cortex. For each participant the lateralization index (L-R)/(L+R) was computed for each homologous pair of vertices on the cortical sheet. Bars indicate the mean lateralization index of 80 vertices in superior temporal gyrus (these 80 vertices had the highest coherence in left and right superior temporal cortex combined). In the delta band (N = 88) 55% of participants were right lateralized, while in the theta band (N = 91) 56% of participants right lateralized.

2.5 Discussion

Entrainment – the frequency-specific phase synchronization of cortical oscillatory activity to the envelope of the auditory input signal – has been proposed to provide an initial temporal parsing mechanism of the relevant linguistic structures needed for speech processing. In the current study, using a larger population than before (*N* = 102), we clearly replicated entrainment of neuronal oscillations in the delta and theta frequency bands. We also presented novel findings of considerable individual variability in the peak frequency for entrainment and the preferred laterality of the entrainment.

Low frequency entrainment

We found entrainment to the speech envelope for delta (0.5 – 3 Hz) and theta (4 – 7 Hz) oscillations. The topographical distribution at the sensor level was characteristic of auditory responses – bilateral temporal sensors showed the highest amount of entrainment, and source estimates localized to bilateral primary auditory cortex and posterior superior temporal regions. This is consistent with our knowledge that auditory cortices are the first cortical areas to respond to speech input, and that the posterior superior temporal lobes are consistently involved in speech processing (for a review see Hickok & Poeppel, 2000). Furthermore, for these two frequencies, we defined clear spectral peaks in the coherence spectrum at the single subject level, demonstrating the robustness and reliability of entrainment (discussed in detail below).

Most studies have compared the entrainment of meaningful, regular sentences to a contrast (or control) condition to demonstrate that entrainment is not simply due to acoustic properties but the meaning (intelligibility) of the sentences. Furthermore, studies using a contrast condition have demonstrated entrainment between speech and higher-order areas, mainly frontal regions (Gross et al., 2013; Molinaro, Lizarazu, Lallier, Bourguignon, & Carreiras, 2016; Park, Ince, Thut, Gross, & Schyns, 2015). Choices of contrast conditions include noise-vocoded, reversed speech, and baseline coherence between auditory signals and resting state MEG (Gross et al., 2013; Molinaro et al., 2013; Peelle et al., 2013). In the current study, our word list condition (created by scrambling the words in a sentence) did not suffice as a control condition because of low-level acoustic differences to the sentence condition (see Methods). Nevertheless, given the clear spectral peaks and spatial topography we argue that our results of entrainment in the delta and theta band are meaningful and convincing.

Our findings replicate previous studies of low frequency entrainment (Abrams et al., 2008; Ahissar et al., 2001; Bourguignon, De Tiège, De Beeck, et al., 2013; Luo & Poeppel, 2007; Peelle et al., 2013). The importance of low frequency oscillations for perception is also supported by the association between theta entrainment and speech intelligibility (e.g., Doelling, Arnal, Ghitza, & Poeppel, 2014; Peelle et al., 2013) and the observation that the removal of speech spectral modulations below 4 Hz (using a modulation transfer function) greatly impairs speech comprehension (Elliott & Theunissen, 2009). Together, this suggests that low frequency entrainment is a robust and reliable phenomenon.

Lack of Gamma Entrainment

We did not replicate the earlier finding of phase-amplitude coupling between the envelope of the gamma oscillations (30 – 50 Hz) and the speech envelope. Several studies have been performed on entrainment (Luo et al., 2010; Luo & Poeppel, 2007; Peelle et al., 2013), but only one has demonstrated evidence for gamma oscillations coupling to speech (Gross et al., 2013). Modulation of the gamma band by speech has also been shown by other studies but only in terms of oscillatory power (Ding, Melloni, Zhang, Tian, & Poeppel, 2016; Nourski et al., 2009). On this basis, entrainment of the gamma envelope to speech may not be a reliable phenomenon. Alternatively, certain stimuli, methods or task designs may be required to measure the oscillatory response in the gamma band. Gross et al., (2013) found coupling between the phase of the gamma envelope and the speech envelope using mutual information. As this measure, unlike coherence, can measure non-linear relationships between signals, this might be why we did not capture the relationship between gamma and speech. A second, possible, explanation might pertain to the high individual variability in the peak frequency (and amplitude) of gamma band activity. For instance, in the visual system, variation in peak frequency has been observed between about 40 – 90 Hz (Hoogenboom et al., 2006; Suresh Muthukumaraswamy, Edden, Jones, Swettenham, & Singh, 2009; Suresh Muthukumaraswamy, Singh, Swettenham, & Jones, 2010; van Pelt, Boomsma, & Fries, 2012). With this variation, our definition of the gamma band between 30 – 50 Hz (based on previous entrainment and speech literature) may have hindered our finding of gamma to speech coupling. Since we did not find gamma entrainment we could not replicate the other analyses from Gross et al. (2013): (i) whether lateralization exists in the gamma band and (ii) whether a hierarchical relationship between neuronal oscillations exists, as indicated by cross-frequency coupling between the gamma band and theta or delta bands. As of now, there remains a lack of evidence for gamma entrainment.

Individual Variability

Until now, individual variation in oscillatory entrainment to speech has not been quantified even though it has the potential to provide further insight on the characteristics of entrainment that are not obvious with group average data. Here, for the first time, we show that both delta and theta entrainment vary across individuals in two aspects: the peak frequency of entrainment, as well as the degree and extent of lateralization of entrainment.

Variability in peak frequency suggestive of individual differences in entrainment

We defined the delta range between 0.5 to 3 Hz (in 0.5 Hz increments) and the theta range between 4 to 7 Hz (also in 0.5 Hz increments), and in both ranges we observed peaks at all frequencies (Fig. 2A). For delta, 2.5 Hz was the most common peak frequency, and for theta it was 7 Hz. As participants received one of the six sets of stimuli (see Methods), we wanted to ensure that differences in low-level stimulus properties between sets was not the cause of the variation in peak frequency. First, we inspected the peak frequencies within each set, and noted that the variation was maintained in each set (Fig. 2B). Second, we calculated the set-specific power spectra of the stimulus envelopes to inspect the dominant frequency of each set-specific speech envelopes. We observed a strong overlap in power between the speech envelopes of each set. As shown in the power spectra (Fig. 2C), 5 out of the 6 sets had a peak at 3 Hz for the delta band and at 5 Hz for the theta band. Since these sets of stimuli had similar energy profiles (envelopes), this suggested that the variation in peak frequency within each set was not due to properties of the speech signal.

There has been a recent rise in popularity on the theory that entrainment is a result of the phase-resetting of ongoing oscillations. This theory assumes that the nature of oscillations are suited to track the rhythm of speech, and segregate speech into smaller chunks for processing (Ghitza, 2011; Giraud & Poeppel, 2012; Giraud et al., 2007; Poeppel, 2003). At the core of this proposal, oscillations track speech by adjusting their rhythm (phase) to match the rhythm of the speech signal (determined predominantly by the sharp edges of syllable/word onsets). Building on this proposal, we provide a tentative explanation of the observed variability in peak frequency of entrainment. The exact rhythm of the oscillations depends on the neural environment (e.g. balance between excitatory and inhibitory connections, distribution and expression of ion channels etc.), which are subject to interindividual differences. This variability could explain our observed variability in the peak frequency of entrainment. If entrainment was merely driven by the speech rhythm, then we would have expected all participants to have an oscillatory peak frequency that matched the predominant rhythm of the speech signal (i.e. at 3 and 5 Hz). In this manner, we speculate that entrainment is not simply a response to the speech rhythm but also influenced by factors intrinsic to the brain.

There is however, an alternative explanation for entrainment based on the superposition hypothesis drawn from early studies on auditory steady state responses (e.g.,Bohórquez & Özdamar, 2008; Capilla, Pazo-Alvarez, Darriba, Campo, & Gross, 2011; Galambos, Makeig, & Talmachoff, 1981; Hari, Hämäläinen, & Joutsiniemi, 1989). Specifically, the phenonmenon of entrainment could well be the result of a series of overlapping transient (event-related-like) responses to sharp rises in the envelope of the speech signal. In such a scenario, intrinsic ongoing oscillations are irrelevant, and the estimated entrainment would be just the frequency domain representation of the cross-correlation function between the brain's and the speech envelope's impulse response functions. In the case of the current study, evoked-responses will also have occurred in response to edges in the speech signal, and when quantified in the frequency domain might have produced activity that highly resembles oscillations in the theta band. Given interindividual variability in brain structure and function, our results on the variability in the peak frequency of theta entrainment could also be explained by variability in the transient response, expressed in the frequency domain.

To address which of these two theories holds more merit, we propose further investigations that build on our current findings of peak frequency variability. First, one could seek evidence for oscillations underlying entrainment by showing that in auditory regions, the individual frequency peaks of the on-going oscillatory activity in the absence of auditory input, for instance as identified during resting-state recordings, would correlate with the individual frequency peaks identified during auditory stimulation. This would demonstrate that oscillations are influenced by properties of the neural environment, and that in the presence of a stimulus (i.e. speech) will modulate its rhythm to the stimulus. Second, one could quantify the evoked responses to the edges in the speech signal and determine the variability of these responses in the frequency domain in terms of peak frequency in the power spectra. A correlation between the peak frequency in theta power of the transient responses and the peak frequency of entrainment across participants would be evidence for transient responses underlying entrainment.

Variable lateralization of low frequency entrainment as evidence against right-hemisphere bias for slow time scales

Multiple studies have shown entrainment at the delta, theta, and (infrequently at the) gamma band, providing much evidence that the brain is sensitive to information occurring at multiple time scales in the speech signal. However, evidence for the AST theory (Giraud & Poeppel, 2012; Poeppel, 2003) – that that left and right auditory cortex have a different temporal sensitivity profile, with right auditory cortex for slow rhythms and left for fast, remains equivocal. There is little evidence for rightward asymmetry in entrainment for slow rhythms, and even less evidence for leftward asymmetry for fast rhythms(Bourguignon, De Tiège, de Beeck, et al., 2013; Gross et al., 2013; Molinaro et al., 2013). Furthermore, Mcgettigan & Scott (2012) argue for several weakness in theories on asymmetrical speech perception.

In the current study, we found an almost equal division of left- and right-lateralized individuals for delta and theta entrainment (Fig. 4). Moreover, the degree of lateralization varied across individuals. This suggests that theories on asymmetrical speech perception need revision. The fact that we found a significant right-lateralization for theta entrainment at the group level was because on average, right-lateralized subjects had a higher normalized lateralization value (0.50) than left-lateralized individuals (0.31). In comparison, for the delta entrainment, the average normalized lateralization values were similar between left-lateralized (0.36) and right-lateralized individuals (0.36). Given the individual variation, we were also interested in whether hemisphere of lateralization in the delta band was related to the hemisphere of lateralization in the theta band. We post-hoc quantified this relationship using the McNemar's Test and found no significant effect ($X^2 = 0.26$, $p = 0.87$). This test suggested that there is insufficient evidence for an association between hemisphere of lateralization and frequency band. Altogether, our findings on lateralization are evidence against the AST theory that the right auditory cortex is biased for processing slow time scales (Giraud & Poeppel, 2012; Poeppel, 2003). Rather, we argue that there exists a hemispheric bias for slow time scales in the delta and theta band, but importantly, this bias is individually determined, and not with the right hemisphere as the default.

Previous studies that explicitly tested the AST theory have not used measures of oscillatory phase. The initial effort by Boemio et al. (2005) operationalized sensitivity to a specific temporal rate (in speech) as stronger activation i.e. an increase in the hemodynamic response. In support of the theory, they found bilateral primary auditory cortices to be sensitive to slow and fast time scales, and a lateralized sensitivity for slow time scales in right superior temporal regions (Boemio et al., 2005). Maintaining the same definition of sensitivity, evidence of oscillations supporting the AST theory was then demonstrated: a positive correlation between delta/theta power and the hemodynamic response in the right hemisphere, and a positive correlation between gamma power and the hemodynamic response in the left hemisphere (Giraud et al., 2007).

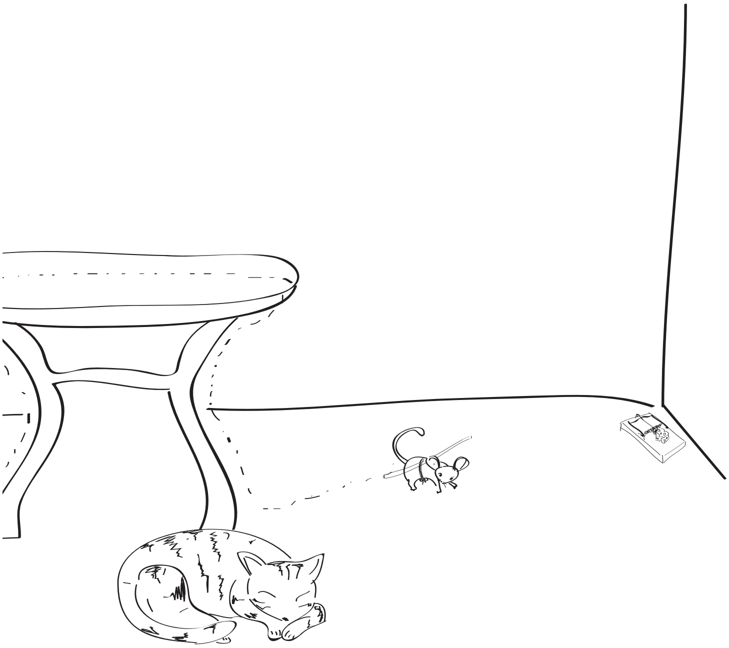
Importantly, the definition of sensitivity to temporal rate has evolved (or an alternative definition has become more popular), and is now operationalized as oscillations following the temporal rates in speech, i.e. oscillations are the underlying mechanism to auditory cortex being sensitive to speech rhythms. Under this new definition, the findings on oscillatory power, although valuable, do not truly demonstrate that oscillations in left and right auditory cortex preferentially follow fast and slow rhythms, respectively. This is because an increase in power demonstrates either (i) an increase in local synchrony between neurons within a focal region, or (ii) no change in local synchrony but stronger firing. These changes indicate that the brain responds to the speech input, but does *not* indicate that auditory cortex is *following*, i.e. truly sensitive to the rhythm in the speech. To demonstrate tracking between signals, one needs to quantify the degree to which one signal has a constant phase relationship to another signal. If the relationship is relatively constant, then this is evidence for one signal following the other. Measures of phase synchrony indicate whether oscillatory processes are in sync, in other words, whether neuronal oscillations follow the quasi-rhythmic events in the speech signal. A change in power has no direct bearings on (a change in) the phase relationship between two processes. Accordingly, previous studies looking at whether the brain is sensitive to the speech by means of rhythm tracking (regardless of lateralization) have used measures of phase synchrony such as Coherence, Phase-locking value, and Mutual Information (e.g., Bourguignon, De Tiège, De Beeck, et al., 2013; Joachim Gross et al., 2013; Luo & Poeppel, 2007; Peelle et al., 2013). Logically, to determine if this sensitivity differs between hemispheres, one should continue to use phase information. Consequently, in the current study we used coherence to quantify entrainment, and lateralization of coherence to determine the lateralization of entrainment. The use of power to quantify lateralization would not have provided definitive evidence against or for lateralization of entrainment.

2.6 Conclusion

Entrainment of cortical oscillations to speech has received increasing attention in the field of speech perception. Here, we performed a replication study on entrainment while improving on the stimuli and sample size used relative to previous studies. To date, our study with 102 participants is the largest, most powered MEG study done on entrainment. We quantified entrainment in terms of phase coupling between oscillations and the speech signal, in a wide range of frequencies from delta to gamma. We replicated entrainment in the low frequencies, but did not observe gamma entrainment. Importantly, for the first time in the field of entrainment, we showed individual differences in entrainment. The variation in peak frequency of entrainment is suggestive of the endogenous nature of the frequency at which oscillations entrain to speech, while the variation in the hemisphere to which low frequency entrainment lateralizes is evidence against a strict right-hemisphere bias for processing signals on a slow time scale. In summary, our findings shine new light on the oscillatory entrainment to speech. They motivate further investigation and revision of theories on neural entrainment to speech, and are a statement to the impressive speed at which the human auditory cortex responds and processes speech.

3

A QUEST ON WHETHER OSCILLATIONS OR EVOKED FIELDS UNDERLIE NEURAL ENTRAINMENT TO SPEECH



3.1 Abstract

A prominent hypothesis on what gives rise to the neural entrainment to speech is the phase alignment of oscillations to the speech envelope. Here, we argue that independent of intrinsic oscillations, it is the temporal superposition of evoked responses to salient edges in the speech envelope that give rise to entrainment. We recorded MEG during rest and during a speech listening task, and sought to provide evidence for or against both hypotheses by correlating the variation found in entrainment with the variation in intrinsic oscillations during rest, and with the variation in evoked fields during a listening task. In addition we created a surrogate MEG data set as a proof of principle for the superposition hypothesis. We found no significant correlations, and therefore no empirical evidence for either hypothesis but with our surrogate dataset we demonstrate the strong likelihood that the interaction between auditory evoked responses and speech edges can give rise to entrainment.

3.2 Introduction

Natural speech is a complex, continuous signal with information embedded at multiple temporal scales – on average phonemes occur every 25 – 40 ms, syllables every 125 – 250 ms, and words/phrases every 300 – 500 ms. To digest and comprehend this information, a series of brain processes are involved in parsing, extracting and combining various units of speech. The neural response to speech can be captured using Magnetoencephalography (MEG) and electroencephalography (EEG). One particularly robust phenomenon is the entrainment of neuronal oscillations in the theta band (around 4 – 7 Hz) to the speech signal, putatively resulting from frequency-specific phase alignment of neural activity with the sharp edges in the speech signal. The consistent observation of theta band entrainment, across a variety of speech stimuli and experimental manipulations, as well as its association with speech intelligibility (e.g., Abrams, Nicol, Zecker, & Kraus, 2008; Bourguignon, De Tiège, de Beeck, et al., 2013; Cogan & Poeppel, 2011; Gross et al., 2013; Luo, Liu, & Poeppel, 2010; Luo & Poeppel, 2007; Molinaro, Barraza, & Carreiras, 2013; Peelle, Gross, & Davis, 2013) suggests that theta entrainment is more than a useful neural marker for investigating how the brain processes speech. In particular, frequency-specific entrainment has been hypothesized to mechanistically facilitate the processing of speech.

Oscillatory phase-alignment hypothesis for entrainment

Many speech entrainment theories advocate that entrainment is a result of the phase alignment of intrinsic neuronal oscillations to the speech signal (Ghitza, 2011; Giraud & Poeppel, 2012; Goswami, 2011; Poeppel, 2003). Oscillations reflect cyclic fluctuations in the excitability of neuronal populations, and high phases of excitation within each cycle are optimal for processing input from the environment (e.g., Buzsáki & Draguhn, 2004; Schroeder & Lakatos, 2009; Schroeder, Wilson, Radman, Scharfman, & Lakatos, 2010; Van Rullen & Koch, 2003). The speech signal itself is quasi-rhythmic, alternating between phases of high and low information content. The envelope of the speech signal captures these linguistics fluctuations, and had a stable, quasi-periodic rhythm around 4 – 8 Hz, which makes it well suited for entrainment. Thus, the alignment of the high and low excitatory phase in oscillations to the high and low information content in the envelope, respectively, is argued to allow information to be optimally received and gated by the brain (e.g., Henry & Obleser, 2012; Schroeder & Lakatos, 2009). The alignment itself is argued to be triggered by salient changes, also referred to as edges, in the speech signal. The idea is that these edges occur at more or less regular intervals, in close temporal proximity, for a sufficient duration which allows entrainment to build up over time, given favourable input (e.g., Giraud & Poeppel, 2012)

The superposition of event-related responses hypothesis for entrainment

While the oscillations perspective holds merit, we argue that an alternative explanation for the entrainment may suffice. This proposal draws from investigations of steady-state visual responses. In this field, it has been a long-standing debate whether or not the steady-state response is a neural response that is qualitatively different from just a series of transient responses. Over the past decades, various studies have addressed the so-called superposition hypothesis (e.g., Bohórquez & Özdamar, 2008; Capilla et al., 2011; Galambos et al., 1981; Hari et al., 1989), which aimed at parsimoniously explaining the observed data in terms of overlapping transient responses. We advocate the idea that a continuous series of partially overlapping transient auditory responses to salient speech edges may result in signals that show 'entrainment'. In this scenario, ongoing oscillations do not play a role; rather, the estimated entrainment is simply the frequency domain representation of the relationship between the transient brain responses and the temporal characteristics of salient edges in the speech envelope. Below, we draw from basic signal processing and linear systems theory to explain our proposal. Subsequently, we present a set of tests done to evaluate both proposals on the nature of entrainment.

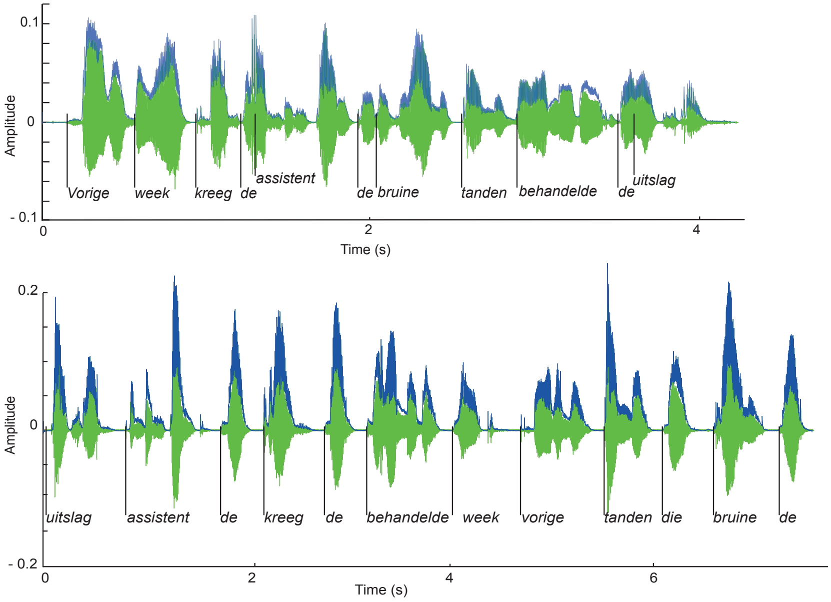


Fig. 1. Speech waveform (green) with envelope (blue). A spoken sentence (top) and a spoken word lists (below) from the stimuli used in this study are shown here. A transcription of each speech signal is shown in italic font and the onset of each word is marked with a black line.

By means of Fourier analysis, the speech signal can be decomposed into sinusoids (sine waves and cosine waves) of various frequencies, each with its own amplitude modulation over time. These sinusoids embody the acoustic properties of the various types of information in the speech signal such as phonemes, syllables, phrases, and intonation. Phonemic information (e.g., fricatives) is predominantly found in the high, broadband frequencies of the speech signal (Monson, Hunter, Lotto, Story, & Obleser, 2014; Vitela, Monson, & Lotto, 2015), whereas information regarding syllables and intonation are found the lower frequencies (Peelle & Davis, 2012). These amplitude modulations are captured in the temporal envelope of the speech signal (Fig. 1).

The speech envelope contains edges, which are sharp rises in amplitude, and in turn these edges trigger transient, evoked responses in the auditory cortex. In signal processing terms, in the temporal domain, these edges reflect *impulses* that impact the brain. Specifically, in response to the edges, the brain produces fast, transient signals referred to as *impulse response functions*. When a series of neural transients occur, this is referred to as an *impulse train*. In the case of speech, because it is a quasi-rhythmic signal, the speech edges occur at a quasi-rhythmic rate i.e. at reasonably regular intervals. These speech edges will thus produce impulse response functions in the auditory cortex (quantified as evoked potentials or evoked fields). As words are spoken quickly, one after another, the profile of these impulse responses functions will overlap and mimic a continuous quasi-periodic signal. In other words, if we consider the brain to be a linear system, the response of the brain can then be predicted in a straightforward way by means of a convolution of the impulse train with the impulse response function of the brain.

The average rate at which syllables occur in speech is about 125 – 250 ms, which translates to about 4 – 8 Hz in the frequency domain. Since syllable-related amplitude modulations are prominent in the speech envelope (Drullman, Festen, & Plomp, 1994; Ghitza, Giraud, & Poeppel, 2013; Greenberg, Carvey, Hitchcock, & Chang, 2003), and the onset of syllables form a subset of the edges in the speech envelope, this means that the average duration between auditory impulse response functions is likely to be driven by the syllable rate, producing a impulse train with a rhythm around 4 – 8 Hz.

Signals (like those representing speech and brain activity) are recorded in the time domain, but the relationship between times series in terms of rhythmic components are often quantified in the frequency domain. Indeed, most studies on entrainment have calculated the cross-correlation between the neural signal and the speech signal in the frequency domain (using measures like coherence, phase-locking value, and mutual information on band-limited signals). As they found correlations in the delta, theta, and gamma band, they concluded this to be evidence for intrinsic, ongoing oscillations giving rising to entrainment. Here, we argue that independent of oscillations, sequences of transient auditory evoked responses to speech edges that occur close in time will overlap, and thereby produce a pseudo-periodic signal that highly resemble oscillations. Thus, in fact the interaction between auditory evoked responses and the temporal sequence of edges in the speech envelope may be the cause of entrainment. As mentioned above, the concatenation and partial superposition of impulse response functions produces a signal that may mimic the profile of a true oscillation, and notably may show frequency-specific consistent phase relationships with the speech envelope signal. Thus, the phenomenon underlying the observed entrainment (as quantified as frequency-resolved coherence between the speech envelope and the neural signal) does not necessarily require the presence of intrinsic ongoing oscillatory activity ‘responding’ to the incoming speech signal. In the current study, we performed a series of tests to further determine whether the intrinsic oscillations hypothesis or the superposition of evoked responses hypothesis holds more merit.

Current study

In an earlier study (Chapter 2), we observed individual variability in the theta peak frequency of entrainment (as quantified by coherence) to spoken sentences. Here, we hypothesize that if intrinsic neuronal oscillations are necessary for the observed entrainment, then the variation in peak frequency should be inherent to the oscillatory dynamics of the neural system, and visible in different situations as well. Notably, for all participants reported in chapter 2, we had also obtained resting state measurements; thus, in the current chapter we set out to investigate the relationship between the peak frequency of intrinsic theta band activity during the resting-state, and the peak frequency of the entrainment. Studies by Giraud and colleagues (Giraud et al., 2007; Morillon et al., 2010; Morillon, Liégeois-Chauvel, Arnal, Bénar, & Giraud, 2012) have shown evidence for theta (and gamma) oscillations during rest. These oscillations were particularly prominent in auditory regions and correlated with resting state fMRI BOLD measures (Giraud et al., 2007; Morillon et al., 2010). The authors interpreted the results as evidence that oscillations work as an endogenous system for sampling speech. As such, one goal of the current study was to provide further evidence for this hypothesis.

On the other hand, if the observed entrainment results from the superposition of auditory evoked responses to speech edges, we would expect the variability in peak frequency of the entrainment to be related to variability in the evoked responses. To assess this relationship, we quantified the evoked responses to speech edges, and subsequently computed their power spectra, and assessed whether peak frequency in these power spectra covaried with the peak frequency of the entrainment, across individuals. In addition, we created surrogate MEG data by convolving an estimate of the brain's impulse response to speech edges with a data-derived temporal sequence of impulses. Our aim was to establish a high similarity between real MEG data and surrogate data. This serves as a proof of principle that evoked responses may provide a parsimonious explanation for the observed entrainment. In sum, this study compared the observed entrainment to speech (measured as coherence between the brain signals and the speech envelope of spoken sentences) with measures of resting state power, evoked field power (to spoken sentences), and simulated coherence (between surrogate brain and speech signals) to determine the necessity of assuming that intrinsic oscillations are a prerequisite for the observed entrainment.

3.3 Methods

Participants

A total of 102 native Dutch speakers (51 males), with an age range of 18 to 33 years (mean of 22 years), participated in the experiment. These participants formed part of the MOUS study (Mother of all Unification Studies; *N* = 204), and all participated in an fMRI and a MEG session. Half of these participants completed both sessions where they read the stimuli, and the other half listened to recordings of the stimuli. The current study pertains to participants from the MEG session in the auditory modality. All participants were right-handed, had normal hearing, normal or corrected-to-normal vision, and reported no history of neurological, developmental or language deficits. The study was approved by the local ethics committee (CMO – the local “Committee on Research Involving Human Participants” in the Arnhem-Nijmegen region) and followed the guidelines of the Helsinki declaration.

Language stimuli

The stimuli consisted of 360 sentences and their word list counterparts. The sentences varied between 9 and 15 words in length, of which half contained an embedded clause and half did not. The stimulus material was recorded by a native female Dutch speaker in a sound-proof recording booth. The speaker read the stimuli in a natural manner: the sentences were read at a regular pace with an average duration of 4.2 s (min: 2.8 s, max: 6.0 s), and the word lists were read with a brief pause between words, averaging 7.7 s (min: 5.5 s, max: 11.1 s). Subsequently, all stimuli were equalized to the same amplitude, and an onset and offset ramp of 10 ms was applied.

Sentence	**Word list**
Bij de opening van de nieuwe sporthal kregen de talrijke bezoekers een consumptie	sporthal bij van talrijke opening een de de kregen consumptie bezoekers nieuwe de
At the opening of the new sports hall received the many visitors a (free) drink	sports hall at from many opening a the the received (free) drink visitors new the

Table 1. Exemplar sentence and word list in Dutch, and literal English translation.

Task and Procedure

Experimental Design

All stimuli were presented using Presentation software Version 16.0, Neurobehavioral Systems, Inc).
Visual stimuli were presented with an LCD projector (with a vertical refresh rate of 60 Hz) situated outside the MEG, and projected via mirrors onto the center of the screen inside the MEG room, within a visual angle of 4 degrees. During the resting state session and speech session, to reduce eye movements, participants were instructed to focus on a fixation cross. Specific to the speech session, questions were presented in black mono-spaced font, on a gray background. The auditory stimuli were presented only in the speech session (sentences and word lists), binaurally via MEG-compatible tubes.

Resting State session

Each MEG session began with an eyes-open resting state recording for 5 minutes.

Speech session

We divided the sentences into 6 groups of 60 sentences. Using a Latin square design we created 6 sets of stimuli, each consisting of 2 groups (i.e. 120 sentences). Participants were exposed to one of the 6 sets. Participants assigned the same set had sentences presented in a different (randomized) order. In the experiment, the stimuli were presented in a mini block design, and alternated between a sentence block (containing 5 sentences) and a word list block (containing 5 word lists), for a total of 24 blocks. The first mini block (sentences or word lists) was randomized across participants.

At the beginning of each block, the block type was announced for 1500 ms: *zinnen* (sentences) or *woorden* (words), followed by a 2000 ms blank screen. At the beginning of each trial a fixation cross was presented for a jittered duration between 1200 – 2200 ms. Subsequently, the auditory signal was presented for each trial (sentence or word list), and the fixation cross remained on the screen until the auditory signal was completed. Within each block, the inter-trial interval was a blank screen with a jittered duration between 1200 – 2200 ms.

In order to check for compliance, 10% of the trials were randomly followed by a yes/no question about the content of the previous sentence/word list. Half of the questions on the sentences addressed sentence comprehension (e.g. *Did grandma eat a pancake?).* The other half of the sentences, and the questions following the word lists addressed a content word (e.g. *Was a music instrument named?*). Participants answered the question by pressing a button for 'Yes'/ 'No' with their left index and middle fingers, respectively. For both question types, half of the trials had a yes-response as the correct answer.

Prior to performing the sentence listening task, we adjusted the hearing level for each subject. To ensure a sufficient cortical auditory response, the minimal auditory threshold was determined, and subsequently all auditory stimuli were presented at 50 dB above the minimum threshold. For task familiarization purposes participants completed a practice task (using a separate set of stimuli from the actual task).

MEG data acquisition

MEG data were collected with a 275 axial gradiometer system (CTF). The signals were digitized at a sampling frequency of 1200 Hz (the cutoff frequency of the analog anti-aliasing low pass filter was 300 Hz). Three coils were attached to the participant's head (nasion, left and right ear canals) to determine the position of the head relative to the MEG-sensors. Throughout the measurement the head position was continuously monitored using custom software (Stolk et al., 2013). During breaks the participant was allowed to reposition if needed. Participants were able to maintain a head position within 5 mm of their original position. Three bipolar Ag/AgCl electrode pairs were used to measure the horizontal and vertical electro-oculogram, and the electro-cardiogram.

Data processing

All analyses were done with custom written Matlab scripts and FieldTrip (Oostenveld et al., 2011).

Artifact detection

The analysis for both the resting state and speech data began with the same processing step of artifact detection. Physiological artifacts (eye movements and muscle contractions) and *superconducting* quantum interference device (SQUID) jumps were identified using a semi-automatic artifact identification procedure (http://www.fieldtriptoolbox.org/tutorial/automatic_artifact_rejection), followed by visual inspection. Data segments that contained artifacts were not subjected to further analysis. After rejection, the average percentage of data retained was 85% for the resting state data and 80% for the speech session. Data collected in the speech session was subsequently analyzed in 2 ways: For coherence between the MEG data during the speech session and the speech envelope, and for the frequency domain representation of the evoked fields in the form of a power spectrum.

Speech session

From the speech session, we quantified coherence between oscillations in the frequency domain and the speech envelope, and the frequency domain representation of the evoked response. All analysis steps for calculating coherence was performed in an earlier study (see Chapter 2) but repeated here for ease of reading.

Preprocessing

The envelope of each speech signal was constructed from the original audio files (sampled at 44 kHz) as the sum of the Hilbert envelopes of 10 distinct bandpass filtered frequency bands of the original auditory signal (as per Gross et al. 2013). Subsequently, each envelope signal was downsampled to 1200 Hz, and temporally aligned to the corresponding MEG data. The MEG signal was initially epoched into the individual sentences, demeaned, and the power line interference was removed using a band stop filter (finite impulse response window sinc filter) between 49 to 51 Hz. Subsequently, the MEG signal and speech signal were downsampled to 300 Hz, and cut into 2 s long epochs (with a 50% overlap) which produced a frequency resolution of 0.5 Hz. To facilitate the combination of MEG topographies across subjects, the data was transformed to a synthetic horizontal and vertical planar gradient representation using spatial interpolation. Subsequently, sensor level coherence was computed between brain signals and the speech envelope.

Coherence Analysis

To quantify entrainment of the MEG signal to the speech envelope we calculated coherence. To do this, we first computed the power spectrum for each signal, and the cross spectrum between the speech signal and brain signals. To do this, each epoch was tapered (using multiple tapered versions of the epoch) to achieve a spectral smoothing of ± 2 Hz. Subsequently each tapered epoch was Fourier-transformed and the cross- and power-spectra were calculated.

$$S_{ab}(f) = F_a(f) \times F_b(f)^* \qquad (1)$$

F_a denotes the Fourier-transform of the signal a (a particular MEG channel or the speech envelope) at frequency f, while * represents the complex conjugate. The cross spectrum was obtained by multiplying the Fourier-spectrum of one signal (e.g., from an MEG channel) with the conjugate of the Fourier-spectrum of another signal (e.g., speech). When a = b, then the Fourier-spectrum of one signal is multiplied with its own conjugate which produces the power spectrum. Coherence Coh_{ab} was then calculated as follows:

$$Coh_{ab} = \left|\frac{S_{ab}}{\sqrt{S_{aa} \times S_{bb}}}\right| \qquad (2)$$

In this formula, the power spectrum and cross spectrum reflect the average across trials. Coherence values range from 0 to 1, with 0 indicating no consistent phase relationship between signals, and 1 indicates a fully consistent phase difference between signals.

Resting state session

Preprocessing

The resting state data was high pass filtered at 0.5 Hz, downsampled to 200 Hz and then cut into 2 s long epochs (with 50% overlap). Power spectra typically demonstrate a fall-off that is proportional to 1/f, with the exception of alpha band oscillations (8- 12 Hz), which are prominent during rest. This 1/f characteristic is typically dealt with in experimental situations by computing a contrast between 2 conditions, or comparing against a baseline. This allows for peaks in the power spectrum to become more pronounced. As we aimed to detect peaks in the theta band (4 – 7 Hz) of the resting state power spectra, where no control condition is possible, band-limited features could be buried within the 1/f noise and be undetected. To solve this, we made use of temporal pre-whitening, which aims to make the power spectra 'white' by flattening the 1/f profile as a function of frequency, which in turn makes the band-limited peaks stand out. To achieve this, for each epoch, we applied a univariate autoregressive model (order = 1) to the signal. While the low order model does not fit the data well, it is able to capture the salient aspect of the temporal structure in signal which is the 1/f profile. Subsequently, the modeled time series is subtracted from the data and results in the residuals which are used in the subsequent step.

Time-Frequency Analysis

Prior to computing the power spectrum, each epoch was zero-padded to 2 seconds because one sample of data was lost due to the multivariate autoregressive model applied during pre-whitening. Then, a set of multitapers (Mitra & Pesaran, 1999) were applied to achieve $\pm$1 Hz from 1 to 12 Hz, and the Fourier transform applied.

Evoked Fields

Preprocessing

To obtain the evoked responses the MEG signal was epoched into individual sentences, artifactual segments were removed, and a band pass filter (finite impulse response window sinc filter) between 1 and 40 Hz was applied. Then, both the MEG signal and the speech envelope were downsampled to 300 Hz.

To determine the evoked fields that occur in response to the speech edges, we identified the speech edges from the speech envelope signals, which we quantified as upward going ramps. To do this we computed the temporal derivative of the speech envelopes, to which we applied boxcar smoothing (with 5 samples) and normalization (Z-scoring). Subsequently, we applied a peak detection algorithm with a threshold of 1) which produced a set of indices that marked the location (time points) of the edges in the speech envelope. Finally, the MEG signals were epoched according to the identified edges, and averaged in order to produce the evoked fields to the speech edges.

Frequency Analysis

The power spectrum were calculated only from the MEG sensors overlying the temporal lobes (68 sensors) as the auditory response is usually most prominent in these sensors. A zero-padding of 2 seconds was applied to have all epochs at the same length in duration, and the linear trend was removed. Then, the Fourier transform was applied using a Hanning taper for each integer frequency from 0 to 20 Hz.

Peak frequency selection

In a previous study (see Chapter 2) we observed considerable variability across participants for the frequencies at which peaks occurred. In the current study, we sought to identify whether the variation previously found across participants would also be present in the power spectrum of oscillations during MEG resting state, or in the power spectrum of the auditory evoked responses. Evidence for this variation in the former would be support for oscillations giving rise to entrainment, and evidence for the latter would be support for evoked fields giving rise to entrainment.

For each participant the same peak detection process was used for the coherence spectrum and the two sets of power spectra. First, a peak detection algorithm was used to identify, for each channel, the frequency bins that showed a distinct peak in the spectrum. For the coherence spectrum, the threshold was set at 0.02, while for the power spectrum of the resting state and evoked fields the threshold was set at 0. This yielded a binary vector (as a function of frequency), with a 1 indicating a peak, for each channel. Next, these binary vectors were summed across channels yielding a single vector with a spectrum of peak counts across channels. The assumption here was the higher the peak count, the more reliable the peak, since it showed up as a peak in a larger number of sensors. Then, this vector was multiplied to a second vector containing the standardized coherence/power across frequencies. This accounted for variance in strength of coherence/power. The weighted vector was then smoothed (boxcar of 2 samples). Finally, a second peak detection on this vector was performed to identify the peak frequencies across the sensor array. For both the coherence and resting state power spectrum, a threshold was set to 2, while for the evoked field power spectrum a threshold was set at 0. Comparison of the estimated peak frequency with visual identification of the peak frequency for 10 subjects determined this peak detection process to be adequate.

Thresholds used for the first and second round of peak detection of each spectrum were optimized to fit the data. For the coherence spectrum, the threshold at the first round was set to 0.02, and in the second round to 2. For the resting state power spectrum, the threshold at the first round was set to 0, and the second round to 2. For the evoked field power spectrum, the threshold at the first and second rounds were set to 0. For all three analyses, peak detection was performed between (and including) 4 to 7 Hz, at 0.5 Hz steps, and across all MEG channels.

Construction of surrogate data

To demonstrate that auditory evoked fields may explain the observed entrainment we constructed surrogate data and performed a coherence analysis, similar to the entrainment analysis of the real data. This was done as follows. First, we calculated the evoked fields in response to the edges of the spoken word lists, in the same manner as we did for the spoken sentences (see Evoked Fields section above). Then, these evoked fields were convolved with an impulse train (a vector containing only zeros and ones, with a '1' defining the occurrence of a speech edge) created from the estimated distribution of edge intervals from the spoken sentence data, producing surrogate MEG and speech envelope data. Next, we added pink noise (with a 1/f profile) to the surrogate MEG data, to better mimic the original MEG data. Finally, we computed coherence between the surrogate MEG and speech envelope data, a measure we refer to as 'surrogate coherence'.

Correlation

We were interested in whether there would be a covariation between the peaks in the coherence spectrum (used to quantify entrainment of the supposed neuronal oscillations to speech) with the peaks in the power spectrum of resting state oscillations, in the power spectrum of evoked fields, or the coherence spectrum from the surrogate data (surrogate coherence). To assess this we performed the Pearson's correlation across subjects between the peak frequencies obtained from the coherence spectrum and the peak frequencies obtained from each of the power spectrum.

3.4 Results

Coherence spectrum

In a previous study (see Chapter 2) we quantified the entrainment of neuronal oscillations to the speech envelope using the coherence coefficient. We observed phase coupling between oscillations and speech in the theta band (4 – 7 Hz). At the single subject level, the peak in the theta band is clearly discernible and has a spatial distribution which is maximal over temporal-parietal sensors, which is characteristic of a response in auditory regions (Fig. 2). Across all participants (*N* = 102), we observed a peak frequency in 91 participants, and the peaks varied between 4 – 7 Hz, with 7 Hz being the most common (Fig. 2). In the current study, we hypothesized that if entrainment result from intrinsic oscillations, then the characteristics should be similar between the coherence coefficient and resting state power. Alternatively, if entrainment arises from evoked responses, then we expect similar characteristics between the coherence coefficient and evoked field power. That is, one of these measures (resting state power or evoked field power) would have a topography and interindividual variability in peak frequency that is similar to that shown for the coherence coefficient.

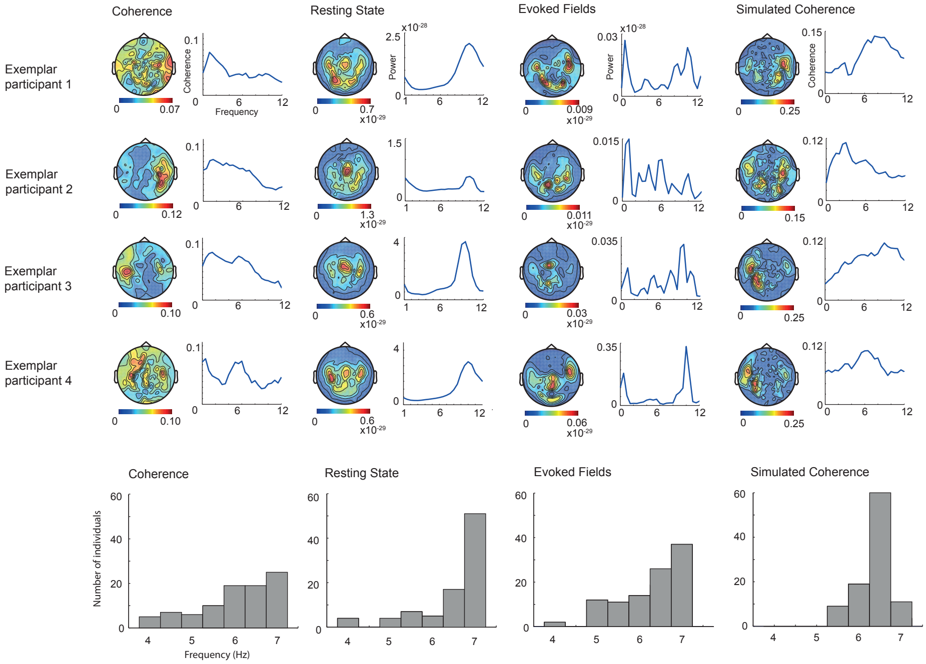


Fig. 2 Topoplots in the theta band (4 - 7 Hz) and spectra for measures of coherence and power for 4 exemplar participants. Spectra are chosen from the average of the top 10 strongest sensors across all sensors above temporal lobes. Coherence is calculated between oscillations and the speech envelope of spoken sentences. Resting state oscillatory power is calculated from an eyes-open resting state session of 5 minutes. Evoked fields are auditory evoked fields to the speech edges in spoken sentences. Surrogate coherence was calculated from the surrogate MEG dataset created by convolving evoked fields to edges in spoken word lists with an impulse train of the estimate distribution of edges intervals from spoken sentences. *Bottom*, Histogram of peak frequencies in the theta band for coherence and power measures.

Resting state power spectrum

We computed the power spectrum for oscillations during MEG resting state. To facilitate the detection of theta peaks in oscillatory power, we pre-whitened the MEG signal prior to computing the Fourier Transform. Figure 3 shows the effect of the pre-whitening step for a few example participants. As expected, the pre-whitening reduced the 1/f profile, and resulted in a relatively more prominent peak in the alpha range. Yet, there was no clear indication that the pre-whitening facilitated the more reliable extraction of a peak in the theta range. Note that not all participants had a peak in the theta band, as seen in Fig. 3, the theta peak is more prominent in participant 3 than participant 2, while participant 1 does not appear to have one. Across all participants, we extracted a theta peak in 88 participants, where the frequency varied across participants, with 7 Hz was the most common peak. Given the differences between resting state power and the coherence coefficient in spatial distribution and spectral profile, we were unlikely to observe a significant covariance between measures. Indeed, using the pearson's correlation we found no significant relationship between the peak frequencies of the measures (r = -0.02, *p* = 0.88) (Fig. 4).

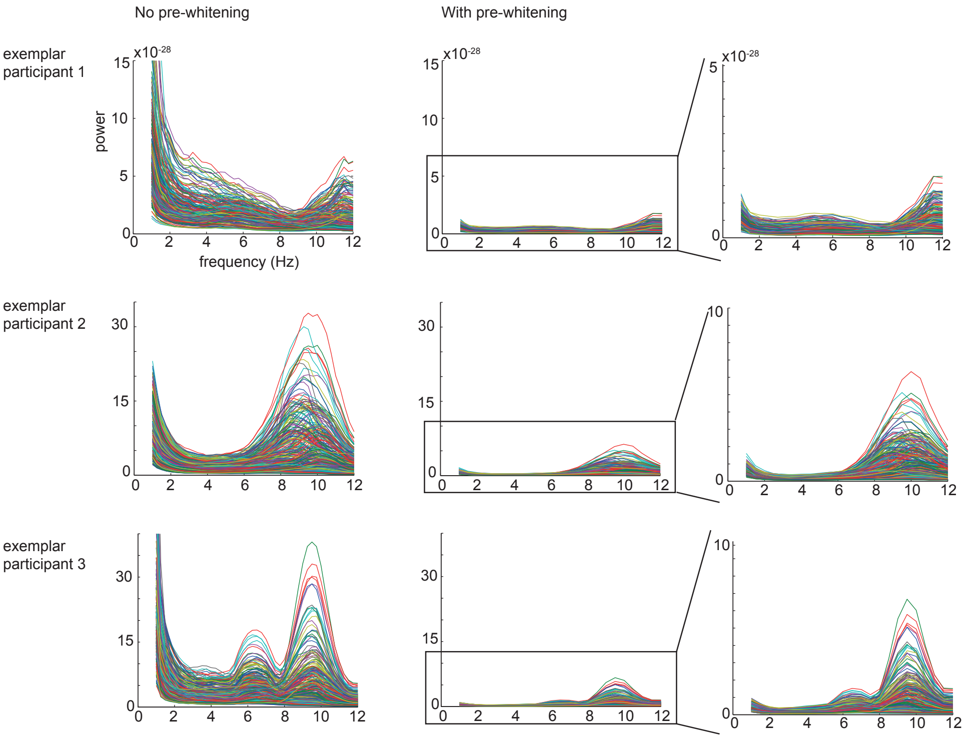


Fig. 3 Power spectra without and with pre-whitening in 3 exemplary participants. Across participants is a degree of variation, but in general the pre-whitening step reduced the 1/f characteristic in the power spectra which in turn improved the clarity of the peak in the theta band (4 - 7 Hz).

Evoked fields power spectrum

We identified the evoked fields associated with the speech (onset) edges in the time domain (Supp. Fig. 1), and quantified them in the frequency domain by calculating the power spectrum of the evoked fields. As shown in Fig. 2, we observed peaks in the theta band, but also in many of the other nearby frequencies. We found a theta peak in all 102 participants, and again, the peak frequency varied between 4 to 7 Hz, with 7 Hz being the most common peak. The spatial distribution of the theta peak was found to vary across participants, some had a maximal distribution in temporal (and occipital) channels while others had a maximal distribution in central sensors. The differences between the coherence coefficient and the evoked potential power suggested that there was unlikely covariation between the peak frequencies of these two measures. Indeed, using a Pearson's correlation to assess covariance we found no significant relationship (r = -0.07, *p* = 0.5) (Fig. 4).

Surrogate Coherence

As another approach to try to demonstrate that evoked responses can give rise to entrainment we calculated a coherence coefficient from a surrogate MEG dataset created by concatenating the evoked fields to the speech edges in spoken word lists, referred to as surrogate coherence. As shown in Fig. 2, at the single subject level, the spatial distribution of surrogate coherence between 4 – 7 Hz was maximal over temporal-parietal sensors, resembling that of original coherence. Also, the theta peaks in the surrogate coherence spectra are clearly displayed at the single subject level, and in some participants have a similar spectral profile to the original coherence spectra (see participant 2 and 4 in Fig. 2). To further assess the relationship between simulated coherence and original coherence we quantified the covariance in peak frequencies between the two measures with the Pearson's correlation. Although we found a positive correlation it was non-significant (r = 0.12, *p* = 0.27) (Fig. 4).

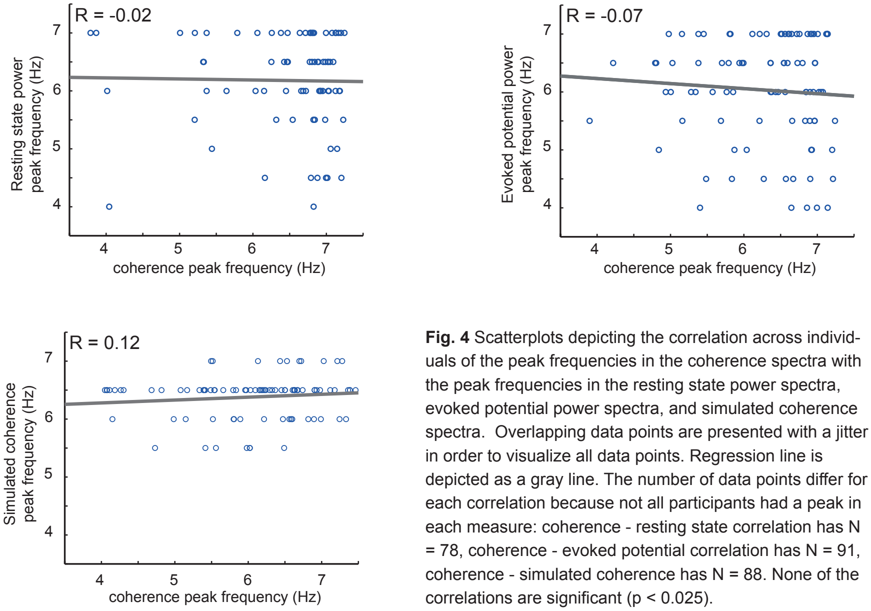


Fig. 4 Scatterplots depicting the correlation across individuals of the peak frequencies in the coherence spectra with the peak frequencies in the resting state power spectra, evoked potential power spectra, and simulated coherence spectra. Overlapping data points are presented with a jitter in order to visualize all data points. Regression line is depicted as a gray line. The number of data points differ for each correlation because not all participants had a peak in each measure: coherence - resting state correlation has N = 78, coherence - evoked potential correlation has N = 91, coherence - simulated coherence has N = 88. None of the correlations are significant (p < 0.025).

3.5 Discussion

The entrainment of intrinsic neuronal oscillations to speech is popularly considered as a means for the brain to track and parse spoken language (Ghitza, 2011; Giraud & Poeppel, 2012; Giraud et al., 2007; Goswami, 2011; Morillon & Schroeder, 2015; Poeppel, 2003). Many theories advocate that the phase-resetting of oscillations to the quasi-periodic edges in speech aligns oscillations to that of speech. As oscillations reflect the temporal fluctuation of excitability in neuronal populations, oscillatory alignment is argued by these theories to allow the brain to selectively track and amplify relevant information in speech. In the current study, we sought to provide evidence in favour of or against the hypothesis that intrinsic neuronal oscillations are a necessary prerequisite for the observed entrainment. We did so by quantifying the relationship between the original coherence (between brain signals and the speech envelope) with resting state oscillations and auditory evoked activity, and performing a data simulation.

Do intrinsic oscillations give rise to entrainment?

We hypothesized that if entrainment arises from intrinsic oscillations, then the individual variability in peak frequency of speech-brain coherence would correlate with the variability in peak frequency power from the resting state session. We extracted theta peaks from the resting state power spectrum but they did not have a similar spectral distribution or spectral profile that resembled the coherence peaks, (Fig. 2) nor was there a correlation between the peak frequencies of the two measures. Thus, we did not have convincing evidence for the hypothesis that intrinsic oscillations give rise to entrainment.

One reason for a lack of correlation could be because we could not adequately detect theta peaks despite the use of pre-whitening to decrease the 1/f profile and better extract the theta band activity. Of the 88 participants that had a theta peak, not all peaks were distinct. In addition, when we performed the peak detection a second time, using a broader definition of the theta band (4 – 8 Hz, instead of 4 – 7 Hz) we noticed that 40 of the participants now, instead, had a peak at 8 Hz. This suggests that some theta activity was simply from activity in the alpha band, which is next to the theta band and has a prominent presence (higher power). The necessity to distinguish theta from alpha activity is further highlighted in a recent study by Keitel and Gross (2016). They showed that listening to speech, compared to at rest, leads to an increase in delta and theta oscillatory power, and a disappearance of alpha activity. As alpha activity is not consistently present in both rest and task, if part of the theta activity in our study is due to alpha activity, then this could partially explain the lack of correlation. To improve the detection of theta band activity, it would be worthwhile to consider the joint-decorrelation method from de Cheveigne and colleages (Cheveigné & Arzounian, 2015; Cheveigné & Parra, 2014). This method is optimized to deal with situations of non-optimal signal-to-noise ratio by exploiting information on how the data is correlated between channels in order to suppress noise (activity outside the limited bandwidth of interest), and thereby extracting band-limited activity.

At a conceptual level, if intrinsic oscillations are involved in entrainment, temporally inhibiting these oscillations should reduce entrainment. Several studies have demonstrated the field of cortical stimulation techniques (such as transcranial magnetic stimulation, transcranial direct current stimulation, and transcranial alternating current stimulation) to 'inhibit', 'enhance', or 'entrain rhythms' and produce behavioural consequences (Kanai et al., 2008; Wolfgang Klimesch, Sauseng, & Gerloff, 2003; Marshall, Helgadóttir, Mölle, & Born, 2006) but we are still in the early days of brain stimulation research. The precise nature of the effects of cortical stimulation is not yet well understood. For instance, we know that cortical stimulation pulses can produce oscillatory-like rhythms in the brain (e.g., Herring, Thut, Jensen, & Bergmann, 2015; Marshall, Helgadóttir, Mölle, & Born, 2006), and there is evidence that TMS produce oscillations that have the same neural origin as intrinsic oscillations (Herring et al., 2015). However, to make use of brain stimulation to inhibit entrainment, we first need to address the following questions: (i) How and where do the oscillations in entrainment come about (assuming they are oscillations)? (ii) What is being inhibited (how does inhibition occur neurobiologically) with cortical stimulation and what is its extent of influence in the brain? (iii) Can we use to (ii) to address (i)? Should we be able to tackle these questions, then can we can attempt to use brain stimulation to address the role of oscillations in speech entrainment

Do evoked fields give rise to entrainment?

An alternative explanation for the observed entrainment is the superposition of auditory evoked activity that occurs in response to edges in the speech envelope. This could be investigated by exploration of the spectra of the evoked fields. Again, we did not find a correlation between variability in peak frequency of the power spectrum of the evoked fields with the variability in peak frequency of coherence. As with the resting state power results, theta activity of the evoked field power did not have a spatial distribution or spectral profile similar to that for coherence. Furthermore, as in the resting state results, by relaxing the peak detection boundary to 4 to 8 Hz, we found that 35 of the 102 participants now had a peak at 8 Hz, suggesting that a subset of the theta peaks were due to alpha power leakage. However, the lack of evidence for an interaction between evoked field power and coherence may not be surprising from a signal processing perspective. The measure of coherence results from the interaction between the speech envelope and the brain signal, and makes use of phase information whereas the evoked fields were quantified on their own (not with their interaction to the speech envelope) and makes use of power information. To better relate the coherence measure, which was quantified as a frequency-domain cross-correlation between the speech envelope and the brain signal, one approach is to also perform a frequency-domain cross-correlation between the auditory evoked fields and the speech envelope. The approach used in the surrogate coherence is of a similar note, where we concatenate the evoked fields into a continuous brain signal and used it to perform a cross-correlation with the speech signal.

Surrogate coherence: a case for the superposition of evoked responses

As a proof of principle that evoked fields may provide a parsimonious explanation for the observed entrainment we calculated surrogate coherence. Here, we temporally concatenated auditory evoked fields to edges in the spoken word list, and then convolved it with the inter-edge interval from the spoken sentences to create a surrogate MEG dataset. In support of the superposition hypothesis, the coherence of this surrogate dataset produced a similar spatial topography (and in some participants, a similar spectral profile) as the original coherence measure. Albeit non-significant, we also found a positive correlation between simulated coherence and original coherence. This finding suggests that the observation of entrainment does not need to assume the presence of intrinsic oscillations.

Based on our simulated findings, we consider the possibility of how having superimposed evoked responses underlying entrainment influences current theories on entrainment. The first issue is that these theories consider speech edges as an important factor that drives entrainment. For instance, in their model, Giraud & Poeppel (2012) proposed that speech edges cause oscillations to phase-reset and thereby align to the speech envelope for accurate parsing. In support of this Doelling, Arnal, Ghitza, & Poeppel (2014) demonstrated that the removal of speech edges at the syllabic rate reduced entrainment in the delta – theta bands, while the artificial reinsertion of edges restored entrainment. Crucially, our advocacy for the superposition of evoked responses maintains the importance of speech edges. But instead of eliciting phase-reset, we argue that these speech edges elicit evoked responses. With speech edges occurring at a reasonable pace and at a close temporal distance, this leads to a sequences of transient auditory evoked responses which overlap in time, producing a pseudo-periodic signal that highly resemble oscillations. As such, when quantifying the brain signal in relationship to the speech signal in the frequency domain, this produces a clear measure of entrainment.

A second issue is that of speech intelligibility. Several studies have found that entrainment has been associated with speech intelligibility in several studies (Ahissar et al., 2001; Drullman et al., 1994; Ghitza, 2011; Nourski et al., 2009; Peelle & Davis, 2012; Peelle et al., 2013) but there is an ongoing debate as to whether a decrease in phase-locking leads to acoustic cues leads to lower intelligibility, or whether less intelligible (i.e. a decrease in linguistic cues) leads to lower intelligibility. Recently, there has been more evidence that acoustic cues drive entrainment. Howard & Poeppel (2010) showed that phase-information from reversed speech was just as accurate at speech discrimination as was the phase-information from regular sentences. Furthermore, it has been shown that both intelligible speech and unintelligible speech (reversed speech, noise-vocoded speech) can elicit entrainment (Ahissar et al., 2001; Howard & Poeppel, 2010; H. Luo & Poeppel, 2007; Millman, Johnson, & Prendergast, 2015; Park et al., 2015; Peelle et al., 2013). Although one could argue that intelligible speech might elicit stronger entrainment than unintelligible speech, that has been found in some studies (Doelling et al., 2014; H. Luo & Poeppel, 2007; Park et al., 2015; Peelle et al., 2013) but not others (Howard & Poeppel, 2010; Millman et al., 2015; Zoefel & VanRullen, 2016). In support of the acoustic cues hypothesis, our surrogate coherence results lend further support to the idea that entrainment is driven by acoustic cues – edges in the speech envelope – in the absence of linguistic information such as meaningful syntactic or semantic structure.

3.6 Conclusion

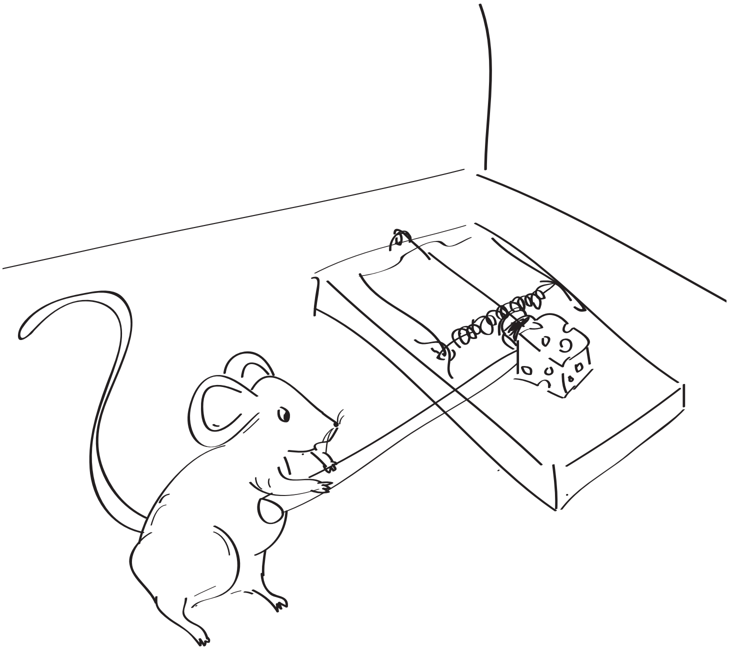
The comprehension of spoken language requires rapid processing of the auditory signal. In the current study we focused on the robust phenomenon of entrainment whereby neural activity is able to adapt to the rhythm of speech to facilitate speech perception. Here, we investigated whether the entrainment requires intrinsic oscillations, as proposed by many models, or whether a superposition of evoked responses is sufficient to observe entrainment. Although unable to provide empirical evidence, using a simulated MEG dataset, we demonstrated that evoked responses to edges in the speech signal are a plausible candidate for giving rise to entrainment. Further investigation on how evoked responses interact with the speech signal will be important for understanding spoken language processing.

4

NEURAL ACTIVITY DURING SENTENCE PROCESSING AS REFLECTED IN THETA, ALPHA, BETA AND GAMMA OSCILLATIONS

This chapter is based on:

Lam, N. H. L., Schoffelen, J., Uddén, J., Hultén, A., & Hagoort, P. (2016).
Neural activity during sentence processing as reflected in theta, alpha, beta, and gamma oscillations. *NeuroImage*. http://doi.org/10.1016/j.neuroimage.2016.03.007



4.1 Abstract

We used magnetoencephalography (MEG) to explore the spatio-temporal dynamics of neuronal oscillations associated with sentence processing, in 102 participants. We quantified changes in oscillatory power as the sentence unfolded, and in response to individual words in the sentence. For words early in a sentence compared to those late in the same sentence, we observed differences in left temporal and frontal areas, and bilateral frontal and right parietal regions for the theta, alpha, and beta frequency bands. The neural response to words in a sentence differed from the response to words in scrambled sentences in left-lateralized theta, alpha, beta, and gamma. The theta band effects suggest that a sentential context facilitates lexical retrieval, and that this facilitation is stronger for words late in the sentence. Effects in the alpha and beta band may reflect the unification of semantic and syntactic information, and are suggestive of easier unification late in a sentence. The gamma oscillations are indicative of predicting the upcoming word during sentence processing. In conclusion, changes in oscillatory neuronal activity capture aspects of sentence processing. Our results support earlier claims that language (sentence) processing recruits areas distributed across both hemispheres, and extends beyond the classical language regions.

4.2 Introduction

How are you reading this sentence? Conceptually, the reader needs to retrieve and understand the meaning of individual lexical items (words), and combine these items to derive an interpretation spanning its entirety. The latter process is referred to as unification (Hagoort, 2003, 2005, 2013). At the neural level, the fast and incremental nature of sentence processing likely involves multiple brain regions. Yet, we know little about how the brain orchestrates sentence processing because the majority of neuroimaging studies on language processing have focused on the single word level. Of the studies that focused on sentence processing, most used syntactic or semantic anomalies as an experimental manipulation. Considering daily language exposure, this questions the ecologically validity of such stimuli. Moreover, although the experimental designs were well controlled, these studies related neural responses only to specific critical events within a sentence. Consequently, the processing of each word in a sentence, and how it is affected by an incremental context, has not been studied in detail. In the current study, we address these two aspects of sentence processing using natural sentences. We focused on the modulation of neuronal oscillations in response to individual words in the context of a sentence, and examined how this modulation changed as the sentence unfolded.

Oscillatory neural activity

When studying electrophysiological signals, spectral analysis techniques are aimed at quantifying frequency specific neural activity. These techniques were initially used to study rhythmic activity during visual processing, or low-level motor behavior, and then gained popularity in the 2000s to study higher order cognition, such as language (Hari & Salmelin, 2012). Beyond capturing the transient response to external events, estimates of frequency specific activity reflect oscillatory neural activity that is not necessarily time- or phase-locked to an event, as opposed to event-related averages. Thus it may provide a different but complimentary perspective on how the brain orchestrates language (including sentence) processing. Furthermore, this technique allows us to investigate the relationship between aspects of sentence processing and the spatio-temporal dynamics of oscillatory activity.

The power of oscillatory activity has been observed to be modulated in many cognitive tasks. These modulations are typically described as relative decreases (event-related desynchronization, ERD; Pfurtscheller & Aranibar, 1977) or relative increases (event-related sychronization, ERS; Pfurtscheller, 1992). Depending on the frequency band, such power changes may indicate either activation or deactivation of a brain region. An ERD in the gamma band (>40 Hz) reflects a reduction in processing in underlying cortical regions, but would reflect increased processing when observed in the alpha (8–12 Hz) or beta (13–30 Hz) bands (Jensen & Mazaheri, 2010; W Klimesch et al., 1997; Osipova et al., 2006). For the theta frequencies, however, it is equivocal as to whether an ERD reflects activation or deactivation. Oscillatory neural activity can be productively studied using MEG. This method has good spatial resolution and excellent temporal resolution (in the order of milliseconds), which enables it to capture rapid (tens of milliseconds) changes associated with cognitive processes in the brain.

Studying sentence processing with oscillations

Both ERS and ERD have been observed in studies concerned with sentence processing, but most studies analyzed the data on the sensor-level which provided poor spatial localization of the effects, and most of them focused on a single word (that produced a grammatical violation) in the sentence (e.g., Bastiaansen, Magyari, & Hagoort, 2009; Davidson & Indefrey, 2007). Across these studies, different frequency bands have been associated with different functional explanations. The theta and alpha bands, for example, have been associated with the lexical-semantic retrieval of words (Bastiaansen, van der Linden, Ter Keurs, Dijkstra, & Hagoort, 2005; Klimesch et al., 1997). Beta and gamma band ERS has been suggested to reflect unification of the semantic and syntactic information in sentences, respectively (Bastiaansen & Hagoort, 2015; Bastiaansen, Magyari, & Hagoort, 2009; Hald, Bastiaansen, & Hagoort, 2006). The alpha and beta bands have also been demonstrated to be involved in syntactic processing (Bastiaansen et al., 2010; Davidson & Indefrey, 2007; Kielar et al., 2015). Overall, these results, whilst suggestive, highlight the need for further study of oscillations in sentence processing, specifically to study multiple frequency bands in one dataset, and to understand their relation to each other.

In sentence processing, words are retrieved from memory and combined into an interpretation of the larger phrase, regulated by semantic and grammatical constraints (Hagoort, 2013). A recent fMRI meta-analysis revealed consistent involvement of the left inferior frontal gyrus (BA 45 and BA 47), left middle temporal gyrus (MTG), and left superior temporal gyrus in sentence processing (Hagoort & Indefrey, 2014). The Memory, Unification, and Control (MUC) model of sentence processing also focuses on these areas (Hagoort, 2003, 2005, 2013). It proposes that the left temporal cortex and angular gyrus are implicated in word retrieval from memory, while unification (maintenance and integration of words) involves the left inferior frontal cortex. Furthermore, as the sentence unfolds, a predictive context results from the interaction between these areas, and this context facilitates the processing of upcoming words. Previous oscillatory studies on sentence processing have, to our knowledge, been restricted to the sensor level. It is therefore unclear whether oscillations localize to similar brain regions as found in event-related M/EEG and fMRI studies. The current study, presenting a thorough source-level analysis of oscillatory activity during sentence processing, addresses this shortcoming.

Current study

In the present study we investigated oscillatory power changes during sentence processing. We obtained MEG data while participants read sentences. As a control condition, participants also read lists of words (created by scrambling sentences). Our study focused on exploring which neural areas, at which frequencies are involved in sentence processing. We analyzed the spatio-temporal dynamics of the oscillatory activity by using a beamformer in the frequency domain. This allowed us to better quantify the spatial aspects of the effects, and to improve on the previous studies that could only report results at the sensor-level.

To obtain a complete picture of oscillations at various frequencies, we investigated five frequency bands: theta, alpha, beta, low gamma, and high gamma. We chose to divide the gamma band because previous studies have shown a distinction between low gamma (around 30 to 60 Hz) and high gamma (above 80 Hz); the precise frequencies for low and high gamma differ between cortical regions and the cognitive task (Crone, Miglioretti, Gordon, & Lesser, 1998; Dalal et al., 2008; Hauck, Lorenz, & Engel, 2007). Furthermore, previous sentence processing studies have only shown effects at around 40–60 Hz, and we were interested in whether effects in higher frequencies were also present. In the current study, we investigated two aspects of sentence processing: The *word analysis* sought to reveal how single words are integrated into a representation of the entire sentence, and the *context analysis* assessed the effect of the incremental context on single word processing.

Word analysis

In order to investigate the oscillatory response to single words within the context of a sentence, we analyzed the responses to each of the single words in a sentence and contrasted them to single words in a random order (word list). Sentences have a structured and meaningful context – semantic and syntactic information that goes beyond the level of the individual words. Word lists on the other hand have no structure and only a weak overarching semantic context (because each word list was created by scrambling a sentence). We hypothesized the sentence context to have a facilitatory effect, since the syntactic and semantic information in preceding words constrain the possibilities of the upcoming word both syntactically and semantically. The effect of the context may be observed in memory retrieval, unification, and prediction (Hagoort & Poeppel, 2013). The sentence context should make memory retrieval easier for sentences than word lists, and because previous studies associated theta power with memory retrieval (Bastiaansen et al., 2005; Hagoort, 2013), we expected differences between the conditions in this frequency band. Since the prediction of the upcoming word within a context has been associated with gamma ERS (Wang, Zhu, & Bastiaansen, 2012), we expected to observe this pattern for sentences but not word lists. Finally, the alpha, beta and gamma bands have been implicated in unification (e.g., Bastiaansen & Hagoort, 2015; Bastiaansen et al., 2009; Hald et al., 2006); therefore, we expected differences between sentences and word lists in one or more of these frequencies.

Context analysis

To analyze how the unfolding sentence context affects oscillatory activity over time we quantified the modulation of the oscillatory response between words at early and late positions in a sentence. This provides a view of the long term changes in power as the sentence progresses. As the sentence unfolds, memory should become taxed because more words need to be retained for unification. As ERS in the theta band has been associated with memory maintenance, we expected an increase in theta power for words in late versus early positions in the sentence. An incremental context can also impose more constraints on how words are being combined, which could facilitate unification as the sentence unfolds. Changes in power across a sentence but not a word list have previously been associated with the beta and gamma bands (Bastiaansen et al., 2010; Hald et al., 2006). Effects in these frequency bands are suggested to reflect unification. Therefore, we hypothesized that a change in beta and/or gamma oscillations would also be observed as the sentence unfolded.

4.3 Methods

Participants

A total of 102 native Dutch speakers (51 males), with an age range of 18 to 33 years (mean of 22 years), participated in the experiment. These participants formed part of a larger study – MOUS (Mother of all Unification Studies; *N* = 204), where all participants took part in an fMRI and a MEG session. Half of these participants completed both sessions where they read the stimuli, and the other half listened to recordings of the stimuli. The current paper pertains to participants from the MEG session in the visual modality. All participants were right-handed, had normal or corrected-to-normal vision, and reported no history of neurological, developmental or language deficits. The study was approved by the local ethics committee (CMO – the local "Committee on Research Involving Human Participants" in the Arnhem-Nijmegen region) and followed the guidelines of the Helsinki declaration. Participants received monetary compensation for the participation.

Language stimuli

The stimuli consisted of 180 sentences and their word list counterparts (see Table 1 for an example). All sentences varied between 9 and 15 words in length.

Sentence	**Word list**
Bij de opening van de nieuwe sporthal kregen de talrijke bezoekers een consumptie	sporthal bij van talrijke opening een de de kregen consumptie bezoekers nieuwe de
At the opening of the new sports hall received the many visitors a (free) drink	sports hall at from many opening a the the received (free) drink visitors new the

Table 1. Exemplar sentence and word list in Dutch, and literal English translation.

The word lists were created from the sentences by scrambling the words so that no more than two consecutive words formed a coherent fragment. The same words in both conditions limited the difference between conditions to sentential semantics and syntax as opposed to lexical differences in orthography, phonology, and word meaning. Each participant saw each stimulus in either the sentence or the word list condition, but not in both. Across participants, each stimulus was presented the same number of times in the sentence and in the word list condition.

Task and Procedure

Experimental Design

All stimuli were presented with an LCD projector (with a vertical refresh rate of 60 Hz) situated outside the MEG measurement room, and projected via mirrors onto the screen inside the MEG room. All stimuli were presented at the center of the screen within a visual angle of 4 degrees, in a black mono-spaced font, on a gray background using Presentation software (Version 16.0, Neurobehavioral Systems, Inc).

The stimuli were divided into three subsets, such that each participant saw 2/3 of the stimulus set in the MEG session (120 trials of each condition); and 1/3 in the fMRI session that will not be further discussed in this paper. Participants presented with the same subset saw the stimuli in a different (randomized) order. In the experiment, the stimuli were presented in a mini block design, and alternated between a sentence block (containing 5 sentences) and a word list block (containing 5 word lists), for a total of 24 blocks. The first mini block (sentences or word lists) was randomized across participants. In addition, for sentences, the first word began with a capital letter and the last word ended with a full stop.

At the beginning of each block, the block type was announced for 1500 ms: *zinnen* (sentences) or *woorden* (words), followed by a 2000 ms blank screen. At the beginning of each trial a fixation cross was presented for a jittered duration between 1200 and 2200 ms. Then, the words for each trial (sentence or word list) were presented one at a time. Each word was separated by a blank screen for 300 ms.
The presentation time of each word was varied in order to allow for a 'naturalistic' reading experience, and to avoid a strict entrainment of ongoing activity to fixed interstimulus intervals. For any given sentence (or word list) the variable duration of a single word was a function of the following quantities: (i) the total duration of the audio-version of the sentence/word list (*audiodur*), (ii) the number of words in the sentence (*nwords*), (iii) the number of letters per word (*nletters*), and (iv) the total number of letters in the sentence (*sumnletters*). Specifically, the duration (in ms) of a single word was defined as: (*nletters/sumnletters)*(audiodur+2000-150*nwords*). The minimum duration of short words was set to 300 ms irrespective of the relative weighting described by the formula. In practice, however, the exact presentation times of the words slightly deviated from those obtained from the above formula. This was due to the fact that the presentation timing was dictated by the refresh rate of the projector (60 Hz). As a consequence, the actual presentation time was lengthened by a duration between 0 and 33 ms. The median duration of a single word on the screen was 434 ms (range 300-1344 ms). Taking into account the 300 ms gap between the words, the median duration of a whole sentence/word list was 8.3 s (range 6.2-12 s). Within each block, the inter-trial interval was a blank screen with a jittered duration between 1200–2200 ms.

In order to check for compliance, 10% of the trials (n = 12) were randomly followed by a yes/no question about the content of the previous sentence/word list. Half of the questions on the sentences addressed sentence comprehension (e.g. *Did grandma eat a pancake?).* The other half of the sentences, and the questions following the word lists addressed a content word (e.g. *Was a music instrument mentioned?*). Participants answered the question by pressing a button for 'Yes'/ 'No' with their left index and middle fingers, respectively. For both question types, half of the trials required a yes-response. The experiment began with participants reading written instructions for the task. The experimenter clarified any questions from the participant. Then, for familiarization purposes, participants completed a practice task (using a separate set of stimuli from the actual task). Subsequently they performed the actual task as described above.

MEG data acquisition

MEG data were collected with a 275 axial gradiometer system (CTF) at the Donders Centre for Cognitive Neuroimaging in Nijmegen, The Netherlands. The signals were digitized at a sampling frequency of 1200 Hz (the cutoff frequency of the analog anti-aliasing low pass filter was 300 Hz). Three coils were attached to the participant's head (nasion, left and right ear canals) to determine the position of the head relative to the MEG-sensors. Throughout the measurement the head position was continuously monitored using custom software (Stolk et al., 2013). During breaks the participant was allowed to reposition to the original position if needed. Participants were able to maintain a head position within 5 mm of their original position. Three bipolar Ag/AgCl electrode pairs were used to measure the horizontal and vertical electro-oculogram, and the electro-cardiogram.

Data processing

All analyses were done with custom written Matlab scripts and FieldTrip, an open source toolbox for EEG and MEG data analyses (Oostenveld et al., 2011).

Preprocessing

Electrocardiogram artifacts were estimated using denoising source separation (DSS, Särelä & Valpola, 2005), identified based on their topography and subtracted from the data. Physiological artifacts (eye movements and muscle contractions) and jump artifacts in the SQUIDs (superconducting quantum interference device) were identified using a semi-automatic artifact identification procedure (http://www.fieldtriptoolbox.org/tutorial/automatic_artifact_rejection), followed by visual inspection. Data segments that contained artifacts were excluded from further analysis. Next the power line interference at 50 Hz and its harmonics at 100 and 150 Hz were estimated and subtracted from the data (for details see Schoffelen, Oostenveld, & Fries, 2005). Finally, the data were downsampled to a sampling frequency of 300 Hz.

Frequency-domain beamforming

We used a frequency domain beamformer (DICS; Gross et al., 2001) to reconstruct the sources of the oscillatory responses. First, for each time window and frequency band the sensor-level cross-spectral density matrix was computed across all conditions. The frequency bands were selected based on earlier studies. For the low frequencies, they were centered at the following frequencies (with effective spectral bandwidth in brackets): 5 Hz (3.75–6.25 Hz) for theta, 10 Hz (8.75–11.25 Hz) for alpha, and 16 Hz (14–18 Hz) for beta. Here, each discrete frequency designates the centre frequency of a band-limited frequency bin, and this centre frequency encompasses the average signal power across the frequency range in that bin, referred to as the effective bandwidth. This bandwidth is dictated by the combination of the chosen window length and tapering scheme. The theta and alpha band were analyzed in 50 ms time steps from -100–500 ms (around word onset at 0ms) using a sliding time window of 400 ms in combination with a Hanning taper, which produced an effective bandwidth of 2.5 Hz (which is 1.25 Hz around the defined centre frequencies). Beta was also analyzed in 50 ms time steps from -150–500 ms, but with a 250 ms time window in combination with a Hanning taper, which produced an effective bandwidth of 4 Hz. The higher frequencies, were a priori defined as 36 – 76 Hz (low gamma), and 76 – 108 Hz (high gamma), and thus encompassed spectral estimates across multiple frequency bins. We analyzed them at 50 ms time steps, at 4 Hz steps, between -150–500 ms. Here we used a 250 ms time window in combination with multitapers (Mitra & Pesaran, 1999), which achieved an effective bandwidth of 16 Hz.

The sensor-level cross-spectral density matrix was then used in combination with the forward solution to compute a set of spatial filters to obtain an estimate of the activity for dipoles placed on a volumetric grid with ~8 mm spacing (see below). The spatial filters assumed a fixed orientation of the underlying dipoles, defined by means of a singular value decomposition of the dipole cross-spectral density, taking the orientation along the first singular vector to explain the maximum amount of variance. The activity (power) was estimated for each condition of interest.

Processing of the anatomical MRI and digitized headshape for MEG source reconstruction

For source reconstruction purposes, we coregistered the anatomical MRI to the MEG-sensors. This was achieved by manual alignment of two reconstructions of the head surface. A digitized head shape was obtained with a Polhemus device (a 3D digitizer from Fastrak, Polhemus Inc. Colchester, VA, USA). This consisted of approximately 500 points across the scalp and was used to reference the location of MEG sensors relative to the head (and the fiducials). The second head shape was created from the participant’s T1-weighted anatomical MRI image. Subsequently, the aligned anatomical image was used to create (i) a volume conduction model based on a single shell description (Nolte, 2003) of the inner surface of the skull, using the segmentation function in SPM8, (ii) a set of spatial normalization parameters to bring each participant’s brain into a normalized volumetric space, using SPM8, and (iii) a description of the cortical surface, using Freesurfer 5.1 (Dale et al., 1999). The spatial normalization parameters were used to create individual volumetric grids which in turn were used for a beamformer source reconstruction of the oscillatory responses. A template volumetric grid with a resolution of 8 mm was warped into individual brain space, using the inverse of the normalization parameters.

Statistical Analysis

The frequency bands selected for source analysis were also used for statistical inference. For each frequency band, statistical inference was done for a selected set of time windows (indicated below in each analysis) using a non-parametric permutation test together with a clustering method (Maris & Oostenveld, 2007), to correct for multiple comparisons.

For the observed data, a dependent samples *t*-statistic for the difference between the conditions was computed for each sample (space-frequency-time point). For each of the lower frequencies, this yielded a single 3-dimensional volumetric map of t-values for each of the time windows tested. For the gamma range this yielded 4-dimensional volumetric maps of t-values (three spatial dimensions + frequency). Samples that exceeded the uncorrected significance level of 1% were clustered according to adjacency (in the spatial domain for theta, alpha, and beta, and in the spatial and frequency domain for the gamma band). For each cluster, the cluster-level *t*-statistic was calculated by summing the *t*-statistics across the individual elements. Next, to test the observed *t*-statistic, a reference distribution was computed. This distribution was created by permuting (randomly exchanging) data between the conditions, and then calculating the maximal positive and negative cluster-level *t*-statistic for each permuted data set. Finally, the observed *t*-statistic was tested against the reference distribution. The observed *t*-statistic was considered significant if it was located beyond the determined threshold, on the negative or positive end of the reference distribution. The statistical threshold is specified in the section of each analysis below (2.7.1, and 2.7.2).

To address the multiple tests performed across 3 time windows and 5 frequency bands we applied a conservative Bonferroni correction to the critical threshold to infer statistical significance from the p-values. The details on this correction are provided below in each analysis section. For visualization, the thresholded volumetric images were interpolated onto the cortical sheet extracted from the MNI template brain, exported as a cifti-file and displayed using the workbench software package (Marcus et al., 2011).

Word Analysis

To compare the condition specific (sentences or word lists) response to individual words, for each condition, we first subtracted the estimated power in the period preceding word onset (baseline) from the power following word onset. Changes in oscillatory activity in response to a single word require time to develop, and probably more than 100 ms to become apparent. Therefore, the choice of a pre-word baseline allowed us to study word-induced changes in frequency specific activity, above and beyond the ongoing nature of oscillations. Furthermore, it mitigated the possible effect of a block design producing different pre-window activity for each condition. For the alpha and theta bands, we used a baseline estimate centered at -100 ms. For the beta and gamma bands, the baseline estimate was an average of two time windows centered at -150 and -100 ms. As a consequence, the estimated power at these time windows included a short duration of data following word onset (up to 100 ms for the theta band, and up to 25 ms for all other frequencies). We did not use an earlier time window e.g., -200 ms, because this would potentially include transient oscillatory activity from the previous word. To study the neural response to each word we chose three time windows following word onset: centered at 250, 350 and 450 ms, referred to as the first, second, and third time window, respectively. We excluded the initial 250 ms because previous studies have suggested that this is the time window of visual processes (Dehaene, Le Clec'H, Poline, Le Bihan, & Cohen, 2002; Tarkiainen, Helenius, Hansen, Cornelissen, & Salmelin, 1999) while the majority of higher order processes, which are the main focus of our interest, such as lexical and context effects, occur later in time (e.g.,Vartiainen, Parviainen, & Salmelin, 2009). As visual inspection of the oscillatory power time courses (Fig. 1) revealed variations in differences between conditions across time windows, we chose to statistically test the data for each time separately.

To address how words are processed in a sentence, we compared words embedded in a sentence to words embedded in a word list. For each participant, we analyzed the averaged single-word response (power) for each condition. The number of epochs available for averaging was different across conditions, due to artifact rejection. To avoid effects due to differences in signal to noise ratio, we equalized the number of epochs across conditions for each participant. For each of the 3 time windows and 5 frequency bands we performed a separate test. In our tests we applied a conservative Bonferroni correction, and used a corrected critical p-value of 0.0017 (0.025/15, for a two-sided test).

Context Analysis

In this analysis, we were interested in the change in neural activity as the sentence unfolded. To do this, we quantified the difference in the neural response to late versus early words in a sentence, and in a word list. We accounted for non-specific variability in overall power values across participants by subtracting a condition averaged estimate of the power preceding word onset from each of the condition-specific power following word onset, for each participant. Note that the subtraction of the same 'baseline' will yield the same average difference across participants, in comparison to contrasting the raw power values. As in the word analysis, for the context analysis we chose the same time windows following word onset (centered at 250, 350 and 450 ms) for analysis.

The statistical analysis here addressed the effect of an incremental context on word processing. We assessed the neural activity during word processing as a function of word position across a sentence. We extracted the early words (2nd,3rd, and 4th word position) and the late words (n-2nd, n-3rd, and n-4th word position; where n is the total number of words in a sentence/word list) in both sentences and word lists, resulting in four conditions (sentence-early, SE; sentence-late, SL; word list-early, WE; and word list-late, WL). To control for lexical frequency we used a stratification approach. First, the lexical frequency value for each word was determined, using the SUBTLEX-NL database of Dutch word frequencies (Keuleers, Brysbaert, & New, 2010), and log transformed. Then, for each condition, a histogram of log transformed lexical frequencies was created, using 10 bins. For each of the bins we determined the minimum number of contributing trials across conditions. Subsequently, trials were randomly removed from each bin of each condition to meet the minimum which produced the same number of trials per bin per condition. This yielded about 200 trials per condition. Subsequently, we calculated an average power for each condition.

To test for significance, we first determined whether there was an interaction between word position (late vs. early) and sentence type (sentence vs. word lists): ([SL-SE] – [WL-WE]), at each of the five frequency bands. To correct for doing multiple tests, we applied a Bonferroni corrected threshold of $p < 0.005$. For frequencies showing a significant interaction, we performed a second statistical test for each condition: SL-SE and WL-WE, to determine an effect of late vs. early context within each condition. Here, we visually inspected the power time courses, and found a consistent power difference between conditions over time (Fig. 2). Therefore, we chose to perform one test for each frequency, across all time windows. In addition, to determine whether the late vs. early context effect was specific to sentences, we performed post-hoc tests comparing SL - WL and SE – WE. Here, we selected an individual grid point for each region that showed the most prominent, significant difference for the SL – SE contrast. We selected grid points from (i) spatially distinct regions, and (ii) regions involved in language processing. In the case where similar regions were activated in both hemispheres, as indicated by visual inspection of homologous grid points, we chose the grid point from the hemisphere that showed a stronger effect. All grid points are indicated with black circles in Fig. 2.

4.4 Results

Task compliance

The mean percentage of correct answers for questions that followed a sentence or word list was 81.1% (SD = 6.7%). Performance was significantly higher for sentence questions on a main content word (M = 84.2%, SD = 11.6%) than for a word list question (M = 78.4%, SD = 9.6%; $t_{101} = 5.75$, $p < 0.001$). Potentially, the difference in performance was because sentences are easier to process than word lists. Nevertheless, with all participants performing well above chance in both cases, they were attentive and processed the language materials. Note that there was no difference between the sentence comprehension questions (M = 83%, SD = 11.7%) and the sentence content word questions ($t_{101} = -1.2$, $p = 0.4$).

Word Analysis

In the word analysis we compared whether individual words in a meaningful and structured context were processed differently from words in a word list. We observed significant differences between sentences (S) and word lists (W) in the theta, alpha, beta, and gamma frequency bands in multiple brain regions, as show in Fig. 1. The oscillatory power time courses (as a relative percent change to a baseline averaged over conditions; see Fig. 1) suggests that for most frequencies the effect was driven by a difference in magnitude and not shape of the time course, with the exception of left temporal theta. In general, differences between conditions resulted in an ERD for frequencies below 40 Hz (except for left temporal theta), and an ERS for frequencies above 40 Hz. Here, we focus on the statistically significant results, and will refer to the first (250 ms), second (350 ms), and third (450 ms) time windows, relative to word onset. For an in depth description and visual depiction of the spatio-temporal evolution of frequency specific power, the interested reader is directed to supplementary material 1.

Theta band

Significant differences were found in the bilateral occipital cortex, and left posterior temporal regions in all three time windows (S < W; p = 0.0005, corrected for multiple comparisons). The left temporal region in the first time window was also significant but only when uncorrected for multiple comparisons, (p = 0.005, S > W; Fig. 1).

Alpha band

Significant differences were found in all three time windows, in bilateral occipito-parietal, left frontal, and left temporal regions (p = 0.0005, S < W; corrected for multiple comparisons).

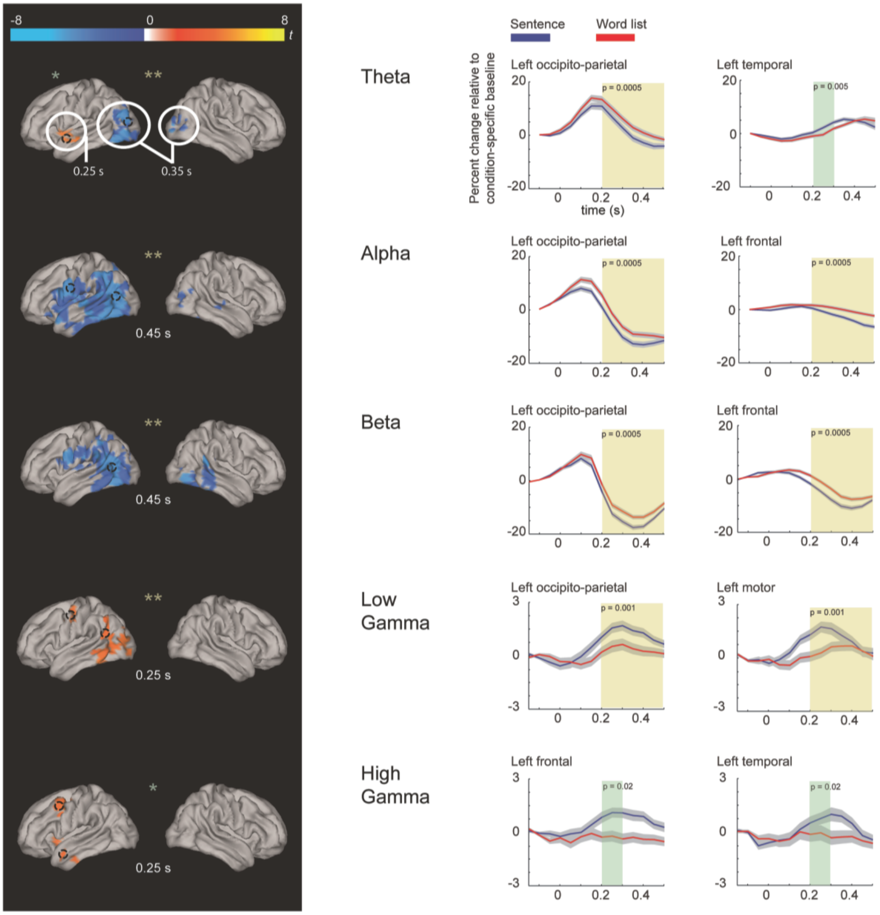


Figure 1 Word analysis results (words in a sentence vs. words in a word list) as brain maps (left panel) and time courses (right panel). *Left* Brain maps depict the surface representation of beamformed frequency specific power differences between conditions in t-values, for theta, alpha, beta and gamma bands. Light/dark blue colors reflect lower power in sentences than word lists, and yellow/orange colors reflect higher power in sentences than word lists. Brain maps are selected for different time points at each frequency, to best reflect the observed effects. Significant results corrected for multiple comparisons across space (grid points) are marked with *. Significant results after further correction for multiple comparisons across time windows and frequency bands are marked with **. *Right* Time courses reflect the percentage change in frequency specific power relative to baseline. The baseline is the averaged baseline between the sentence and word list condition. The blue line is for sentences, and the red line for word lists. Grey areas around the time course reflect the +/- 1 standard error of the mean. Time windows shaded in green reflect significance after correction for multiple comparisons across space (equivalent to *); time windows shaded in yellow are significant after further correction for multiple comparisons across time windows and frequency bands (equivalent to **).Time courses were chosen from spatially distinct cortical regions that are (i) known to be involved in language processing and (ii) shown to have a statistically significant difference between sentences and word lists. For frequencies in which homologous regions between hemispheres showed a similar effect, time courses are portrayed for the left hemisphere. This was because visual inspection indicated similar time courses for homologous grid points, and because the overall effects for this analysis were left hemisphere dominant. Black circles on the brain map indicate the region of the chosen grid points.

Beta band

Significant differences were found in all three time windows, in left occipito-parietal cortex, left posterior temporal areas, and left frontal cortex (p = 0.0005, S < W; corrected for multiple comparisons).

Gamma band

In the gamma band, effects were more left lateralized than in the lower frequency bands. Across time windows we observed a posterior to anterior activation sweep (Fig. 1). Visual inspection revealed that low and high gamma showed distinct spatio-temporal dynamics. The statistical test for low gamma (40 - 68 Hz) revealed a significant difference only in the first time window in left occipital, left parietal, left motor, and left temporal regions *(p* = 0.001, S > W; corrected for multiple comparisons). In the subsequent time windows, the effect reduce in effect size (*p* = 0.008, S > W). The statistical test for high gamma (84 – 100 Hz) revealed a significant difference in left frontal and temporal regions when uncorrected for multiple comparisons (*p* = 0.02, S > W).

Context Analysis

The context analysis focused on how oscillatory activity changes as the sentence unfolds. The accumulation of words in a sentence, but not a word list, should form a more meaningful and structured context to facilitate the processing of each subsequent word. Here, we assessed whether there was a change in oscillatory power between late and early words in a sentence, and compared this to the same contrast in word lists. Early words were the 2nd, 3rd, and 4th words in a sentence (or word list), and late words were the 4th, 3rd, and 2nd to last words in a sentence (or word list). The interaction analysis [S(L-E) - W(L-E)] for theta, alpha, and beta was significant (*p* < 0.0083). Therefore, for each condition, we compared late versus early words, within each condition (SL-SE, and WL-WE) across all three time windows. In all three frequency bands, late words were significantly different from early words (context effect) for sentences, and word lists, but the effects were stronger for sentences than word list (Fig. 2), details for each frequency are reported below (3.3.1 – 3.3.3).

As a complementary test to the one above, we contrasted late words in sentences with those in word lists (SL – WL; late word comparison), and contrasted early words in sentences with those in words lists (SE – WE; early word comparison). This demonstrated that the difference between late and early words was predominant in sentences, details reported below for each frequency (Fig. 2). A detailed description and depiction of the evolution of power over time is available in the supplementary materials (Fig. S1b). Two alternative analyses for the context effects are presented in the supplementary materials (see sentence progression analysis and adapted context analysis, Fig. S2).

Theta band

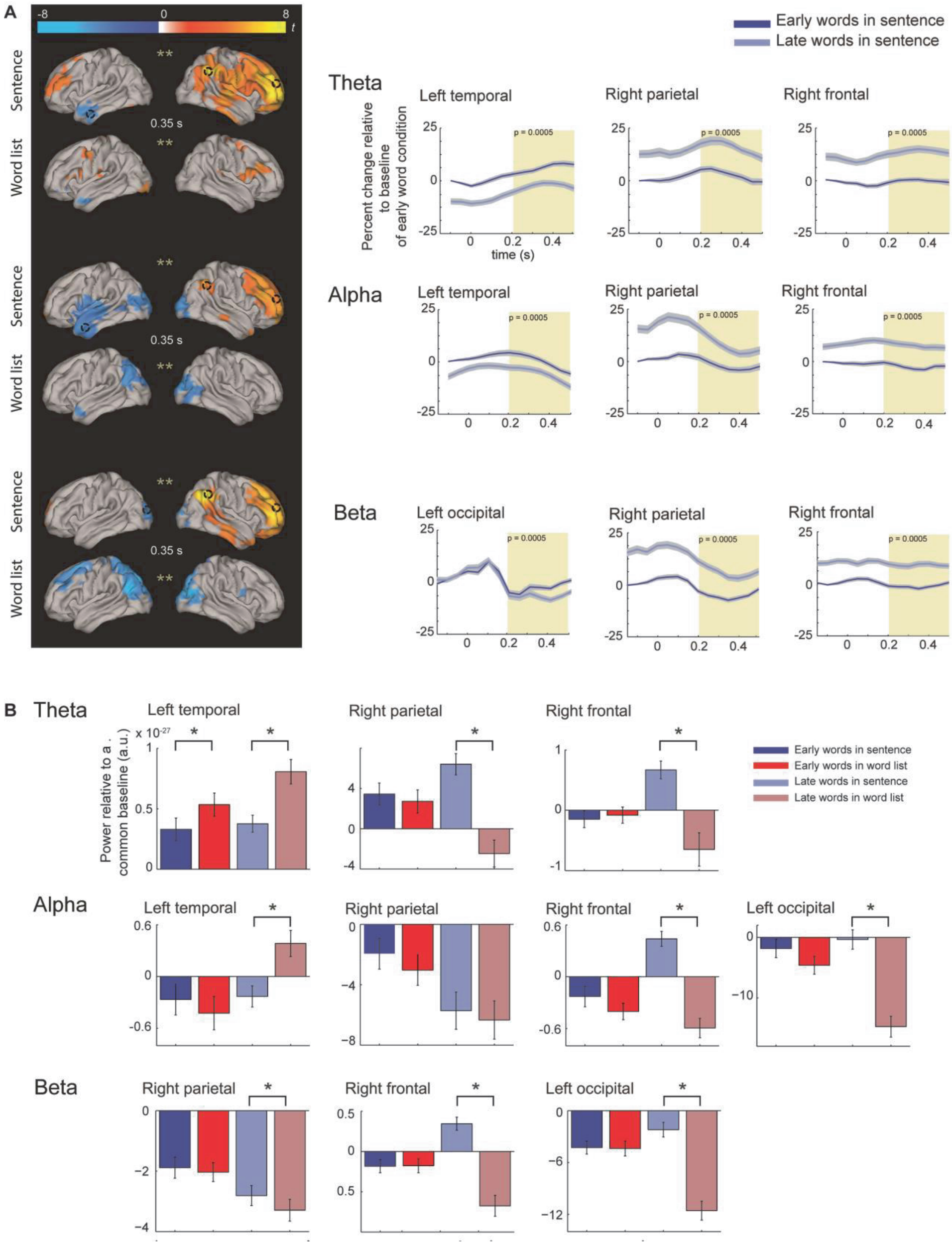
For sentences, we observed statistically significant context effects in bilateral frontal and right parietal regions (L > E), as well as, in left anterior temporal regions (L < E; *p* = 0.005; corrected for multiple comparisons). In word lists, the context effect was significant in areas similar to the context effect in sentences (*p* = 0.005; corrected for multiple comparisons). However, the spatial extent was limited, the difference in power was smaller, and the difference remained constant across time. The test for SL-WL and SE-WE were only significant ($p < 0.025$) for the late word comparison in grid points in right parietal and right frontal regions. However, in the left anterior temporal region these effects were significant ($p < 0.025$) in both the early word and late word comparisons.

Alpha band

For sentences, we observed a significant difference in left temporal and inferior frontal regions (L < E; $p = 0.005$; corrected for multiple comparisons), as well as, in bilateral frontal, right parietal and right temporal regions (L > E; $p = 0.005$; corrected for multiple comparisons). For word lists, significant differences were observed in the left temporal and bilateral occipito-parietal regions (L < E; $p = 0.005$; corrected for multiple comparisons), as well as, right temporal and right frontal areas (L > E; $p = 0.005$; corrected for multiple comparisons). These differences were spatially more focal than those in the sentence condition. The test for SL-WL and SE-WE were only significant ($p < 0.025$) for the late word comparison in grid points in left occipital, left temporal, right parietal, and right frontal regions.

Beta band

For sentences, we observed a significant difference in bilateral frontal, right parietal and right temporal regions (L > E; $p = 0.005$; corrected for multiple comparisons), as well as, in bilateral occipital regions (L < E; $p = 0.005$; corrected for multiple comparisons). For word lists, bilateral occipital, parietal, and middle frontal regions were significant for all time windows ($p = 0.005$; corrected for multiple comparisons). The test for SL-WL and SE-WE were only significant ($p < 0.025$) for the late words comparison in grid points in left occipital, right parietal, and right frontal regions.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-8
0
8
t
Sentence
Word list
0.35 s
**
Early words in sentence
Late words in sentence
Theta
Alpha
Beta
Left temporal
Right parietal
Right frontal
Left occipital
Percent change relative to baseline of early word condition
time (s)
25
0
-25
0.2
0.4
p = 0.0005
B
Theta
Alpha
Beta
Power relative to a common baseline (a.u.)
x 10^-27
*
Early words in sentence
Early words in word list
Late words in sentence
Late words in word list

Fig. 2 A Context analysis (late words vs. early words) results as brain maps (left panel) and time courses (right panel). *Left* Brain maps depict the surface representation of beamformed frequency specific power differences between conditions in t-values for theta, alpha, beta and gamma bands. For each frequency band, the top brain map is the sentence context analysis, and the lower brain map is the word list context analysis. Light/dark blue colors reflect lower power in sentences (late - early words) than word lists (late - early) , and orange/yellow colors reflect higher power in sentences (late words – early words) than word lists (late - early). Brain maps reflect a single time point that is representative of the difference between conditions across all time points (because the difference between conditions does not differ greatly across time). Significant results corrected for multiple comparisons across space (grid points) are marked with *. Significant results after further correction for multiple comparisons across time windows and frequency bands are marked with **. *Right* Time courses reflect the percentage change in frequency specific power relative to the baseline period of early words, with early words in sentences in dark blue, and late words in sentences in light blue. Grey areas around the time course reflect +/- 1 standard error of the mean. Time windows shaded in green reflect significance after correction for multiple comparisons across voxels space (equivalent to *); time windows shaded in yellow are significant after further correction for multiple comaparisons across time windows and frequency bands (equivalent to **). Time courses were chosen from spatially distinct cortical regions that are (i) known to be involved in language processing, (ii) shown to have a statistically significant difference between conditions. For frequencies in which homologous regions between hemispheres showed a similar effect we chose to portray time courses from the right hemisphere. This is because visual inspection indicated similar time courses for homologous grid points, and because the overall effects for this analysis were right hemisphere dominant. Black circles on the brain map indicate the region of the chosen grid points. B Bar graphs depicting sentence early words vs. word list early words,and sentence late words vs. word list late words. Error bars reflect +/-1 standard error of the mean.

4.5 Discussion

In this study we investigated neuronal oscillatory activity during sentence processing with MEG. We used source reconstruction techniques to quantify the spatio-temporal response in five well-established frequency bands. The word analysis determined how individual words are processed in a sentence by comparing the oscillatory response to words embedded in a sentence (i.e. within a syntactically and semantically meaningful context) to that of a word list (which lacked a structured context). To determine the effect of an incremental context on sentence processing, the context analysis quantified the changes in the word induced modulations of oscillatory activity at different stages of the unfolding sentence. Here, we focused on the context effect (late versus early words) in sentences, and compared it to the context effect in word lists as a control. We evaluated which regions and time-frequency points showed significantly more or less activity in the sentence than word list context analysis.

The *word analysis* revealed effects of (a sentence) context on word processing in the theta, alpha, beta, and gamma bands, predominantly in left hemisphere inferior frontal, temporal and parietal regions. The *context analysis* captured effects of the incremental context in left temporal and occipito-temporal regions, and in right-lateralized frontal and parietal regions in the theta, alpha, and beta bands. We consider the findings from these two comparisons to be complimentary and will discuss them in light of each other.

Task-related modulations of oscillatory activity can occur in multiple frequency bands that vary in the direction of the effect (ERS or ERD). This heterogeneity across frequency bands poses challenges to the interpretation of the findings. Common practice in cognitive studies has been the attribution of a specific functional role to a specific frequency band within the given experimental context. However, adopting such strict task-related functional interpretations of particular frequencies might be too ambitious given that different types of rhythmic activity occur in multiple brain regions, across multiple temporal and spatial scales. Moreover, these rhythms may not be specific to any task. Here, we propose a set of explanations that account for the various effects by taking into account the neural areas and frequencies of the observed effects, and previous studies that analyzed oscillations in the context of language and non-language tasks.

Theta oscillations in sentence processing

In the theta band, we observed effects in the word and context analyses in left anterior temporal regions.

Stronger theta synchronization was present for sentences compared to word lists in the word analysis. Inspection of the time course of theta activity suggests that this difference reflects a latency shift, with theta peaking earlier in sentences (around 350 ms; word lists around 400 ms). We tested this latency shift post-hoc. This latency shift was significant across subjects (Wilcoxon Signed-rank test, $Z = -2.84$, $p = 0.004$). The observation of this theta synchronization soon after word onset (around 200 ms) for both sentences and word lists could indicate a common, early process, most likely word retrieval. Since the theta peak is earlier for sentences than word lists, this suggests a stronger facilitatory context effect on lexical retrieval for sentences compared to word lists.

In the context analysis, for sentences and word lists, late words compared to early words were associated with a decrease in theta power in left anterior temporal regions. We speculate that this lower theta activation is the effect of an incrementally more informative context which increases the facilitatory effect on retrieval as the sentence (or word list) unfolds. As each word list was created by scrambling a sentence, the words in a word list also had an associative relation at the lexical level, which could provide an associative context for upcoming words, and therefore a context facilitatory effect on retrieval. Importantly, because sentences are grammatical and meaningful, they have stronger constraints and thus a higher predictive value for the upcoming word, which results in a stronger context facilitatory effect for sentences than word lists. In line with our interpretation, many previous studies have shown that left anterior temporal regions are associated with conceptual relations between words at the lexical level (e.g., Mummery et al., 2000; Patterson, Nestor, & Rogers, 2007)**.** Together, these findings suggest that having a context allows for easier lexical retrieval, and when this context becomes more informative (more preceding words in a sentence context) less cognitive resources are needed for lexical retrieval.

Our interpretation of theta band effects in left temporal regions as being associated with lexical retrieval is in line with other oscillatory studies on memory. Memory retrieval (or attempted retrieval) has resulted in theta band synchronization in response to language stimuli (single words, word in a sentence) and non-language stimuli (e.g., shapes and faces) with a widespread sensor-level topography (Bastiaansen, van Berkum, & Hagoort, 2002; Klimesch et al., 2010; Klimesch, Freunberger, Sauseng, & Gruber, 2008; Mormann et al., 2005; Osipova et al., 2006). At the source-level, an earlier study on memory retrieval localized effects to medial temporal, prefrontal and visual areas (Guderian & Düzel, 2005), which is a partial overlap with our findings. The additional areas reported by this earlier study could be due to the type of information being retrieved, since their study used faces and a background scene, whereas we used words.

In bilateral frontal and right parietal regions, we also observed theta effects specific to the context analysis: theta power was significantly higher for late words than early words in sentences. The spatial topography of our results is similar to the frontal-parietal network associated with cognitive task demands (Chein, Moore, & Conway, 2011; Fedorenko et al., 2013). Words late in the sentence are likely to increase task demand, since a more extended context representation has to be maintained in memory. In line with previous studies, an increase in theta synchronization in frontal and parietal sensors has been observed with an increase in working memory load (e.g., Cashdollar et al., 2009; Deiber et al., 2007; Jensen & Tesche, 2002). In addition, active maintenance of item(s) increases theta synchrony between right frontal and parietal regions (Cashdollar et al., 2009; Deiber et al., 2007). Support also comes from a language study that found an increase in theta power in right-centro parietal MEG sensors as a sentence unfolded (Bastiaansen et al., 2010), which was thought to reflect the memory trace of the unfolding sentence representation.

In bilateral occipito-temporal regions, we observed a theta effect in the word analysis. Theta power was significantly lower in bilateral occipito-temporal regions for words in a sentence versus words in a word list. The difference begins around 100 ms, becomes larger and remains stable over time. Potentially, this reflects a difference in visual word recognition between sentences and word lists. Specifically, the sentence context narrows down certain aspects of the upcoming word (e.g., word category, semantics) which could modulate the response in occipital regions to the incoming word. The neural mechanism underlying this modulation may be top-down influences from higher to lower cortical regions. Studies on visual and motor processing have shown that neural activity in response to a visual stimulus in occipital cortex can be directly modulated by activity from frontal and parietal regions (Engel et al., 2001; Silvanto, Muggleton, Lavie, & Walsh, 2009; Taylor, Nobre, & Rushworth, 2007). In one case, transcranial magnetic stimulation of the posterior parietal cortex led to an increase in primary visual cortical excitability (Silvanto et al., 2009). We speculate that the larger desynchronization for words in a sentence compared to words in a word list in occipito-temporal regions reflects facilitation and/or prediction from the sentence context (activity in higher cortical regions) to specific word forms in occipito-temporal regions (e.g., the Visual Word Form Area).

Alpha and beta oscillations in sentence processing

Word Analysis

We observed a similar spatial topography and time course in the alpha and beta bands – a stronger desynchronization in left-lateralized temporal, parietal, and frontal areas for words in a sentence context compared to words embedded in a word list. For both frequency bands, in temporo-parietal regions, the difference begins around 150 ms, and is strongest around 350 ms, while in left frontal regions, the difference begins around 150 ms, and becomes stronger over time. The similarity between these two frequency bands is suggestive of a broadband desynchronization. A decrease in alpha/beta power is typically interpreted to reflect more (an increase in) activation of the underlying neuronal population, while a power increase reflects less (a decrease) in activation (Bastiaansen, Oostenveld, Jensen, & Hagoort, 2008; Jensen & Mazaheri, 2010; Klimesch et al., 1997; Osipova et al., 2006). On this basis, the desynchronization effect indicates stronger neural activation for sentences than word lists. This effect could reflect unification of the incoming word in sentences (but not in word lists). The difference between sentences and word lists is in structure and sentence-level meaning (syntax and semantics), and not orthography, phonology, word meaning, or morphology because the same words were used in both conditions. Therefore, we are likely observing the unification of semantic and syntactic information. Importantly, the difference between late and early words in a sentence is not due to a difference in lexical frequency. We controlled for this using stratification methods.

A recent source-level MEG study observed a desynchronization between 8 and 30 Hz in bilateral occipital and parietal regions and left posterior temporal regions, following a semantic, or a syntactic violation (Kielar et al., 2015). In our study, reading a sentence also required processing of semantic and syntactic information, which could explain the similarity of the spatio-temporal distribution between our studies. The study of Kielar et al. thus supports our interpretation that semantic and syntactic unification involves the alpha and beta bands – by stronger recruitment of areas relevant for unification as indicated by the ERD in these frequency bands.

Context Analysis

As the sentence unfolds the context imposes more constraints on what the upcoming word will be, which in turn should facilitate unification. Here, we observed two context effects in the alpha and beta band.

First, a decrease in alpha and beta power (an increase in neural activation) for late words compared to early words in left frontal, temporal, and bilateral occipital regions. We interpret these findings as a context facilitatory effect, drawing inspiration from the MUC model (Hagoort, 2003, 2005, 2013). The model proposes that the lexical information of a word is represented in the activation of (predominantly) left temporal regions. The activation spreads to left frontal regions, which returns input to left temporal and parietal regions, and initiates a second wave of activation. Continuous cycles of activity sent between these regions build the context of the unfolding sentence. Applying this theory to our findings, the decrease in alpha and beta power as the sentence unfolds reflects the build-up of a context in left temporal regions, which spreads to left frontal regions to facilitate unification, and bilateral occipital regions to boost the activation (i.e. a power decrease) for recognizing certain words (orthographic properties). Evidence of interaction between context (semantics) and word recognition is found in several studies (e.g., Kim & Lai, 2012; Yap, Pexman, Wellsby, Hargreaves, & Huff, 2012).

The second effect was in bilateral (but clearly right dominant) frontal and right parietal regions – an alpha and beta band power increase for late words compared to early words. These right-lateralized effects are absent from the context analysis for word lists, which suggests that the right-lateralized effects in sentences are due to a change in context (which is not present in word lists). The word analysis is a high-level linguistic contrast (sentence vs. word list), and a lack of effect in this contrast in the right frontal and parietal regions further suggests that the consequence of a differential context between late and early words does not strictly involve linguistic processes, but might be due to a domain general, cognitive control process. On this basis, we speculate that the right-lateralized frontal-parietal regions reflect a network of regions that are less involved (hence more power) in unification late in a sentence when the context has a stronger facilitatory effect on unification.

In support of our interpretation, the spatial topography of our results is similar to the frontal-parietal network associated with domain general cognitive demands, which is referred to as the cognitive control, executive control, or multiple demand network (Corbetta & Shulman, 2002; Duncan, 2010; Fedorenko et al., 2013; Niendam et al., 2012). For example, Fedorenko et al., demonstrated at the single subject- and group-level that this network is activated when comparing difficult and easy versions of a task, independent of task type (non words vs. sentences, and simple vs. difficult math, working memory, and interference tasks). Previous studies have often found this frontal-parietal network to be bilateral (e.g., Duncan, 2010; Fedorenko et al., 2013). However, in certain tasks attentional processes have been demonstrated to be present in language tasks, in the form of a right-lateralized fronto-parietal network (Cristescu, Devlin, & Nobre, 2006; Kristensen, Wang, Petersson, & Hagoort, 2012). On this basis, we propose that with these effects we tapped into an attentional network that directs more resources to the early than to the late words in a sentence, since early on in a sentence the context is weaker than towards the end of a sentence.

Gamma oscillations in sentence processing

In the word analysis, we observed an ERS for sentences compared to word lists at low and high gamma frequencies (Fig. 1). Low gamma effects were in left occipital, left parietal, left motor and left temporal regions, while high gamma effects were in left frontal and left temporal regions. Interestingly, we observed low gamma effects to be earlier and located more posterior than late gamma effects (Fig. 1, right panel).

In a sentence, compared to a word list, the words form a meaningful and structured context which can be used to predict the next upcoming word. A plausible interpretation for the gamma ERS is that it reflects a correct prediction, i.e. a match between the predicted and observed word. As a correct prediction is only possible for semantic and syntactically well-formed sentences, this interpretation can explain the reduced lower gamma ERS, and the lack of high gamma ERS observed in word lists (Fig. 1, right panel). Our interpretation stems from Herrmann, Munk, & Engel (2004) who proposed a model that explains gamma responses (ERS) in terms of a match between bottom-up and top-down information. The sentences used in this study contained neither strong ambiguities nor grammatical violations, and thus allowed for preceding words to be used to predict the upcoming words – to narrow down the possibilities of various linguistic aspects of the upcoming word, such as, for instance, animacy, word category, and tense. Further support for our interpretation comes from a study that explicitly showed a gamma ERS (40–50 Hz) in left temporal and central sensors that was associated with words that had a high cloze probability given the preceding context (sentence), but not with words that could grammatically combine with the preceding sentence context and had a low cloze probability (Wang et al., 2012). Based on the above interpretation, we would expect an effect in the context analysis for sentences – as the context becomes stronger for late words, the match between the prediction and actual word has a higher probability of being correct. A similar effect is also expected based on previous studies that showed an increase in gamma power across grammatically correct sentences (albeit with EEG; Bastiaansen & Hagoort, 2015; Hald et al., 2006; Rommers, Dijkstra, & Bastiaansen, 2013). In our study, we did observe a higher gamma power for late than early words in sentences, but this was also the case in word lists (Fig. 1).

Distinguishing oscillatory activity from evoked responses

One general concern related to the interpretation of modulations in oscillatory activity is that the reported differences could reflect differences in the spectral representation of the event-related activity, which may not be strictly oscillatory in nature. This interpretational limit is particularly acute when the stimulus protocol leads to transients in the signal that are time-locked to the onset of the stimuli, as was unavoidable in our study. Since the transient event-related signal components typically contribute signal power in the frequency range up to about 20

Hz, the above concern applies predominantly to the interpretation of frequency components up to the beta range. To address this concern, we performed a set of control analyses, in which we computed our contrasts of interest (for the theta, alpha and beta ranges) for the event-related average of the band-limited signals, and for the power estimated after subtraction of the event-related average. The results of these analyses are shown in supplementary materials Fig. S3 (a description is also provided in the supplementary materials), and provide confirmatory evidence that the large majority of the results reported can be interpreted in terms of modulations in oscillatory activity. One exception may be the context effect for the theta band in left temporal regions, which shows a similar topography in the power and ERF contrasts (Fig. S3A). Yet, that does not exclude that we observed a modulation in a band-limited (centered at 5 Hz) phase-locked oscillatory component, related to memory retrieval processes.

Roles of left and right hemisphere in sentence processing

Reviews of language studies demonstrate coordination and interaction between multiple brain areas during language processing (Fedorenko & Thompson-Schill, 2014; Halgren et al., 2002; Price, 2010). The extent to which specific regions are activated appears to be task dependent. High-level core language tasks, such as sentence understanding, activate the dominant (left) hemisphere (Snijders et al., 2009; Xiang, Fonteijn, Norris, & Hagoort, 2010), whereas low-level tasks (e.g., orthographic and word sound analysis), and language tasks that involve non-language specific components (e.g., attention, memory) have been shown to recruit bilateral fronto-parietal regions (Bozic, Tyler, Ives, Randall, & Marslen-Wilson, 2010; Fedorenko & Thompson-Schill, 2014). Our results are in agreement with this distinction. The word analysis aimed to tap aspects of combinatoriality in language (unification), and produced left hemisphere dominant results. In addition, the context analysis reflected changes in cognitive demands whereby effects were found in bilateral (but right hemisphere dominant) frontal, temporal and parietal regions.

4.6 Conclusion

To summarize, we investigated the spatial and temporal dynamics of neuronal oscillations during sentence reading. We quantified the response to individual words in a sentence compared to a word list to determine the effects of context. In sentences, we observed changes in oscillatory power at the theta, alpha, beta, and gamma frequencies. We also quantified differences between words early versus later in a sentence to observe the changes in individual words as the context strengthened. We observed changes in left and right hemispheres in the theta, alpha, and gamma bands.

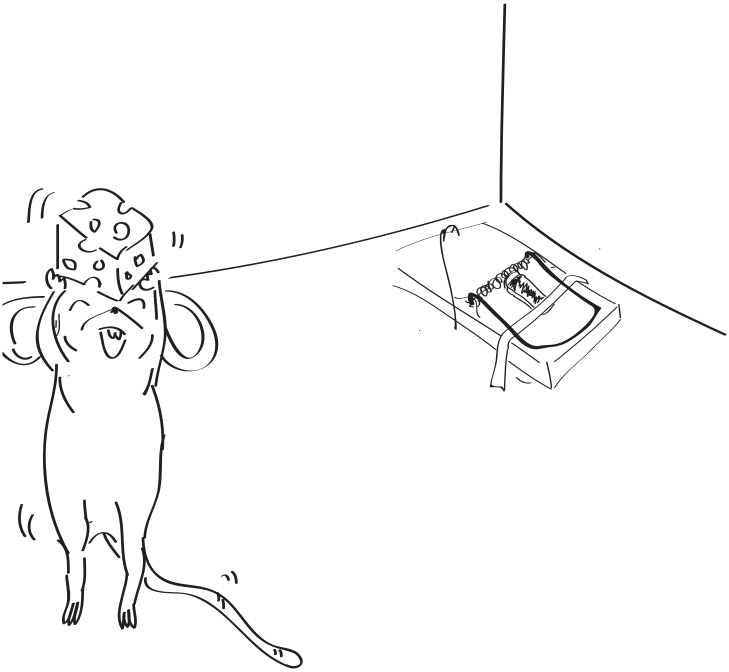
To the best of our knowledge, this is the first MEG source-localized sentence processing study that investigated how individual (grammatical) words are processed, and how this is influenced by an unfolding sentence context. Moreover, with 102 participants this is the largest, most powered MEG study of its kind. Source-localization allowed us to conclude that oscillations localize to similar brain regions as those found in the fMRI literature: first, sentence (language) processing recruits a widely distributed network (Fedorenko & Thompson-Schill, 2014; Friederici & Singer, 2015; Hagoort & Indefrey, 2014). Second, the presence of effects in left temporal and left frontal regions suggests that within this widely distributed network these two regions are important in sentence processing. This is also in agreement with the MUC model of sentence processing (Hagoort, 2003, 2005, 2013). Third, involvement of the right frontal-parietal regions in sentence processing likely reflects engagement of the domain general cognitive control network according to task demands at different points in a sentence.

In this study, we also made use of the temporal resolution in MEG. We demonstrated that unification processes involved in reading a sentence begin around 200 ms when statistically comparing sentences with word lists. Moreover, visual inspection of the oscillatory power time courses show that differentiation between the wave forms for sentences and word lists occurs around 100 ms, which suggests that the semantic and syntactic context effects can begin as early as 100 ms (see Fig. 1, e.g., in the left frontal region in the beta band, and left occipito-parietal region in the lower gamma band). The early onset of language effects following the language stimuli is in accordance with the abundance of MEG and EEG studies reporting language effects within the first 400 ms following word onset (see Salmelin, 2007 for a review of MEG language studies at the single word level and beyond).

We analyzed multiple frequencies and found that the theta, alpha, beta, and gamma bands are all involved in sentence processing. This highlights the importance of studying multiple frequencies to provide a broader perspective on which oscillations are and which are not involved in any given cognitive task. The observation of oscillatory changes in multiple brain regions at several frequency bands suggests no simple mapping between a specific region and function. Almost certainly, the effects in the different frequency bands have different functional significance. The presence of effects in the frequency bands that we observed indicate that higher order language processing (i.e. unification) depends on multiple networks, including memory networks in temporal cortex and attentional networks in the right parieto-frontal network, in addition to the core language network in left perisylvian cortex. The abundant effects in occipital areas, moreover, imply that higher order language processes interact with the extraction of relevant information from the feedforward visual processing stream. The timing of all these effects are a testimony of the exquisite speed at which the human brain is able to complete the complex cascade of processes that are involved in extracting meaning from a series of orthographic scribbles entering primary visual cortex.

5

COMMON GENETIC VARIANT OF *CNTNAP2* rs7794745 IS ASSOCIATED WITH MEG OSCILLATORY ACTIVITY IN SENTENCE PROCESSING



5.1 Abstract

The search for language-related genes in combination with neuroimaging methods is a promising and growing endeavour. Most studies have used fMRI in the clinical population. Here, we present one of the first studies to test for associations between MEG-derived neuronal oscillations and a common *CNTNAP2* polymorphism in healthy individuals. Previous evidence favours the *CNTNAP2* polymorphism rs7794745 over other polymorphisms, as it has been associated with behavioural language difficulties, and with variation in neuroimaging measures during language tasks in both clinical (e.g., Autism, Specific Language Impairment, Dyslexia) and healthy populations. We genotyped a 102 individuals, and quantified their neural oscillatory activity when reading sentences compared to reading word lists. Our results demonstrated that rs7794745 is associated with variability in theta oscillatory power during sentence processing. Individuals with one or more T alleles (AT/TT) showed a larger effect size of oscillatory theta power between sentences and word lists, in left inferior frontal gyrus, in comparison to individuals with an AA genotype. Our study also supports the use of MEG and neuronal oscillations to discover neural variability in the language network in relation to genetic variability.

5.2 Introduction

The interaction between our genome and the environment influences the unique human ability of language. Definitive evidence of a genetic basis for language was found 15 years ago in the *FOXP2* gene. Studies on a 3 generation family (KE family) found that members with a single point mutation (G to A) in *FOXP2* displayed severe speech and language difficulties (Fisher, Vargha-Khadem, Watkins, Monaco, & Pembrey, Marcus, 1998; Lai et al., 2001; Lai, Gerrelli, Monaco, Fisher, & Copp, 2003). Subsequently, evidence has steadily accumulated, with more support for the influence of FOXP2 on speech and language phenotypes (Fisher & Scharff, 2009; Harold et al., 2006; Macdermot et al., 2005; Nelson et al., 2013; Peter et al., 2011; Vernes et al., 2006). Several other genetic regions and candidate genes that influence speech and language phenotypes have also been discovered, such as *CNTNAP2, DCDC2, ATPC2C,* and *DYX1 – DYX9* (Carrion-Castillo et al., 2013; Marcus & Fisher, 2003; Newbury, Fisher, & Monaco, 2010).

Brain-imaging genetics studies have begun to bridge the connection between genes and behavior by investigating how genes influence the brain (in terms of structural and functional neural measures), and in turn how the brain supports language-related cognition and behavior (e.g., Durston, Zeeuw, & Staal, 2009; Hariri, Drabant, & Weinberger, 2006; Meda et al., 2008; Renvall et al., 2012; Scott-Van Zeeland et al., 2010). These neural measures are considered as biological markers of language, and may be used as an endophenotype (not a directly observable trait) if they meet certain criteria such as heritability and robustness (Gottesman & Gould, 2003). With brain-imaging genetics being a young field, most studies have used (f)MRI, and few studies have been replicated; therefore, there is an opportunity and necessity for development. To address this, the current study sought to identify a new neurobiological marker by determining whether individual differences in neural oscillatory activity during sentence processing can be explained by the variation in *CNTNAP2,* in a healthy population.

CNTNAP2

CNTNAP2 (contactin-associated protein-like 2), is a downregulated target of *FOXP2*[3], which has garnered much attention for influencing language and communication abilities (Fisher & Vernes, 2015; Vernes et al., 2007, 2008) in clinical (Alarcón et al., 2008; Fletcher et al., 2010; Newbury et al., 2011; Peter et al., 2011; Strauss et al., 2006) and healthy populations (Folia, Forkstam, Ingvar, Hagoort, & Petersson, 2011; Kos et al., 2012; Whalley et al., 2011; Whitehouse, Bishop, Ang, Pennell, & Fisher, 2011). Strong evidence for the role of this gene in language and communication comes from children with focal epilepsy. These children had a homozygous mutation in *CNTNAP2* and demonstrated language regression, abnormal social behavior (e.g., aggression and hyperactivity), and abnormal neural structure (in terms of the histology, organization and density of neurons) in lateral and medial temporal regions (Strauss et al., 2006). Expression studies showed that in the early stages of development (17-22

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[3] *FOXP2* is a transcription factor; it regulates the transcription of other genes by either reducing their expression (down-regulation) or increasing their expression (up-regulation). Down-regulation means the targeted gene will produce fewer products (proteins), while up-regulation leads to an increase in gene product. With *CNTNAP2*, its expression is reduced by *FOXP2*.

weeks of gestation) *CNTNAP2* is highly expressed in frontal and temporal cortical regions (Abrahams et al., 2007; Alarcón et al., 2008). These regions eventually form core areas of the neural network involved in high order cognitive processes like language processing (and others like planning and decision making), lending further support to the potential of *CNTNAP2* influencing language and communication.

Currently, rs7794745, located in intron-2 of *CNTNAP2*, is one of the most frequently studied common variants (it can have a nucleotide base of A or T). Within healthy populations, this variant has been associated with variability in neural measures of sentence processing in a few studies (Folia et al., 2011; Kos et al., 2012; Whalley et al., 2011). In a sentence completion task during a functional Magnetic Resonance Imaging (fMRI) scan, TT carriers showed a larger Blood-oxygen-level dependent (BOLD) activation in right frontal and temporal regions, respectively, in comparison to individuals with AT or AA genotype. When measuring event-related potentials, the reading of syntactic anomalous sentences led to an anterior negativity potential prior to a P600 in T-carriers (AT/TT), and only a P600 in the AA individuals. In yet another study, the processing of ambiguous sentences showed that variation in rs7794745 was associated with a variation in neural activation (both BOLD activity and event-related potentials), in frontal and temporal regions (Snijders, 2010). Together, these studies consistently suggest that genetic variation in rs7794745 influences neural measures of sentence processing.

Oscillations to capture downstream effects of *CNTNAP2*

Oscillations are a measure of synchronized neural activity which is considered to play a role in the coordination and transfer of information in the brain (Fries, 2005, 2015; Siegel, Donner, & Engel, 2012; Singer, 1999; Varela et al., 2001). As molecular research has showed that *CNTNAP2* affects neuronal structure and activity (Poliak et al., 2003; Rodenas-Cuadrado, Ho, & Vernes, 2014; Vernes et al., 2008), the use of oscillations could therefore provide a relatively more direct link between genetics, the brain and behavior, in comparison to the frequently used (indirect) measures of the haemodynamic response (e.g., Belton, Salmond, Watkins, Vargha-khadem, & Gadian, 2003; Liégeois et al., 2003; Liu et al., 2009; Peter et al., 2011; Pinel et al., 2012; Silani et al., 2005; Watkins et al., 2002). The modulation of oscillatory activity has been associated with various cognitive tasks, including sentence processing (e.g., Bastiaansen et al., 2010; Kielar et al., 2015; Lam, Schoffelen, Uddén, Hultén, & Hagoort, 2016; Wang et al., 2012).

Current Study

Recently, we performed a thorough analysis of neural oscillatory activity during sentence processing in a dataset of 102 individuals, and demonstrated that the neural oscillatory responses at theta, alpha, beta and gamma frequencies are modulated by the processing of sentences (Lam et al., 2016). In the current study, using the same group of participants as before, we were interested in whether genetic factors underlie the interindividual variability that we observed in neuronal oscillations during sentence processing.

Given our limited sample size, at least in the light of genetic studies, we selected specific cortical regions and frequencies, motivated by earlier findings on the neurobiological substrates of language processing. We focused on the left inferior frontal gyrus (LIFG) and the left superior temporal gyrus (LSTG) for two reasons. First, in early human (fetal) development *CNTNAP2* expression is highly enriched in anterior neural regions, which subsequently form the frontal and anterior temporal cortex (Abrahams et al., 2007; Alarcón et al., 2008). This suggests that effects of CNTNAP2 in our selected regions would be strong. Second, these two regions have consistently been found to be involved in sentence processing (Fedorenko, Duncan, & Kanwisher, 2012; Fedorenko & Thompson-Schill, 2014; Friederici & Gierhan, 2013; Friederici, 2012; Hagoort & Indefrey, 2014; Hagoort, 2013; Snijders, 2010; Snijders et al., 2009; Snijders, Petersson, & Hagoort, 2010). We adopted a step-wise approach for testing frequency bands. We began with the theta band because at the group level (in our previous study) this activity in this frequency band showed a significant difference (sentences vs. word lists) within our chosen regions. In comparison, the other frequencies (alpha and beta) showed effects in other areas that overlapped but did not fully include LIFG and LSTG (Lam et al., 2016). If a significant association was found at the theta band, we would progress to test a subsequent frequency band.

In sum, the present study investigated the individual differences in oscillatory dynamics of sentence processing. Here, we extracted brain activity that pertained to how individual words are processed and combined into a meaningful sentence, while controlling for lower-level linguistic differences such as orthography, word length and word frequency. To do this, we had participants sit in the MEG while they read sentences (word in a structured, meaningful manner) and word lists (words in an unstructured manner, created by randomizing the order of words in a sentence). Then, for each genetic group (T-carriers (TT/AT) and the AA group) we calculated the difference in oscillatory power between these two conditions as a measure of sentence processing. Subsequently, to determine whether individual differences in sentence processing are mediated by a common variant in *CNTNAP2*, we contrasted the difference in oscillatory power between groups, in LIFG and LSTG.

5.3 Methods

Participants

A total of 102 native Dutch speakers (51 males), with an age range of 18 to 33 years (mean of 22 years), participated in the experiment. These participants formed part of a larger study – MOUS (Mother of all Unification Studies; $N = 204$), where all participants took part in an fMRI and a MEG session. Half of these participants completed both sessions where they read the stimuli, and the other half listened to recordings of the stimuli. The current paper pertains to participants from the MEG session in the visual modality. All participants were right-handed, had normal or corrected-to-normal vision, and reported no history of neurological, developmental or language deficits. The study was approved by the local ethics committee (CMO – the local "Committee on

Research Involving Human Participants" in the Arnhem-Nijmegen region) and followed the guidelines of the Helsinki declaration. Participants received monetary compensation for the participation.

Language stimuli

The stimuli consisted of 180 sentences and their word list counterparts (see Table 1 for an example). All sentences varied between 9 and 15 words in length.

Sentence	**Word list**
Bij de opening van de nieuwe sporthal kregen de talrijke bezoekers een consumptie	sporthal bij van talrijke opening een de de kregen consumptie bezoekers nieuwe de
At the opening of the new sports hall received the many visitors a (free) drink	sports hall at from many opening a the the received (free) drink visitors new the

Table 1. Exemplar sentence and word list in Dutch, and literal English translation.

The word lists were created from the sentences by scrambling the words so that no more than two consecutive words formed a coherent fragment. The same words in both conditions limited the difference between conditions to sentential semantics and syntax as opposed to lexical differences in orthography, phonology, and word meaning. Each participant saw each stimulus in either the sentence or the word list condition, but not in both. Across participants, each stimulus was presented the same number of times in the sentence and in the word list condition.

Task and Procedure

Experimental Design

All stimuli were presented with an LCD projector (with a vertical refresh rate of 60 Hz) situated outside the MEG measurement room, and projected via mirrors onto the screen inside the MEG room. All stimuli were presented at the center of the screen within a visual angle of 4 degrees, in a black mono-spaced font, on a gray background using Presentation software (Version 16.0, Neurobehavioral Systems, Inc).

The stimuli were divided into three subsets, such that each participant saw 2/3 of the stimulus set in the MEG session (120 trials of each condition); and 1/3 in the fMRI session that will not be further discussed in this paper. Participants presented with the same subset saw the stimuli in a different (randomized) order. In the experiment, the stimuli were presented in a mini block design, and alternated between a sentence block (containing 5 sentences) and a word list block (containing 5 word lists), for a total of 24 blocks. The first mini block (sentences or word lists) was randomized across participants. In addition, for sentences, the first word began with a capital letter and the last word ended with a full stop.

At the beginning of each block, the block type was announced for 1500 ms: *zinnen* (sentences) or *woorden* (words), followed by a 2000 ms blank screen. At the beginning of each trial a fixation cross was presented for a jittered duration between 1200 and 2200 ms. Then, the words for each trial (sentence or word list) were presented one at a time. Each word was separated by a blank screen for 300 ms.

The presentation time of each word was varied in order to allow for a 'naturalistic' reading experience, and to avoid a strict entrainment of ongoing activity to fixed interstimulus intervals. For any given sentence (or word list) the variable duration of a single word was a function of the following quantities: (i) the total duration of the audio-version of the sentence/word list (*audiodur*), (ii) the number of words in the sentence (*nwords*), (iii) the number of letters per word (*nletters*), and (iv) the total number of letters in the sentence (*sumnletters*). Specifically, the duration (in ms) of a single word was defined as: (*nletters/sumnletters)*(audiodur+2000-150*nwords*). The minimum duration of short words was set to 300 ms irrespective of the relative weighting described by the formula. In practice, however, the exact presentation times of the words slightly deviated from those obtained from the above formula. This was due to the fact that the presentation timing was dictated by the refresh rate of the projector (60 Hz). As a consequence, the actual presentation time was lengthened by a duration between 0 and 33 ms. The median duration of a single word on the screen was 434 ms (range 300-1344 ms). Taking into account the 300 ms gap between the words, the median duration of a whole sentence/word list was 8.3 s (range 6.2-12 s). Within each block, the inter-trial interval was a blank screen with a jittered duration between 1200–2200 ms.

In order to check for compliance, 10% of the trials (n = 12) were randomly followed by a yes/no question about the content of the previous sentence/word list. Half of the questions on the sentences addressed sentence comprehension (e.g. *Did grandma eat a pancake?).* The other half of the sentences, and the questions following the word lists addressed a content word (e.g. *Was a music instrument mentioned?*). Participants answered the question by pressing a button for 'Yes'/ 'No' with their left index and middle fingers, respectively. For both question types, half of the trials required a yes-response. The experiment began with participants reading written instructions for the task. The experimenter clarified any questions from the participant. Then, for familiarization purposes, participants completed a practice task (using a separate set of stimuli from the actual task). Subsequently they performed the actual task as described above.

MEG data acquisition

MEG data were collected with a 275 axial gradiometer system (CTF) at the Donders Centre for Cognitive Neuroimaging in Nijmegen, The Netherlands. The signals were digitized at a sampling frequency of 1200 Hz (the cutoff frequency of the analog anti-aliasing low pass filter was 300 Hz). Three coils were attached to the participant's head (nasion, left and right ear canals) to determine the position of the head relative to the MEG-sensors. Throughout the measurement the head position was continuously monitored using custom software (Stolk et al., 2013). During breaks the participant was allowed to reposition to the original position if needed.

Participants were able to maintain a head position within 5 mm of their original position. Three bipolar Ag/AgCl electrode pairs were used to measure the horizontal and vertical electro-oculogram, and the electro-cardiogram.

Genetic Analysis

We collected saliva from participants using the DNA collection kits (OG-500) from DNA Genotek. For genotyping we used the KASP assay technology (LGC Genomics) and a Bio-Rad CFX96 real-time PCR thermocycler. Each 10 µl reaction contained 0.14 µl of 72X KASP primer mix, 5 µl of 2X KASP master mix with standard ROX concentration, and 2 µl of genomic DNA (diluted at 20 ng/ul). Thermocycling was performed as follows: after an initial denaturation of 15 min at 94˚C, 10 cycles were run with 20 s denaturation at 94˚C followed by 45 s of annealing/elongation starting at 61˚C and decreasing by 0.6˚C per cycle, followed by 30 cycles with 10 s denaturation at 94˚C followed by 45 s of annealing/elongation at 55˚C. If necessary, five further cycles were performed using the same parameters as the final 30 cycles from the initial run. Genotypes were called using the CFX96 Manager software (Bio-Rad). The assay was validated by Sanger sequencing of randomly-selected samples of each genotype.

MEG data processing

All analyses were done with custom written Matlab scripts and FieldTrip, an open source toolbox for EEG and MEG data analyses (Oostenveld et al., 2011).

Preprocessing

Electrocardiogram artifacts were estimated using denoising source separation (DSS, Särelä & Valpola, 2005), identified based on their topography and subtracted from the data. Physiological artifacts (eye movements and muscle contractions) and jump artifacts in the SQUIDs (superconducting quantum interference device) were identified using a semi-automatic artifact identification procedure (http://www.fieldtriptoolbox.org/tutorial/automatic_artifact_rejection), followed by visual inspection. Data segments that contained artifacts were excluded from further analysis. Next the power line interference at 50 Hz and its harmonics at 100 and 150 Hz were estimated and subtracted from the data (for details see Schoffelen, Oostenveld, & Fries, 2005). Finally, the data were downsampled to a sampling frequency of 300 Hz.

Frequency-domain beamforming

We used a frequency domain beamformer (DICS; Gross et al., 2001) to reconstruct the sources of the oscillatory responses. First, for each time window and frequency band the sensor-level cross-spectral density matrix was computed across all conditions. The frequency bands were selected based on earlier studies. For the low frequencies, they were centered at the following frequencies (with effective spectral bandwidth in brackets): 5 Hz (3.75 to 6.25 Hz) for theta, 10 Hz (8.75 to 11.25 Hz) for alpha, and 16 Hz (14 to 18 Hz) for beta. Here, each discrete frequency designates the centre frequency of a band-limited frequency bin, and this centre frequency encompasses the average signal power across the frequency range in that bin, referred to as the effective bandwidth. This bandwidth is dictated by the combination of the chosen window length and tapering scheme. The theta and alpha band were analyzed in 50 ms time steps from -100 to 500 ms (around word onset at 0 ms) using a sliding time window of 400 ms in combination with a Hanning taper, which produced an effective bandwidth of 2.5 Hz (which is 1.25 Hz around the defined centre frequencies). Beta was also analyzed in 50 ms time steps from -150–500 ms, but with a 250 ms time window in combination with a Hanning taper, which produced an effective bandwidth of 4 Hz. The higher frequencies, were a priori defined as 36 to 76 Hz (low gamma), and 76 to 108 Hz (high gamma), and thus encompassed spectral estimates across multiple frequency bins. We analyzed them at 50 ms time steps, at 4 Hz steps, between -150 to 500 ms. Here we used a 250 ms time window in combination with multitapers (Mitra & Pesaran, 1999), which achieved an effective bandwidth of 16 Hz.

The sensor-level cross-spectral density matrix was then used in combination with the forward solution to compute a set of spatial filters to obtain an estimate of the activity for dipoles placed on a volumetric grid with ~8 mm spacing (see below). The spatial filters assumed a fixed orientation of the underlying dipoles, defined by means of a singular value decomposition of the dipole cross-spectral density, taking the orientation along the first singular vector to explain the maximum amount of variance. The activity (power) was estimated for each condition of interest.

MEG source reconstruction

For source reconstruction purposes, we coregistered the anatomical MRI to the MEG-sensors. This was achieved by manual alignment of two reconstructions of the head surface. A digitized head shape, consisting of approximately 500 points across the scalp, was obtained with a Polhemus device (Fastrak, Polhemus Inc. Colchester, VA, USA). The other scalp surface was obtained by segmenting the participant's T1-weighted anatomical MRI image.

Subsequently, the aligned anatomical image was used to create a volume conduction model based on a single shell description (Nolte, 2003) of the inner surface of the skull, using the segmentation function in SPM8. Source reconstruction was performed on a set of 8196 dipole locations distributed across the cortical sheet. Freesurfer 5.1 (Dale et al., 1999) was used to create a high-resolution description of the cortical surface. Next, these cortical surfaces were surface-registered to a template mesh using the Caret Software package (Van Essen et al., 2001), and subsequently downsampled from about 150,000-200,000 dipoles per hemisphere to 4098 dipoles.

The surface registration procedure resulted in individual cortical sheets that were topologically equivalent across participants (i.e. a particular topological point in the cortical sheet of one participant correspond to the same particular point in all other participants). To define our regions-of-interest, we used a parcellation scheme, based on a cortical atlas that maps out the Brodmann areas (the Conte69 atlas,Van Essen, Glasser, Dierker, Harwell, & Coalson, 2012) whereby each topological point is labeled and assigned to an anatomical region, for a total of 86 regions (parcels). In these 86 parcels, the spatial division was relatively coarse. To achieve a finer division, we subparcellated the original atlas into 386 smaller parcels while maintaining the original boundaries between Brodmann areas. Visualization of the parcellated cortical sheet was done with the Connectome Workbench software (Marcus et al., 2011)

Region-of-interest selection

At the group level we found differences in oscillatory activity between sentences and word lists in LIFG and LSTG (Lam et al., 2016). In the current study, we were interested in whether the individual differences in these areas could be partially explained by differences in genotype. We refer the reader to the introduction for our motivation for selecting particular regions and frequencies. The parcellation procedure (as outline above) of the results at the whole group-level (see above) produced multiple parcels in LIFG and LSTG. To narrow our selection, we chose parcels that had the highest difference between sentences and word lists at the theta band. As shown in Fig. 1, this involved 4 parcels: 2 in left inferior frontal gyrus and 2 in left superior temporal gyrus.

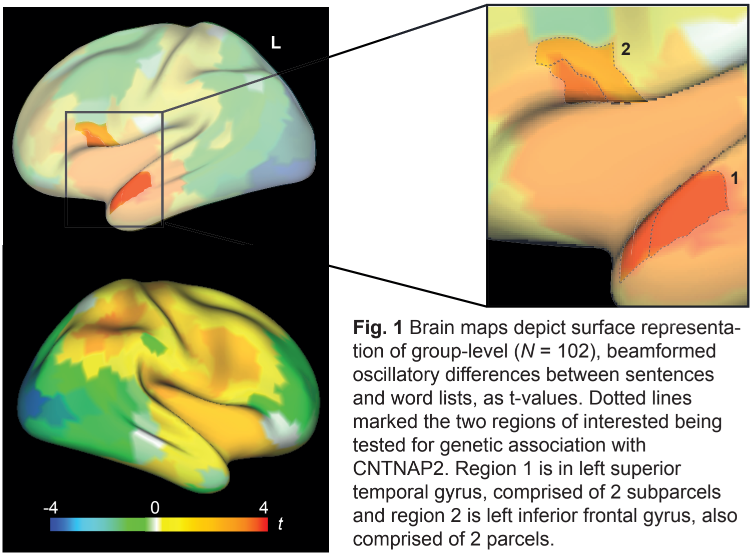

Fig. 1 Brain maps depict surface representation of group-level (*N* = 102), beamformed oscillatory differences between sentences and word lists, as t-values. Dotted lines marked the two regions of interested being tested for genetic association with CNTNAP2. Region 1 is in left superior temporal gyrus, comprised of 2 subparcels and region 2 is left inferior frontal gyrus, also comprised of 2 parcels.

Statistical Analysis

For each selected cortical parcel, we compared the condition specific (sentences or word lists) response to individual words. For each condition, we subtracted the estimated power in the period preceding word onset (baseline) from the power following word onset. Changes in oscillatory activity in response to a single word require time to develop, and probably more than 100 ms to become apparent. Therefore, the choice of a pre-word baseline allowed us to study word-induced changes in frequency specific activity, above and beyond the ongoing nature of oscillations. Furthermore, it mitigated the possible effect of a block design producing different pre-window activity for each condition. We used a baseline estimate centered at -100 ms, which as a consequently included a short duration of data following word onset (up to 100 ms for the theta band, and up to 25 ms for all other frequencies). We did not use an earlier time window e.g., -200 ms, because this would potentially include transient oscillatory activity from the previous word. Then, for each parcel, we calculated a difference value between the sentences and the word lists. Finally, we tested whether the difference between sentences and word lists differed between genotype groups. Given the small number of individuals who were homozygous for the T allele (TT) we chose to group them with individuals who were heterozygous (AT), and test this group against individuals homozygous for the A allele (AA).

5.4 Results

Genotyping

The genetic distribution of rs7794745 was according to the Hardy-Weinberg equilibrium (*p* = 0.45), with 49 individual homozygous for A, and 53 individuals with one or more T alleles (41 AT individuals and 12 TT individuals).

Behavioural measures

Genotype was not significantly associated with age (t_{100} = 0.28, *p* = 0.78), gender (t_{100} = -0.78, *p* = 0.44), handedness (t_{100} = .67, *p* = 0.51), working memory (WAIS standardized digit span score, t_{93} = 0.24, *p* = 0.81), or IQ (t_{100} = 1.26, *p* = 0.21).

	Genotype	**Mean**	**SD**	**SEM**
Age	AA	22.35	2.74	0.39
	AT/TT	22.19	2.97	0.41
Handedness	AA	49.92	3.56	0.51
	AT/TT	49.40	4.25	0.58
IQ (mean percentage correct)	AA	65.98	16.85	2.41
	AT/TT	65.56	16.13	2.22
WAIS standardized digit span	AA	11.53	2.01	0.29
	AT/TT	11.41	2.85	0.39
Working memory	AA	12.39	2.13	0.30
(Number Letter sequence test)	AT/TT	11.79	2.60	0.36

Table 2. Means of age, handedness, IQ, and working memory for each genotype group.

	Sentences	Word lists
AA genotype	85.2 (6.7)	79.1 (9.6)
AT/TT genotype	82.1 (10.2)	77.9 (9.5)

Table 3. *Mean percentage of correct answers for questions following a sentence or a word list. Values in brackets represent the standard deviation.*

For the compliance questions, both groups performed above chance (table 2), with a higher accuracy for sentences than word lists (AA group: $t_{48} = 3.5$, $p = 0.001$, AT/TT group: $t_{52} = 2.3$, $p = 0.025$). This trend, also observed at the group level (Lam et al., 2016) might well because sentences are coherent, and therefore easier to process than word lists. Across groups, there was no difference in the average accuracy for questions that followed sentences (Mann Whitney U test, Z = 1.3, $p = 0.2$) or questions that followed word lists (Mann Whitney U test, Z = 0.4, $p = 0.7$). Altogether, this suggests that participants in both genotype groups were attentive and processed the language material well, and any differences between groups would unlikely be due to differences in comprehension of the material.

Association between oscillatory power and rs7794745

For each parcel and genetic group, we tested the distribution of the difference between condition-specific means of the two genetic groups, using the Shapiro-Wilk's test. As these distributions were skewed (W 's ≥ .157, *p*'s < .001), we used the Mann-Whitney U test to test for a difference between genetic groups. The Mann-Whitney U test revealed a significant difference between genotypes in left inferior frontal gyrus at 250 ms following word onset ($Z = -3.06$, $p = 0.0022$) (Fig. 2).

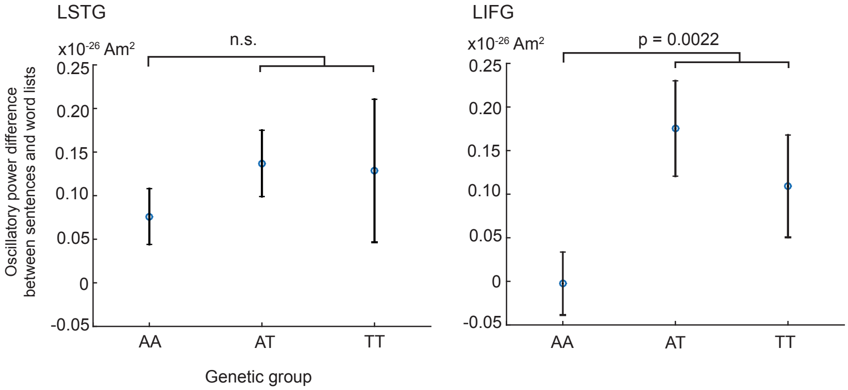

Fig. 2 Mean difference in oscillatory power between sentences and word lists, for each allele group, in left temporal superior gyrus (LSTG) and left inferior temporal gyrus (LIFG). Error bars represent standard error of the mean. Group differences were tested between the AA group and AT/TT group, for each brain region.

A post-hoc test demonstrated that for the AT/TT genotype group the sentence condition had significantly larger oscillatory power than the word list condition (*Z* = 3.05, *p* = 0.0023) but no significant difference was found between these conditions for the AA genotype group (Fig. 3).

Earlier, at the group level we showed earlier that the difference between sentences and word lists was, in part, due to a latency shift of the response between the conditions (Lam et al., 2016). For each genotype group, using the Wilcoxon Signed-rank test we also found this pattern to be significant. For the AA genotype, the median peak was 0.35 s (*IQR* = .15 s) for sentences, and at 0.40 s (*IQR* = .20 s) (*Z* = -2.73, *p* = 0.0062) for word lists, and for the T-carrier genotype, the median peak for sentences was at 0.40s (*IQR* = .15 s), and 0.40 s (*IQR* = .10 s) for word lists (*Z* = -2.43, *p* = 0.0148). Between genotype groups there was no significant difference in (i) the duration of the sentence and word list peak (Mann Whitney U test, *Z* = -0.6, *p* = 0.53), (ii) the time point of the sentence peak (Mann Whitney U test, *Z* = -1, *p* = 0.30) and (iii) the time point of the word list peak (Mann Whitney U test, *Z* = -0.2, *p* = 0.80). This suggested that rs7794745 predominantly affects the difference in oscillatory power, rather than the difference in latency, between sentences and word lists.

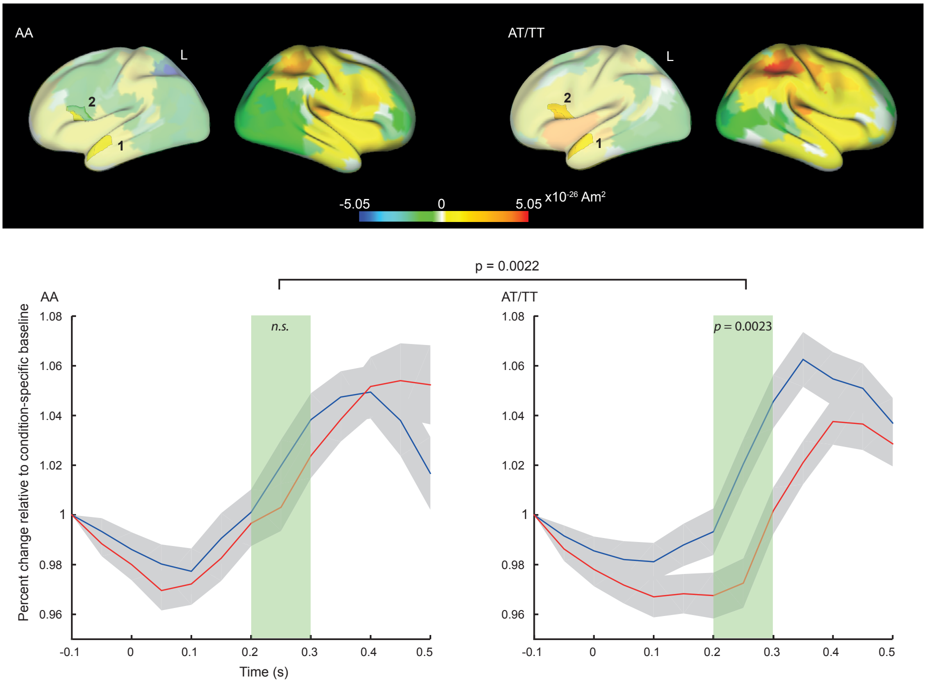

Fig. 3 *Top,* Brain maps depict surface representation of beamformed oscillatory differences between sentences and word lists as power values. *Left,* Differences for the AA allele group. *Right,* Differences for the T-carriers (AT and TT allele groups combined). Unmasked regions of the left hemispheres mark the two regions of interest being tested for genetic association with *CNTNAP2*. Region 1 is left superior temporal gyrus, which was not significantly different between genetic groups. Region 2 is left inferior temporal gyrus which was significantly difference between genetic groups. *Bottom,* Time courses reflect the mean percentage change in theta oscillatory power relative to baseline in left inferior frontal gyrus, for sentences (blue) and word lists (red), for each genotype group. The baseline is the averaged baseline between the sentence and word list condition. Standard error of the mean is represented with the shaded area around each time course. Green bars highlight the time window (centered at 0.25 s following word onset) used to test for a difference between genotype groups, and for differences between conditions within each group.

There was no significant difference in LSTG for the theta band ($p = 0.19$). In the alpha band, we did not observe significant differences in LIFG ($p = 0.19$), nor in LSTG ($p = 0.64$) [4].

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[4] We were predominantly interested in the *CNTNAP2* gene as it has consistently shown to be associated with language processing and communication in comparison to other genes. In addition, we were interested in whether other genes predominantly associated with language processing in clinical populations would also demonstrate an association in our healthy population. Therefore, we tested 4 polymorphisms from 3 candidate genes, as shown below in the table 4. We found no significant association for them (p's > 0.025), and therefore focused on the findings with *CNTNAP2* rs7794745.

Gene	Polymorphism	Allele 1	Allele 2	Allele Distribution			
				Homozygous allele 1	Heterozygous	Homozygous allele 2	Hardy-Weinberg Equilibrium *p*
FOXP2	rs6980093	A	G	34	54	14	.30
FOXP2	rs7784315	C	T	1	24	77	.56
KIAA0319/ TTRAP/THEM	rs17243157	G	A	86	14	1	.62
ROBO1	rs6803202	C	T	23	48	30	.65

Table 4. Genetic information and distribution for 5 polymorphisms from 3 candidate genes

5.5 Discussion

Delineating the genetic basis of language is a major challenge. Language, a higher-order trait, involves complex interactions at multiple levels of biology, including genes, proteins, cell functions, and neural circuits. Genetic variation in *CNTNAP2* has consistently been associated with individual variations in language-related behavioural and neural measures. Molecular studies have implicated *CNTNAP2* in the organization and function of neuronal activity (Anderson et al., 2012; Inda, Defelipe, & Mun, 2006; Peñagarikano et al., 2011; Poliak et al., 1999, 2003). Neuronal oscillations are a measure of the rhythmic activity of synchronous neuronal populations and thought to underlie brain function (Fries, 2005, 2015; Siegel et al., 2012; Singer, 1999; Varela et al., 2001), and they may well capture the influence of *CNTNAP2* on neural variation in sentence processing. With previous brain-imaging genetic studies on language predominantly using fMRI, the use of neuronal oscillations may also demonstrate its potential to provide a different but complementary perspective on how genetics influence neural activity, and ultimately cognition.

In the present study, we tested for a genetic association between the *CNTNAP2* common variant rs7794745 and theta oscillations in left inferior frontal gyrus (LIFG) and left superior temporal gyrus (LSTG), during sentence processing. We demonstrated that rs7794745 explains part of the variation in differential theta power in LIFG. Individuals with an AT/TT genotype demonstrated higher oscillatory power for processing words in a sentence than words in a word list. These patterns suggested that genetic variation in *CNTNAP2* influences language-related brain function whereby the T-allele of rs7794745 has a dominant effect. Below we discuss the possible role of *CNTNAP2*, taking into account past work from the neural level and the molecular level.

Evidence of *CNTNAP2* influencing language processing at the neural and molecular level

Our results are in line with earlier neural studies that *CNTNAP2* is associated with language processing. Across healthy and clinical populations, *CNTNAP2* has a broad effect on language-related processes which encompasses semantics, syntax, phonology, as well as various types of communicative and social behavior (e.g., Folia et al., 2011; Steer, Golding, & Bolton, 2010; Strauss et al., 2006; Vernes et al., 2008; Whitehouse et al., 2011). The *CNTNAP2* common variant rs7794745 has been associated to neural measures of sentence processing in 6 studies (Folia et al., 2011; Kos et al., 2012; Snijders, 2010; Snijders et al., 2009, 2010; Whalley et al., 2011), of which 3 showed effects in LIFG (Folia et al., 2011; Kos et al., 2012; Snijders, 2010). Folia et al. (2011) demonstrated that the AT/TT group compared to the AA group was behaviourally different in their sensitivity to syntactic sequences, and that the AA group had greater BOLD activation in left inferior frontal regions (and left frontopolar regions). Snijders (2010) did an MEG study on event-related field (ERF) during sentence processing. Between the AA and AT/TT group, there was no ERF difference when processing sentences and processing word lists (but only a difference between ambiguous and unambiguous sentences). Snijders surmised this was because the differences were in the non-phase-locked aspect of the electrophysiological signal which could not be revealed by ERFs but only oscillations.

Indeed, in the current study we found a difference in oscillatory power. However, it is also possible that the lack of ERF difference in Snijders' (2010) study could be because the effect of interest is small, and they may not have detected it given a small sample size (10 AA, 14 AT/TT). Nevertheless, keeping with the same language paradigm, this time using fMRI, Snijders et al. (2009) demonstrated that the left posterior middle temporal gyrus and LIFG are involved in, and then (Snijders et al., 2010) showed that they are functionally connected with each other during sentence processing. Subsequently, Snijders (2010) demonstrated that the connectivity between these two regions during sentence processing is stronger for the AA Group than the AT/TT group. As such, these neural studies, together with our current findings lend evidence that rs7794745 influences the neural processes supporting sentence processing.

At the molecular level, *CNTNAP2* is known to be highly expressed in anterior regions (Alarcón et al., 2008; Vernes et al., 2008), which develop into frontal and temporal regions involved in higher order processes like language processing (Alvarez & Emory, 2006; Fedorenko, Behr, & Kanwisher, 2011; Fedorenko & Thompson-Schill, 2014). CASPR2 is the protein encoded by *CNTNAP2*, and it has been implicated in multiple aspects of neuronal function (for a review, see Rodenas-Cuadrado et al., 2014). Its most defined role is in the saltatory conduction of action potentials by modulating the function of potassium ion channels in myelinated axons (Inda et al., 2006; Poliak et al., 1999, 2003). More recently, in cultured cortical neurons, the knockout of CASPR2 cause a decrease in the number of synapses (due to impaired dendritic arborization and spine growth) which in turn impaired neural circuitry (Anderson et al., 2012). In another study, *CNTNAP2* knockout mice (in comparison to Wild Type mice) displayed less synchronous neuronal firing, a decrease in the number of inhibitory neurons, and abnormalities in the neuronal migration of excitatory neurons. In addition, these mice demonstrated abnormal communicative and social behavior (Peñagarikano et al., 2011). These studies indicate that *CNTNAP2* influences the processes at the cellular level in terms of synaptic transmission, synaptic organization, interneuron function, and neuronal migration. On this basis, we infer that a genetic difference between the AA and AT/TT group, leads to a difference in neuronal structure and function, which in turn leads to a difference evident in neural rhythmic activity. But, as we are in the early days of understanding *CNTNAP2,* the nature of this molecular to neural relationship requires further investigation. For now, we have been one of the first to demonstrate that measurements of rhythmic neural activity are able to pick up the downstream effects of *CNTNAP2* on language-related neural function.

Individual differences in theta power explained by *CNTNAP2*

To interpret our findings on the genotype-dependent differences in oscillatory power, we draw on earlier studies and a particular model of sentence processing. The Memory, Unification and Control (MUC) model provides a neurobiological infrastructure for cognitive processes when processing sentences (Hagoort, 2003, 2005, 2013). It proposes that the left temporal gyrus is mainly involved in the lexical retrieval of each word while the LIFG is involved in unification – the integration of individual words with the preceding context to form a meaningful message. The anatomical connections between these two regions (and others) are thought to support the transfer of information, which is required to process each word and its relation to the context, and ultimately comprehend the sentence. On this basis, the model predicts more activation of LIFG when processing sentences than word lists, because unification is not possible in the latter set of stimuli. Support for this model is shown in a meta-analysis that found LIFG to be consistently responsive to the processing of sentences (Hagoort & Indefrey, 2014), and that left temporal gyrus is activated by many lexical tasks, and connected to many language areas (Poeppel, 2014). Furthermore, Xiang, Fonteijn, Norris, & Hagoort (2010) found strong functional connectivity between these regions, and (Snijders et al. (2010) demonstrated effective connectivity between these regions (from LIFG to LpMTG and LpMTG to LIFG).

In the current study, we found a difference in the AT/TT group compared to the AA group in LIFG, but not in LSTG (both groups showed higher theta power for sentences than word lists). This neural difference between groups could lead to different behavioural performances in language processing. An earlier notion has been that T-carriers are less good at language processing but we argue against this. These earlier studies demonstrated that the T-allele was associated with an increased risk of Autism (Arking et al., 2008; Bakkaloglu et al., 2008). Now, because individuals with autism tend to have poor language abilities, the T-allele was thus inferred to also be a risk allele for language and communication. Subsequently, two brain-imaging genetic studies showed that T-allele carriers in a healthy population have a distinct neural signature i.e. a more diffuse, bilateral network during language processing, which was suggested as a sign of less effective language processing (Scott-Van Zeeland et al., 2010; Whalley et al., 2011). However, two recent studies not replicating the association between the T-allele and autism (Sampath et al., 2013; Toma et al., 2010). Furthermore, in the current study, as indicated by behavioural measures, the AA and AT/TT groups were equally capable at processing and comprehending sentences. As such there is little evidence to suggest that the T-allele carriers in our study, and previous studies, are at risk for poor language performance.

Rather, we favour an alternative interpretation of the results. First, the lack of difference in LSTG suggests that word retrieval processes occur in a similar manner and at a similar time frame across the two genetic groups. Second, the difference in LIFG suggests that these two groups may differ in the neural implementation of the unification process, but both groups can unify successfully since both displayed a high accuracy in the compliance questions (to test comprehension and attention). To further this interpretation, we draw on some oscillatory literature. First, the coupling of low frequency oscillations, such as theta (and delta and alpha), between regions is thought to reflect the transfer of information between neural regions (Canolty & Knight, 2010; Siegel et al., 2012; von Stein & Sarnthein, 2000). Second, theta oscillations are also known to play a role in the memory processes whereby the retrieval of (non-)language stimuli is associated with an increase in theta power (Bastiaansen et al., 2008; Jensen & Mazaheri, 2010; Klimesch et al., 1997; Nyhus & Curran, 2010; Osipova et al., 2006). Therefore, one possible interpretation of the difference in theta power between genetic groups is a difference in how LIFG provides input to LSTG during unification. In turn, the context built up from unification can influence how the upcoming word is retrieved. This interpretation would also fit with the earlier finding that these two genetic groups differ in connectivity between LIFG and LMTG (Snijders et al., 2010).

Future work

One approach to further our understanding of the role of *CNTNAP2* is to replicate the current study with three modifications: First, to include more detailed measures of sentence processing ability such as a wider range of sentence comprehension questions and self-paced reading tasks (Farmer, Fine, Misyak, & Christiansen, 2016; Gibson & Fedorenko, 2013). This would allow us to relate genetic differences with the neural signature and the individual's ability to process sentences. Second, to perform connectivity analyses between neural regions, using methods such as Granger causality (Bastos & Schoffelen, 2016), to determine the timing and direction of communication between LIFG and LSTG, and provide more insight on what the difference in LIFG theta power may mean. Potentially, there is a between-group difference in how often these two regions communicate. Third, employ a larger sample size to determine whether the current effects are replicable and reliable.

Language processing likely involves the interaction of multiple genes, it is unlikely that that any one gene is specific to language or any particular type of behavior (Fisher & Scharff, 2009; Glessner et al., 2009; Newbury et al., 2010). In this manner, to further our understanding of the genetic basis of language, we should also investigate less well known genes or new ones. Potential genes include *ATP2C2 and CMIP* which have been implicated in memory processing – a process highly relevant in language processing (Hagoort, 2013; Rudner & Rönnberg, 2008). Further use of genetic pathway analyses and generation of molecular networks will also help seek out the molecular pathways and interactions between multiple genes (Khatri, Sirota, & Butte, 2012; Poelmans, Buitelaar, Pauls, & Franke, 2011; Vernes et al., 2008).

Conclusion

In sum, the current study is one of the first to demonstrate that variability in MEG-derived oscillations is related to the downstream genetic effects of CNTNAP2, and thus quantify a potentially meaningful variability in the neural infrastructure supporting language processing. We found that genetic variation of rs7794745 accounts for some of the variability of the neural response in LIFG, in the theta band. As such, our findings encourage further investigation into electrophysiological measures of oscillatory activity as a biological marker, as a means of relating individual variation in genetic makeup with variations in brain processes, and ultimately with variations in cognition and behavior.

6

GENERAL DISCUSSION

In 1929, Hans Berger discovered that rhythmic, electrical activity of the brain could be recorded on the human scalp, a method now known as electroencephalography (EEG). This was followed up, among others, by work from David Cohen (1972) who demonstrated that the magnetic component of this activity could be measured with Magnetoencephalography (MEG). Now commonly referred to as *neuronal oscillations,* this rhythmic activity has since captivated researchers because they reveal patterns in neural activity that allows us to learn how the brain orchestrates thoughts and behavior.

In this thesis, I made use of neuronal oscillations to further understand how language perception and comprehension are subserved by the brain, by means of organized activity in a wide network of brain regions. In daily communication, we perceived and understand language at an incredible speed – the average speaker produces 160 – 260 words per minute (Rodero, 2012; Tauroza & Allison, 1990), and we read about 200 - 400 words per minute (Rayner, Schotter, Masson, Potter, & Treiman, 2016; Sereno, 2003; Staub & Rayner, 1998). As oscillations are a measure of brain activity with fine temporal resolution, they are well-suited to investigate how the neural infrastructure can parallel the speed of language in order to execute perception and comprehension in a timely manner. Here, I summarize the main goals and findings of each chapter which investigated a particular aspect of sentence processing with a population sample of 204 participants. Subsequently, I consider the broader implication of these findings and address potential, future work in the field of oscillations, and in combination with other neuroimaging methods, to continue this line of investigation.

6.1 Summary

In **Chapter 2,** to investigate speech perception, I measured 102 participants in the MEG as they listened to sentences (and word lists). My main question was whether the rhythmic entrainment of neuronal oscillations to speech was a robust and reliable phenomenon in both slow (delta and theta) and fast (gamma) frequencies. I quantified the cross-correlation between oscillations and the speech envelope and found that participants entrain to speech at the delta and theta frequencies in bilateral superior and middle temporal gyri, but found no evidence for gamma entrainment.

Building on this, I tested for individual differences in entrainment. I first showed that individuals varied in their peak frequency of entrainment. In addition, contrary to the widely accepted proposal that the brain has a right hemisphere bias for slow rhythms (and the left for fast rhythms), I found an even split between the number of individuals left-lateralized for slow frequency entrainment and those who are right-lateralized. I concluded that the brain is capable of tracking speech at speeds similar to which syllabic (theta) and prosodic (delta) information occur but that we do not follow the speech rhythm in a clockwork manner, nor do we have a preference for following speech in the right hemisphere.

In **chapter 3**, I challenged the predominant hypothesis that ongoing, intrinsic, neuronal oscillations are a critical ingredient for the observed entrainment. While this seems to be the case for basic, repetitive auditory tones or visual stimuli, concrete evidence for speech remains to be seen. I predicted that if true oscillations underlie entrainment, then the variability in entrainment peak frequency (found in Chapter 2) would correlate with the variability in peak frequency of resting state oscillatory power. On the contrary, a correlation with the variability in peak frequency of evoked field power in response to edges in spoken sentences would provide support for the superposition of evoked responses underlying entrainment. There was no evidence supporting either hypothesis. However, I then demonstrated that the coherence between the temporal superposition of evoked fields to spoken word lists has a topography similar to the original coherence analysis. This suggests that (i) the mere observation of activity in the frequency domain is an insufficient indication of oscillations, and that (ii) the superposition of evoked fields should not be disregarded as a plausible cause of entrainment.

In **Chapter 4** I turned to the reading and processing of sentences where I tested another 102 participants in the MEG as they read sentences (providing a meaningful syntactic and semantic context) and word lists (non-meaningful context). I demonstrated that the reading of words in a meaningful context involves oscillations at the theta, alpha, beta and gamma bands in parallel, in multiple regions that encompassed more than just the typical language-related regions. Furthermore these frequencies (except gamma) were modulated as a function of word position (early vs. late) in a sentence. I speculated that the oscillatory activity reflected memory, prediction, maintenance and integration processes which change as the reader progresses along the sentence.

In **Chapter 5** I returned to the theme of individual differences and employed genetic information to investigate the systematic, biological differences in the neural system involved in reading sentences (comparing sentences with word lists). Using the *CNTNAP2* polymorphism rs7794745 (with nucleotide base A or T on each chromosome) I compared AA carriers to T-carriers (AT or TT allele). The T-carriers showed a larger difference between the processing of sentences compared to word lists, in theta oscillatory power, in the left inferior frontal gyrus. These results are one of the first to indicate that variability in MEG-derived oscillatory activity is related to the downstream genetic effects of *CNTNAP2,* and that MEG has the potential to identify meaningful variability in the neural infrastructure supporting language.

6.2 Implications and outlook for entrainment

The investigation on the entrainment of neural activity to speech can be carried out along different lines. Based on the findings in Chapters 2 and 3, I will discuss possible adjustments to the models of entrainment, and potential future lines of investigation for this topic.

Modification of models for entrainment

One popular model of entrainment is that by Giraud & Poeppel (2012). They proposed that entrainment occurs at the delta, theta and gamma band, and that slow frequency entrainment is biased to the right hemisphere and fast frequency entrainment to the left hemisphere.

Currently, evidence for gamma entrainment is limited. Gross et al. (2013) and Morillon, Liégeois-Chauvel, Arnal, Bénar, & Giraud (2012) have been the only 2 studies to show gamma entrainment to speech, whereas other studies have not reliably detected it (e.g., Bourguignon et al., 2013; Luo, Liu, & Poeppel, 2010; Luo & Poeppel, 2007; Peelle, Gross, & Davis, 2013; Chapter 2 of this thesis). The lack of gamma entrainment could be because gamma oscillations are difficult to characterize: (i) gamma oscillations are more easily elicited with visual than language stimuli (Hoogenboom et al., 2006), (ii) they encompass a wide search space – all oscillations above 30 Hz can be classified as gamma, and (iii) there is individual variation in the gamma band (Hoogenboom et al., 2006; van Pelt et al., 2012), and this variability was observed when quantifying gamma entrainment to speech (personal communication with Gross, 2015). To determine the reliability of gamma entrainment to speech, it would be worthwhile to replicate the studies by Gross et al. and Morillon et al.. In addition, we should exploit the individual variability by widening the search space for gamma entrainment from 30 – 50 Hz (this frequency range was motivated by the rate of phonemic activity in speech, see Giraud & Poeppel, 2012) to, for example, 25 to 100 Hz, and search for subject-specific frequency bands. Based on whether or not gamma entrainment is observed in subsequent investigations, the models of entrainment should be adjusted accordingly.

Most studies have found support for a right hemisphere lateralization of low frequency entrainment to speech (Abrams et al., 2008; Bourguignon, De Tiège, de Beeck, et al., 2013; Gross et al., 2013; Poeppel, 2003; Zoefel & VanRullen, 2015). Yet, in Chapter 2**,** with our sample of 102 participants, I showed an even division between left-and right-hemisphere lateralization for delta and theta entrainment. This suggests that the division between hemispheres for frequency of entrainment may need to be revised. To determine whether the absence of a right hemisphere bias is reliable, future studies on entrainment should employ a larger sample (*N* >= 50) in order to have sufficient power to detect variation in lateralization, and to investigate the functional and anatomical causes for lateralization.

A third issue is whether entrainment arises from phase-resetting of intrinsic oscillations or from the superposition of evoked responses (SER). To further this line of investigation, one or more models on SER for speech entrainment are pertinent. To be a worthy opponent of the models advocating oscillations for entrainment (e.g., Ghitza, 2011; Giraud & Poeppel, 2012; Goswami, 2011), SER models should be able to address the following issues. First, what gives rise to the evoked responses? Second, can evoked responses explain for the relationship between entrainment and intelligibility of speech (Ahissar et al., 2001; Ghitza & Greenberg, 2009; Luo & Poeppel, 2007; Peelle et al., 2013)? One interpretation is that entrainment is necessary for comprehension. If so, what are the stages in between the elicited evoked responses to being able to parse the necessary acoustic and linguistic features, and then reintegrating them to accomplish comprehension? The alternative interpretation is that entrainment is an output of intelligibility (entrainment occurs if and only if speech is understood). If so, how do regions involved in intelligibility (e.g., frontal and higher-order temporal regions) influence the evoked responses? Third, how do evoked responses account for the observed individual variation in entrainment?

Spectral content

The speech signal can be divided into coarse temporal content and fine temporal content. The former is captured in the speech envelope and contains acoustic information, while the latter contains the spectral content and contains linguistic information. The current thesis and the majority of entrainment studies have focused on coarse temporal content because it has been established to have a major role in speech perception. For instance, modifications to the envelope affect entrainment (Doelling et al., 2014; Ghitza & Greenberg, 2009), and the entrainment between the envelope and neural activity can be used to discriminate between sentences (Luo & Poeppel, 2007). However, there has been increasing evidence that the spectral content plays an equally important role in driving entrainment. These studies have made use of noise-vocoding (Shannon, Zeng, Kamath, Wygonski, & Ekelid, 1995) to vary the degree of spectral information (by manipulating one or more frequency band channels in the original signal) while preserving the speech envelope in its originality, and they all demonstrated that reducing the spectral content reduced entrainment (Lorenzi, Gilbert, Carn, Garnier, & Moore, 2006; Mcgettigan & Scott, 2012; Obleser, Eisner, & Kotz, 2008; Obleser & Weisz, 2012; Peelle et al., 2013). As a next step to understanding entrainment, we could first seek to determine how acoustic and linguistic information individually contribute to entrainment, and then subsequently determine how these two types of information are combined to influence intelligibility. For the first step, we can build on the noise-vocoding study by Peelle et al. (2013). Here, they selected frequencies from 50 to 8000 Hz, divided them into 16, 4 or 1 logarithmically spaced channels, and showed that showed that a higher number of spectral channels (16 vs. 4) i.e. more spectral detail was associated with more entrainment and higher intelligibility. As a follow-up it would be of interest to determine whether a certain subset of spectral information is more relevant for entrainment and/or intelligibility than others. This might be achieved by dividing the frequencies into 16 channels, but presenting varying combinations of only 8 channels and measuring how entrainment and intelligibility change accordingly.

6.3 Implications and outlook for sentence reading

Since 1980s, the N400 (and subsequently also the N400m, its magnetic counterpart) has been a useful electrophysiological tool for studying language processing. It demonstrated that the brain is sensitive to differences in meaning and uses the semantic context (e.g., pairs of words, a sequence of related words, a sentence) to make certain expectations about language. This sensitivity begins early on, around 200 ms following word onset (for a review on N400 literature see Kutas & Federmeier, 2011). Nevertheless, there are limits to the N400(m). First, it only provides a view of phase-locked neural activity, where the process averaging removes any non-phase locked activity that could be useful and complementary for understanding the function of regions supporting language processing. Second, the source of this event-related component remains unknown and debated. Generally, N400(m) activity is begins in posterior temporal regions and sweeps toward anterior regions in temporal and frontal cortex. On this basis, Kutas & Federmeier argue that the important message is not the source(s) of N400(m) but to consider the temporal-frontal regions as a neural network for language processing, and to determine the function of this network.

Oscillations in sentence processing

The non-phase locked neural activity, as captured by oscillations, can address the aforementioned limitations and provide a broader, more dynamic view of how the brain processes sentences. In Chapter 4, I showed that multiple oscillatory frequencies were involved in sentence processing, and these frequencies localized to temporal, frontal and parietal regions. When compared to processing word lists, the processing of sentences is left-lateralized but when focused on how neural activity changes as the sentence unfolds we see contributions from both hemispheres (with right frontal and parietal regions being the main addition).

This work is exciting because it establishes which frequencies are present during normal sentence processing, laying out the grounds for testing the interaction between regions involved in language processing. From the results in Chapter 4, I speculated that the temporal and frontal regions are likely involved with the prediction, retrieval and integration of words in a sentence. I also speculated that the activity in frontal-parietal regions, found as the sentence unfolds, reflect an attention network. Specifically, this network may reduce its support to temporal and frontal regions when progressing further along the sentence where the context becomes more informative (as a build-up from previous words). These ideas can all be empirically tested using connectivity measures like coherence or Granger causality (Bastos & Schoffelen, 2016). For instance, with fronto-temporal communication, we can quantify the connectivity between frontal and temporal regions at different positions along a sentence. In support of this, work by Schoffelen, Lam, Marquand, Hultén and Hagoort (submitted), has identified a feedforward network from bilateral temporal regions to inferior frontal cortex in the alpha band, and top-down input from inferior frontal regions to temporal regions in the beta band during sentence processing.

Functional role of oscillations

The heterogeneity of tasks and effects that modulate oscillatory activity has made it difficult to interpret the functional role of oscillations. As cognitive studies tend to attribute a specific functional role to a specific frequency band this has made it more difficult to consolidate and generalize results and interpretations across studies. In Chapter 4, I speculated that the theta band was involved in memory-related processes and the gamma band with the prediction-related processes, as these tied into oscillatory findings in both language and non-language tasks. For the alpha and beta band, I went for a more language-specific interpretation, namely unification (Hagoort & Poeppel, 2013; Hagoort, 2005). Although unification accounted for the results, here I take the opportunity to highlight that an alternative explanation, namely that the alpha-beta band results reflect the current cognitive state (Engel & Fries, 2010; adopted by Lewis, Wang, & Bastiaansen, 2015 for sentence processing), should not be immediately discounted either. Engel and Fries (2010) proposed that an increase in beta band activity promotes maintenance of the current motor or cognitive state, while a decrease reflects a change due to reasons such as a mismatch in expectation or a change in cognitive load. Lewis et al. (2015) adopted this view point for sentence processing, arguing it provides a more parsimonious and coherent explanation for all oscillatory findings in sentence processing than the unification interpretation. Specifically, in a grammatically correct sentence, beta power increases because there is no need for a change in the cognitive state – prediction of the upcoming word matches the perceive word so the neural system can continue with its current state of interpretation and comprehension. In sentences where a word has a grammatical violation (e.g., number or gender disagreement) this is a cue that the cognitive state needs to change i.e. the neural system cannot continue with its current interpretation, and therefore a decrease in beta power is observed from this word thereon. As for a given word list of unrelated words, because no meaningful interpretation can be made, no change in beta power is observed across this string of words.

The results in Chapter 4 partially fit with the interpretation of Lewis, Wang and Bastiaasen (2013). Across the word list there was no change in beta power, which makes sense as there was no meaningful relationship between the words. However, for the sentence condition (with all grammatical sentences), there was not an increase in beta power but a decrease (see Figure 1 and 2 in Chapter 4). Furthermore, the power decrease observed was not strictly limited to the beta band, but also seen in the alpha band which had a very similar time course and spatial distribution. In addition, another issue with the maintenance interpretation is whether the changes in oscillatory activity reflect the actual maintenance or change itself, or is just a cue to initiate maintenance or change. Although it remains to be seen whether the unification interpretation or the maintenance hypothesis holds more merit it is important to acknowledge that models like these have been, and will continue to be, important for understanding the brain and language.

Modifications to Memory, Unification and Control model

The Memory, Unification and Control model (Hagoort, 2005, 2013) provides a general framework for the neurobiological underpinnings of language processing. This model has lent fuel for testing the neural infrastructure of sentence processing. Evidence for the roles of inferior frontal and temporal regions involved in memory and unification have been found in several (f)MRI studies (Snijders et al., 2009; Willems, Özyürek, & Hagoort, 2008; Xiang et al., 2010), and some oscillatory studies (e.g., Bastiaansen, Magyari, & Hagoort, 2010; Lam, Schoffelen, Uddén, Hultén, & Hagoort, 2016; Schoffelen et al., submitted). However, the terms *memory* and *unification* are broad, umbrella terms, encompassing multiple cognitive processes. To further advance our understanding of sentence processing, a subdivision of these terms into smaller, testable units can be useful.

The term *unification* is defined as “the assembly of pieces [of information] stored in memory into larger structures, with contributions from context”, and involves left inferior frontal regions, while the term *memory* refers to stored knowledge such as syntactic templates and phonological forms, and involves temporal and parietal regions (Hagoort, 2005, 2013). Hagoort (2005, 2013) has distinguished and provided evidence for a division of unification into 3 linguistic levels – phonology, semantics and syntax – as a gradient of regions in LIFG. However, a more cognitive-oriented division, that distinguishes between (i) *retrieva*l and *maintenance* of information (in the MUC model these fall under the definition of memory and unification) and (ii) the *integration* of information, *prediction* of information, and *influence of predictions on integration* (in the MUC model this is under the definition of unification) could help to further propel our understanding of language. These division can be empirically tested, and allow us to go beyond associating changes in neural activity with just unification, or one or more of the possible cognitive processes. As evidence of this progress being made in this direction, a recent study by Wang, Zhu, & Bastiaansen (2012) determined whether gamma oscillations were more likely to be involved in the prediction, than the integration of words in sentence processing. More studies like these are expected, and will help to understanding the neurobiology of sentence processing.

6.4 Individual Differences

A theme that pervades this thesis is individual differences in the neural infrastructure supporting the perception and processing of sentences. Most neuroimaging studies focus on group averages and any inter-individual differences are considered as noise. However, some of these differences are meaningful and useful for understanding the brain. As such, this thesis investigated both group averages and individual differences.

Individual difference in speech perception

Theories on entrainment hypothesize that oscillations follow the speech rhythm in order for information in the speech signal to be received at a time point where neuronal excitability is highest (i.e. ready and able to accept information). Given this interpretation, and the findings of individual variability, this has a couple of implications on the nature of entrainment. First, the necessity for precise entrainment to the speech rhythm and its effects on perception and comprehension: According to the hypothesis, individuals who entrain at a rhythm that is slower or faster than the speech rhythm itself will receive input at a suboptimal level of neuronal excitability, which in turn means that only a subset of all information is received. Might this actually be the case, and if so, is the neural system capable of interpolating missing information (based on prior experience) such that comprehension (intelligibility) does not suffer? Second, is this variability in entrainment robust over time? Could entrainment simply be suboptimal due to differences in attentiveness and focus? One approach to answer these questions might be to repeat the study in Chapter 2 and have participants perceive the original and compressed versions of the speech signal. Using the same individuals will allow us to test for the reliability of peak frequencies in the original study. Previous studies have shown that an increase in the degree of speech compression is correlated with a decline in entrainment and intelligibility (identifying the correct sentence) (Ahissar et al., 2001; Nourski et al., 2009). Therefore, by using a variety of compresse speech signals, we can determine whether different entrainment rhythms have an effect on intelligibility. Potentially, individuals with a peak frequency closer to the speech envelope will consistently demonstrate higher levels of intelligibility than individuals with a peak frequency further away from the speech envelope.

Individual differences in reading sentences

In Chapter 4, I showed that the group average for sentence processing involves a broadly distributed network which included the typical regions seen to support sentence processing, namely left temporal and inferior frontal regions, but also bilateral parietal and superior frontal regions (see Fig. 1 and 2 in Chapter 4). In Chapter 5, I demonstrated that the left inferior frontal gyrus (LIFG) showed systematic differences in neural activity that could be explained by genetic variation in the *CNTNAP2* polymorphism, but no variation in left superior temporal gyrus (LSTG).

Frontal and temporal regions… and more?

More often than not, left frontal and left temporal regions have been shown to be active when processing sentences (e.g., sentences vs. word lists, complex sentence structure vs. simple sentence structure), as indicated in several meta-analyses and review papers (Cappa, 2012; Hagoort & Indefrey, 2014; Price, 2010, 2012; Vigneau et al., 2006). This does not mean that these regions are specific to language processing because these regions could just as well reflect an increase in computing a higher load of information or being involved in memory-related processes during sentence processing (e.g., Keller, Carpenter, & Just, 2001; Makuuchi & Friederici, 2013). What these regions do suggest is that they are important in sentence processing, and thereby act as a good starting point to understand the genetic-dependent variation in the neural infrastructure for language processing. In Chapter 5, I found individual differences in theta oscillations in LIFG associated with *CNTNAP2,* but not in LSTG. As many regions of the temporal cortex have been associated with sentence processing, e.g., left anterior temporal pole and left middle temporal gyrus (Cappa, 2012; Hagoort & Indefrey, 2014; Price, 2010, 2012; Vigneau et al., 2006) it would be worthwhile to recruit a larger sample to replicate the findings in Chapter 5, and test whether genetic variation in *CNTNAP2* can account for neural variation in a wider set of frontal and temporal regions.

Aside from the popular genes *CNTNAP2* and *FOXP2,* there are others of interest when it comes to language processing. One candidate family of genes is the robo genes. In mammals, there are 3 of these genes – *ROBO3* is one of the genes responsible for midline axonal crossing of the nervous system (Evans & Bashaw, 2010), while *ROBO1* is associated with variation in auditory cortical activation (Hannula-Jouppi et al., 2005; Lamminmäki, Massinen, Nopola-Hemmi, Kere, & Hari, 2012; Renvall et al., 2012). Primary auditory cortex is the first neocortical region to receive speech input, and entrainment effects are consistently localized to this region. Therefore, it would be of interest whether one or more robo genes could (partially) explain the variation found in Chapter 2, on whether an individual is left- or right-lateralized individuals for low frequency entrainment.

The neural networks that support language are not limited to left frontal and temporal regions. Other regions that have been observed include left inferior parietal, right inferior frontal and left superior frontal regions (Binder, Desai, Graves, & Conant, 2009; Hagoort & Indefrey, 2014; Price, 2010, 2012; Vigneau et al., 2006). Recently, using 102 participants from the MOUS cohort, Zaadnoordijk et al. (2016) demonstrated that the connectivity strength between brain regions during resting state fMRI, correlated with the activation of regions that are active during sentence processing. This correlation demonstrated that individual differences in sentence processing can partially be explained by intrinsic differences in functional organization, and provided a method to address systematic differences in language-related neural networks. Moreover, the study identified regions that reliably covary across subjects, and have an intrinsic, biological basis in their variation. As such, it would be of interest to adapt this method to our MEG measurements of resting state and sentence processing data. More generally, with neural data being multidimensional and consisting of many regions and time points (and oscillatory frequencies when using MEG or EEG), the use of this method in future studies could help select more robust neural phenotypes for the field of imaging genetics.

Too much excitement

The ability to link individual differences in neural and behavioural measures with genetics is exciting. In particular, the results in Chapter 5 are the first to show that MEG-derived oscillations may capture the downstream effects of genetics on the neural substrates of sentence processing. However, the importance of these results rests on whether they can be replicated. The current state of imaging-genetics has produced many novel findings, but few have yet to withstand the test of time. One case is the popularly cited imaging genetics by Pinel et al. (2012) (N = 94) which showed an association between *FOXP2* with neural activity in left frontal cortex. Using the MOUS cohort (N > 200), Uddén et al. (in prep) did not replicate the findings of Pinel et al. (2012). Similarly, in another replication study, Uddén, Snijders, Fisher, and Hagoort (2016) did not fully replicate an earlier study by Tan, Doke, Ashburner, Wood, and Frackowiak (2010) on the associations between *CNTNAP2* rs7794745 and grey matter volumes in bilateral cerebellum, fusiform gyri, occipital and right frontal cortices. Moreover, in Chapter 5, we only found effects for *CNTNAP2* but not *FOXP2*. Together, these studies demonstrate the necessity to use large sample sizes, and attentive efforts to perform replications in the field of imaging genetics.

It's complicated

At the molecular level, multiple single nucleotide polymorphisms (SNPs) interact to produce a downstream effect that can be observed in neural or behavioural measures. In most cases, these SNPs have a small or moderate genetic effect which is not easy to detect, and results are therefore difficult to replicate. Similarly, at the neural level, various brain regions cooperate to execute the task at hand, therefore, to understand how the brain works we need to quantify both the regions involved *and* how they interact. As such, imaging-genetics is faced with searching for the individual components of a multi-dimensional genetic source to see how they related to a multi-dimensional neural measure.

Aside from doing replication studies, the reliability of imaging-genetic results can and has continued to improve by advancing research methods. In the last 10 years, the field of genetics has seen a rise in popularity to using pathway analyses (Jin et al., 2014; Khatri et al., 2012; Poelmans et al., 2011). One type is the SNP/Genome-wide association study-derived pathway analysis (Jin et al., 2014; Luo et al., 2010). Here, based on acquired genetic information (e.g., Kyoto Encyclopedia of Genes and Genomes) a group of genes or polymorphisms are are identified as an interactive, functional unit that implement specific biological processes or cellular functions (e.g., a signaling pathway or metabolism pathway) that are thought to influence a particular phenotype. These pathway analyses have successfully (i) identified groups of SNPs or genes that (alone have a small effect but) together have a large significant association with the phenotype of interest, (ii) identified novel SNPs/genes and (iii) demonstrated replicability of these pathways across studies (e.g., Luo et al., 2010). Furthermore, by testing the groups of SNPs/genes as a whole, instead of individually, this reduces the multiple comparison problem. Similarly, the approach in cognitive neuroscience is to make use of connectivity analyses (as explained above under 'oscillations in sentence processing') to identify regions and patterns of interation in a neural network. Although a challenge, I believe that successful genetic association studies will require the combination of genetic pathway analysis with neural connectivity analysis to help delineate the path from genotype to phenotype.

6.5 Conclusion

In this thesis, I made use of neuronal oscillations to investigate how the brain orchestrates language. The first theme of investigation was speech perception (spoken sentences). I demonstrated that brain activity robustly entrains the rhythm of the speech envelope at the delta and theta band. Contrary to earlier proposals and empirical studies on entrainment, I showed that the lateralization of entrainment varies between individuals, as does the peak frequency of entrainment. These findings are suggestive that intrinsic differences account for variation in entrainment, and that our brains do not simply follow speech in a clockwork manner. To challenge the predominant assumption underlying entrainment, I subsequently investigated whether oscillations or evoked potentials give rise to entrainment and argued that evoked potentials should be given more consideration as a plausible cause for the observed entrainment. The second theme of investigation was how words are processed in a sentence. I was able to show that multiple frequencies (theta, alpha, beta and gamma), in both hemispheres are involved during sentence processing. This provided the ground work to pursue how oscillations mediate communication between regions during sentence processing. Finally, I also demonstrated that MEG-derived oscillations can capture downstream genetic effects of *CNTNAP2* polymorphism rs7794745 on sentence processing. In sum, in this series of investigations on a cohort of 204 participants, I have provided evidence that neuronal oscillations are well suited for studying language processing. The identification of multiple frequency bands at play has provided the groundwork to further study the interaction between neural regions and frequencies involved in language, and the work on individual differences stresses the importance of studying this variability to provide a well-rounded perspective on how the brain processes language.

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APPENDIX

Supplementary Material for Chapter 4 | Neural activity during sentence processing as reflected in theta, alpha, beta, and gamma oscillations

Description of spatio-temporal evolution of oscillatory power for Word Analysis and Context Analysis

Figure S1A shows the results for the word analysis (sentence vs. word lists) for thresholded significant t-values, and for non-thresholded power values on brain maps. In this analysis, we compared whether individual words with a meaningful and structure context in a sentence were processed differently from words in a word list. Figure S1B shows the results for the context analysis (late vs. early words in sentences, and in word lists), thresholded for significant t-values, and for non-thresholded power values on brain maps. This analysis focused on how word processing changes as the sentence unfolds. We assessed whether there was a change in oscillatory activity between early and late words in a sentence, and how this compared to the activity between early and late words in a word list. Below, we provide a description of the spatio-temporal evolution of oscillatory power which is also depicted in figure S1.

Word Analysis

For each frequency we describe the change in power across space and time. Here, the time bins of 250, 350 and 450 ms following word onset are referred to as the first, second and third time bin. Figure S1a depicts the difference between sentences and word lists, in power values (unthresholded) and t-values (thresholded for significance) on surface brain maps.

Theta band

In the first time bin, theta oscillatory power differences between conditions were most prominently observed in bilateral occipital cortex (S < W), and in left anterior temporal regions and left inferior frontal regions (S > W). In the second and third time bin, the difference in bilateral occipital cortex became stronger and extended into left but not right posterior temporal cortex. Simultaneously, the differences in left temporal and left inferior frontal regions weakened.

Alpha band

In the first time bin, a prominent difference in alpha oscillatory power between conditions was observed in bilateral occipital cortex and bilateral parietal cortex (S < W), and in left anterior temporal regions and left inferior frontal regions (S > W). In the subsequent two time bins, the difference in left temporal and left inferior frontal regions weakened while the difference in bilateral occipital, left parietal and left superior frontal regions strengthened.

Beta band

The difference effect observed in the beta band in left frontal and left occipito-temporal-parietal regions was similar to those in the alpha band. In the first time bin, prominent differences were observed in bilateral occipital, parietal and posterior temporal areas (S < W), which were maintained over time. On the other hand, we observed the difference effect in frontal cortex the difference (S > W) to weaken over time.

Gamma band

In the gamma band, we observed effects to be more left lateralized than in the lower frequency bands. Across time, these effects swept from posterior to anterior regions. Closer inspection reveals posterior and anterior regions to derive from different frequency bands. Between 40 – 68 Hz (low gamma), the most prominent difference was observed in left occipital, temporo-parietal and left motor areas (S < W). The difference in power between these regions was strongest in the first time bin, and weakened over time. Between 84 – 100 Hz (high gamma), in the first time bin the strongest differences were observed seen in left frontal and left temporal (S < W). The difference activity in left frontal cortex weakened across time bins, while the difference activity in left temporal cortex strengthened for the second time bin and then weakened in the third time bin.

Context Analysis

For each frequency we describe the change in power across space and time. Here, the time bins of 250, 350 and 450 ms following word onset are referred to as the first, second and third time bin. Figure S1b depicts the difference between late words and early words (for sentences and word lists separately), in power values (unthresholded) and t-values (thresholded for significance) on surface brain maps. Note that to facilitate comparisons, brain maps from the sentence and word list condition that correspond in time and frequency point have the same color scale.

Theta band

For sentences, prominent positive context effects (L > E) were observed in bilateral frontal and right temporo-parietal regions in the first time bin. In left anterior temporal regions, prominent negative context effects (L < E) were observed in the first time bin. These effects strengthened in the second time bin, and were maintained in the third time bin. For the word lists, context effects in bilateral frontal, and right parietal regions were observed to be in the same direction as in sentences, but the effects were much weaker.

Alpha band

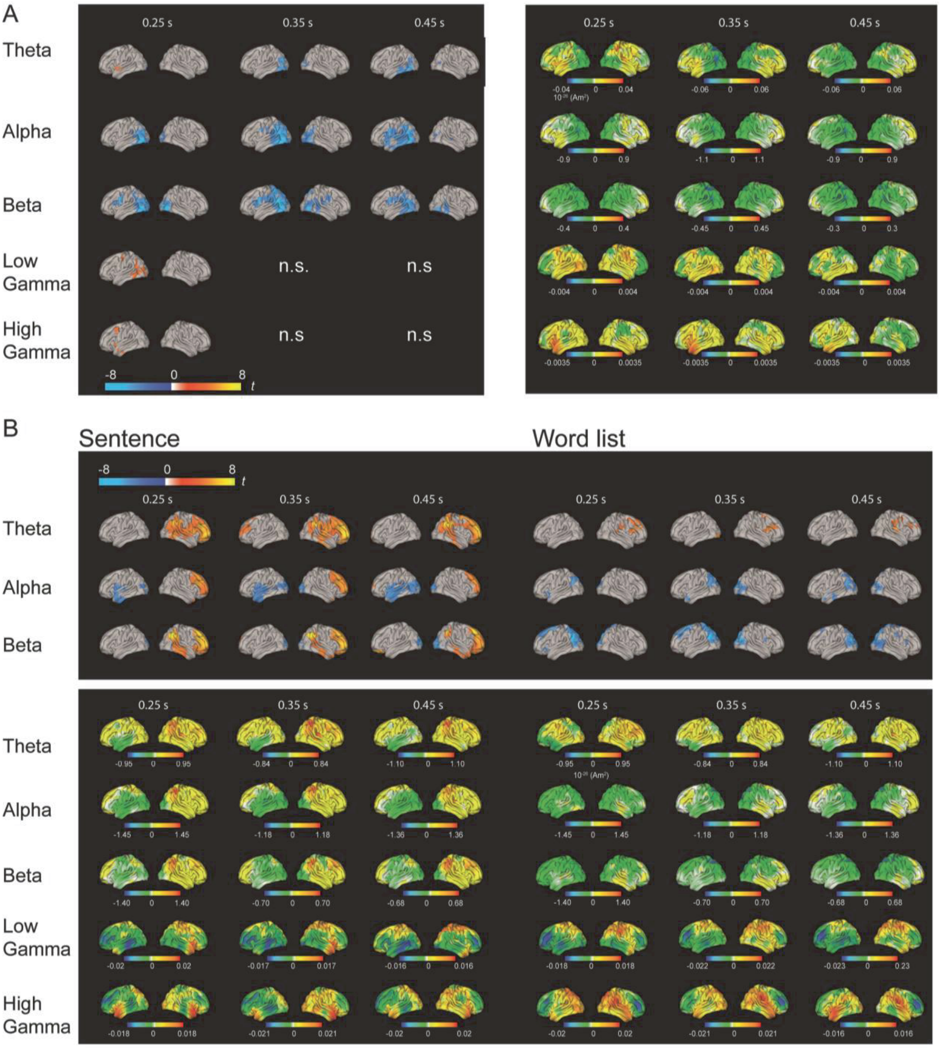
For sentences, prominent negative context effects were observed in left temporal and inferior frontal regions, and bilateral occipital regions, in the first time bin. Prominent context effects were observed in bilateral frontal, and right parietal and temporal regions, in the first time bin. These effects were maintained throughout the second and third time bin. For word lists, the context effect was predominantly negative across the whole brain, except for a positive effect in right temporal and right frontal regions showing an increase. However, in comparison to the sentence context effect, the word list context effect was much weaker.

Beta band

For sentences, prominent positive context effects were observed in bilateral frontal regions, and right temporal and parietal regions in the first time bin. Prominent negative context effects were observed in bilateral occipital regions, and left frontal and temporal regions in the first time bin. These effects were maintained across time. The context effect in word lists was predominantly negative across most of the left and right hemisphere, with the exception of right temporal and inferior frontal regions which showed a positive effect. Again, the context effect in word lists were much weaker than in sentences.

Gamma band

The context effect for sentences and word lists were more similar for this frequency band. In general, both showed a positive effect in bilateral temporal and frontal regions, and negative effect in bilateral parietal regions. Effects in this frequency range were spatially less focal in comparison to the lower frequencies.



Supplementary Fig. 1 *A,* Word analysis results which are statistically thresholded for significance (left), and as non-thresholded power values (right). Brain maps depict the surface representation of beamformed oscillatory differences. *Left* Differences between conditions (sentences vs. word list) are depicted as thresholded t-values, for each time bin. *Right* Non-thresholded power differences between sentences and word list depicted for each time bin (a condition specific baseline was first subtracted from each condition before calculating the differences). For both left and right panels, warm colors indicate higher power for sentences than word list, and cool colors for lower power in sentences than word lists. *B,* Context analysis results which are statistically thresholded for significance (left), and as non-thresholded power values (right). Brain maps depict the surface representation of beamformed oscillatory differences. *Top* Differences for late vs. early word, for each condition (sentence, word list) are depicted as thresholded t-values, for each time bin. *Bottom* Non-thresholded power differences between late vs. early, for each condition, depicted for each time bin (a common baseline was first subtracted from each condition before calculating the differences). Both top and bottom panels, warm colors indicate higher power for sentences than word list, and cool colors for lower power in sentences than word lists.

Sentence progression analysis

Methods

The sentence progression analysis was an alternative way used to study the effects of context as the sentence unfolded. Here, we quantified the word induced changes in oscillatory activity as a function of ordinal word position, as a linear parametric effect (a regression coefficient). For each ordinal word position we estimated the time-resolved oscillatory power, relative to the pre-word baseline. Subsequently, we fitted the linear slope (using least squares regression) as a function of ordinal word position for each time window, separately for sentence words and word list words. For the slope estimation, we excluded the response to the first words (because sentence/word list onset transients may affect the signal) and those of the 11th word position and beyond (to exclude biased estimates in power due to low number of words). As such, the power changes as a function of word position is presented as a regression coefficient. Across participants, the estimated slopes were statistically tested between conditions.

Results

The sentence progression results are presented in supplementary figure 2A.

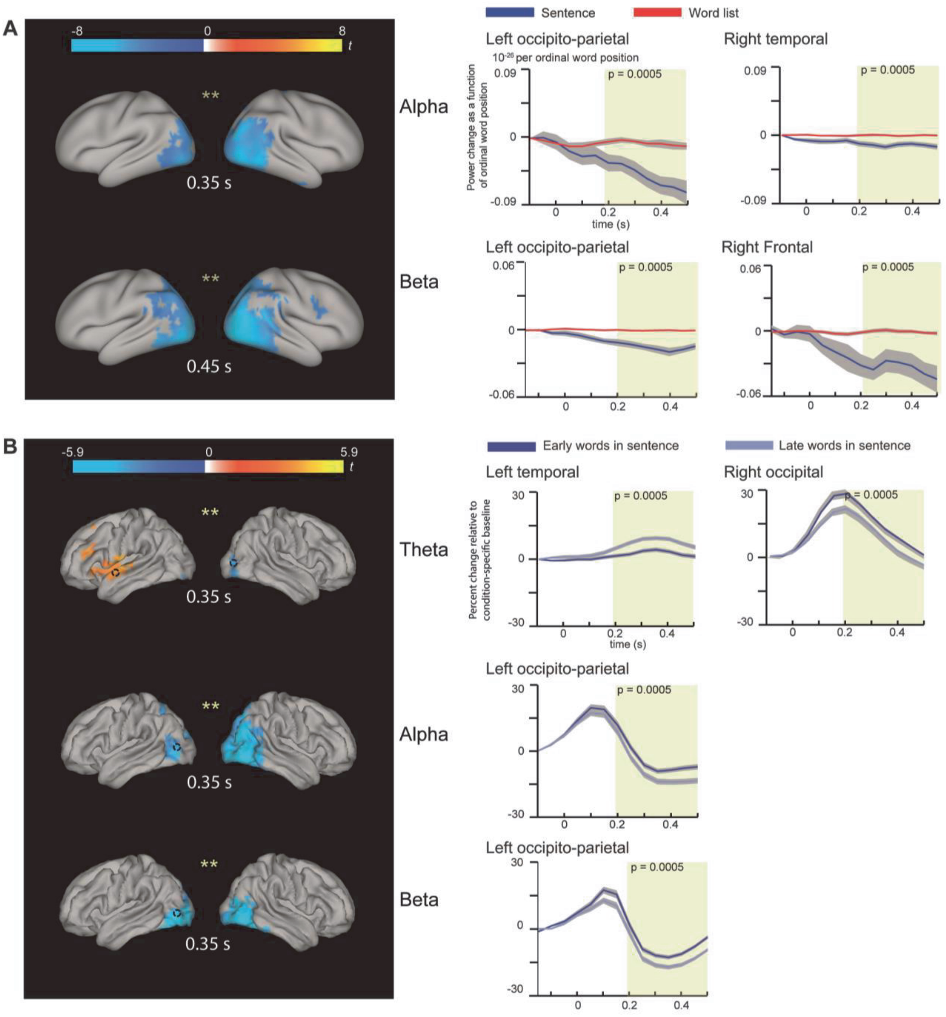
Alpha band We observed a significant difference, in all three time bins, between the slope for sentences and the slope for word lists was observed in bilateral occipital and bilateral parietal regions ($p = 0.0005$, S < W). A small region in left inferior temporal cortex also showed a difference in all three time bins ($p = 0.0005$, S < W).

Beta band We observed a significant difference between slopes of the two conditions in bilateral occipito-parietal cortex, and right frontal cortex ($p = 0.0005$, S < W), in all three time bins.

Discussion

This analysis shows a decrease in alpha and beta power, most prominently in bilateral occipital regions, and this is similar to the Context Analysis in the main text. In addition, unique the Sentence Progression analysis we observed a decrease a power decrease in inferior right temporal regions for alpha, and right frontal for beta. There are a few reasons for the difference between these two analyses. First, the differences in underlying model assumptions: the sentence progression analysis modeled the change in oscillatory activity as a linear effect across the whole sentence. The context analysis only provided a '2-point estimate': early versus late words. (b) Differences in SNR between the two approaches: in the context analysis we pooled the estimates of power across several ordinal words (2nd-4th word for early words, and n-4th-n-2nd word for late words), potentially yielding more robust estimates of power, thus increasing sensitivity. As such, these two analyses both captured changes across a sentence, but differed in their focus. The context analysis captured the global changes in power as the sentence progressed, whereas the sentence progression captured the evolution of the change in power to each incoming word. Consequently, we may find similar and different results between the approaches.

The effect of context on bilateral posterior regions is seen in both the Context Analysis and the Sentence Progression analysis. As argued in the discussion section (Alpha and Beta Oscillations: Context Analysis), these results suggest that as the context unfolds, it provides more information and facilitates regions involved in visual word recognition. Unique to the sentence progression analysis are the linear effects in left temporal and right frontal regions. We speculate that these areas are also involved in the build-up of context to facilitate subsequent word recognition and unification.



Supplementary Fig. 2 *A* Sentence progression analysis results as brain maps (left) and time courses (right). *Left* Brain maps depict the difference in the ordinal word-position-dependent changes in power between sentences and word lists, expressed as t-values, and masked for significance. As an exception, the results are displayed on an inflated cortical sheet to clearly show the focal effects in right frontal and anterior temporal cortex. Light/dark blue colors reflect larger ordinal word position dependent decreases in power across sentences than across word lists. Different time windows are selected for each frequency to best represent the observed effects. Significant results after correction for multiple comparisons across space, and multiple tests are marked with **. *Right* Time courses show a general time dependent decrease is the ordinal word position dependent power change across sentences, but not for word lists. Grey areas around the time course reflect +/- 1 standard error of the mean. *B* Adapted Context Analysis as brain maps (left) and time courses (right). *Left* Brain maps depict the difference in power between late words and early words in a sentence, expressed as t-values, and masked for significance. Crucially, this Adapted Context Analysis used a pre-word condition-specific baseline whereas the Context Analysis in the main text (figure 2) used a pre-word condition-common baseline. Values are t-values, masked for significance. *Right* Time courses show a time dependent change in power for early words and late words in a sentence. Grey areas around the time course reflect +/- 1 standard error of the mean. For all time courses, black circles on the brain map indicate the region chosen for the time course. For frequencies in which homologous regions between hemispheres showed a similar effect, the time course from one hemisphere was chosen. This is because visual inspection indicated similar time courses for homologous grid points.

Adapted Context Analysis

Methods

This analysis was interested in the change in neural activity as the sentence unfolded. Here, we quantified the difference in the neural response between late versus early words in a sentence. The sole difference between this analysis and the Context Analysis in the main text is the choice of baseline. Instead of a common baseline across conditions we used a condition-specific baseline: [(late - late baseline) - (early - early baseline].We chose to only analyze oscillatory activity across sentences but not word lists because the main context analysis demonstrated that the difference between late and early words are only in the sentence condition.

The purpose of using a condition-specific baseline is to demonstrate that after removing local changes at the individual word level (by subtracting the condition-specific pre-word baseline) that there remain changes in power that proceed across the sentence as it unfolds.

Results

Results are presented in supplementary figure 2B.

Theta band We observed a significant difference, in all three time bins, (p = 0.0005) in left temporal and frontal regions (L < E), and in bilateral occipital regions (L > E).

Alpha band We observed a significant difference, in all three time bins, (p = 0.0005) in bilateral occipito-temporal regions and also left parietal regions (L < E).

Beta band Similar the alpha band, we observed a significant difference, in all three time bins, (p = 0.0005) in bilateral occipito-temporal regions (L < E).

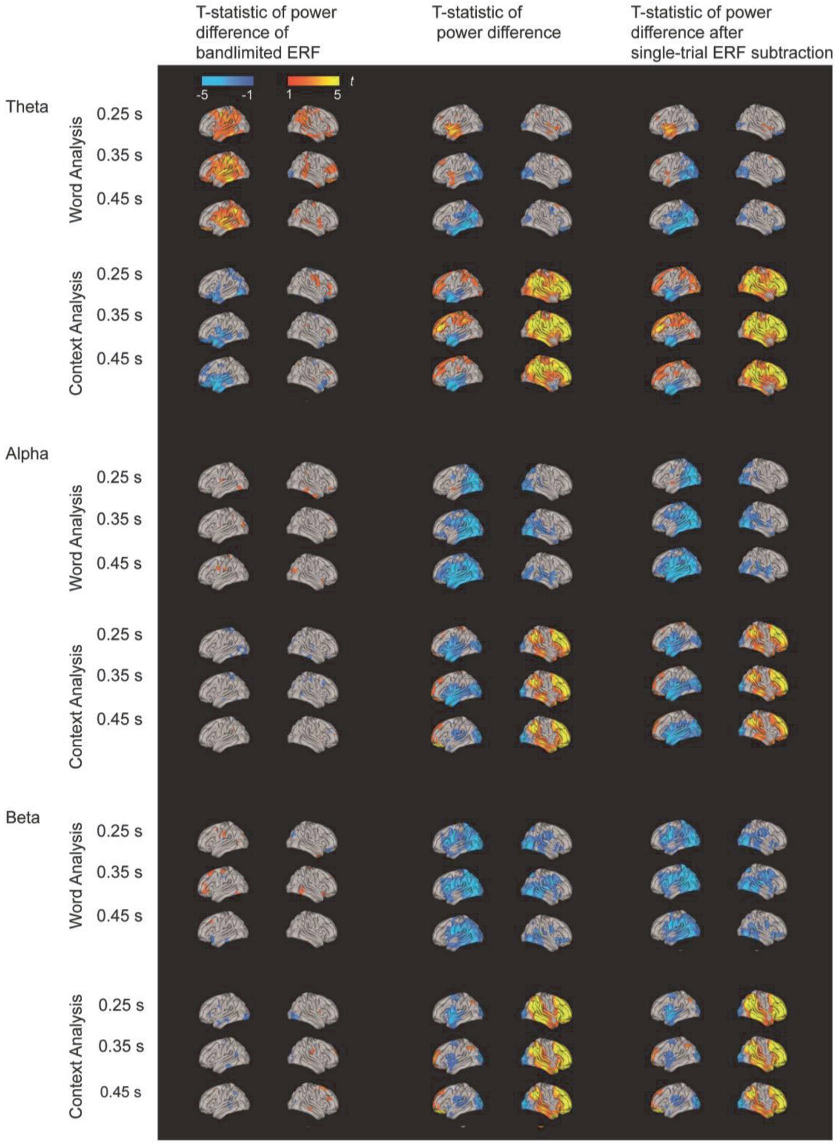
Discussion

Theta band We observed an increase in theta power following word onset for both late and early words, with late words showing a significantly larger increase. Similar to the Word Analysis, the theta band effect here is also located in the left superior temporal region, and in addition in the left frontal region. In the Word Analysis, which showed how individual words induce oscillatory changes (relative to a condition specific baseline), we argued that the theta effect there reflected lexical retrieval. Relating this to the adapted Context Analysis, we suggest that the larger theta increase for late words could reflect a facilitation in lexical retrieval because later words have a more informative (and predictable) context than early words. Potentially, the increase in theta power seen in left frontal reflects unification processes on previous words, which provide a context and information for upcoming words, which are given top down feedback to left temporal regions involved in lexical retrieval (Hagoort, 2003, 2005, 2013). This suggestion is in line with the findings from the main Context Analysis, where we perceive an overall power decrease across a sentence, which we suggested reflect a decrease in cognitive resources for lexical retrieval because late words have a more informative and predictable context than early words.

Alpha and beta band As discussed above in the Sentence Progression analysis, the (adapted) Context Analysis and Sentence Progression analysis are different approaches trying to capture the same phenomenon – power changes across a sentence. Therefore, it is reasonable to find some similar, and some different effects. Given the similarity in the alpha and beta band results observed in this adapted Context analysis and the sentence progression analysis, we refer the reader to the Sentence Progression discussion section.

Control analysis: comparison of power estimates with frequency-resolved ERF power

One general concern related to the interpretation of modulations in oscillatory activity is that the reported differences could reflect differences in the spectral representation of the event-related activity, which may not be strictly oscillatory in nature. To address this concern, we performed a set of control analyses, in which we computed our contrasts of interest (for the theta, alpha and beta ranges) for the event-related average of the band-limited signals, and for the power estimated after subtraction of the event-related average. Supplementary figure 3 shows the results for this control analysis. The difference findings for the word analysis and context analysis are shown in three ways (one for each column). The left column shows frequency-resolved (bandlimited) ERF power estimates of the difference, the middle column shows power difference (the original analyses), and the right column shows the difference in power, computed after subtraction of the ERF from the individual trials, which is a commonly applied (albeit sub-ideal) approach to disentangle the 'induced' signal components from the 'evoked' signal components. In all comparisons between the corresponding panels in the left and middle columns, the spatial topographies of the contrasts are markedly different. The sole exception perhaps is the left anterior temporal negativity in the context contrast for the theta frequency band. Importantly, for each comparison between corresponding panels in the middle and right columns, the spatial topography of the contrasts is very similar. Altogether, this control analysis provides confirmatory evidence that the majority of our results can be interpreted in terms of modulations in oscillatory activity.



Supplementary Fig 3 Word analysis (sentence vs. words) and Context analysis (late words vs. early words, in sentences) thresholded at +/-1 t values for 3 types of calculations. Left: oscillatory power, Middle: frequency resolved event-related field (ERF) power, Right oscillatory power after subtracting ERF power (left column - middle column). High similarities between the left and right column suggest that oscillatory results for both analysis reflect non time- and phase-locked activity. For the word analysis, warm colors indicate higher power for sentences than word list, and cool colors for lower power in sentences than word lists. For the context analysis, warm colors indicate higher power for late words in sentences than early words in sentences, and cool colors for lower power for late words in sentences than early words in sentences.

NEDERLANDSE SAMENVATTING

Onze hersenen bestaan uit ongeveer 86 miljard neuronen (Azevedo et al., 2009), die samen onze gedachten, waarneming en gedrag aansturen. Taal is een opmerkelijk en uniek menselijk vermogen dat de indrukwekkende functies en mogelijkheden van de hersenen goed laat zien. De complexiteit van het proces waarmee we taal begrijpen wordt vaak overschaduwd door het schijnbare gemak waarmee we lezen of luisteren. Bedenk je hoe snel en moeiteloos je de betekenis van een nieuwe zin kan begrijpen - woorden geordend in een volgorde die je nog niet eerder hebt gezien of gehoord. Hoe zorgen je hersenen ervoor dat je op basis van tekens op papier of het geluid van de trillingen van iemands stembanden een zin kan begrijpen als "Het regent buiten"?

Neurale oscillaties als middel om de hersenfunctie te bestuderen in de context van taalverwerking

De studie van neurale ritmische activiteit (ook wel oscillaties genoemd) is nuttig bij het bestuderen van de eigenschappen en functies van de hersenen, en hoe de hersenen gedrag aansturen. Meer dan twee decennia aan onderzoek heeft aangetoond dat de modulatie van neurale oscillaties verband houdt met een breed scala aan processen zoals aandacht, het geheugen, het plannen van bewegingen en het bewustzijn (bv, Jensen, Kaiser, en Lachaux, 2007; Klimesch, Freunberger & Sauseng 2010 ; Klimesch, 2012; Lega, Jacobs & Kahana, 2012; Schoffelen, Oostenveld, & Fries, 2005; Schoffelen, Poort, Oostenveld, & Fries, 2011; Schoffelen, Oostenveld, & Fries, 2008; Staudigl & Hanslmayr, 2013; van Ede, de Lange, Jensen, en Maris, 2011). Taalverwerking is een complexe cognitieve functie die is gebaseerd op veel andere (meer basale) functies zoals visie, gehoor, aandacht en geheugen. Daarom is bij taal een neuraal netwerk betrokken dat is verspreid over de hersenen, bestaande uit meerdere delen die deze gespecialiseerde subprocessen ondersteunen. De precieze bijdragen van deze individuele hersengebieden en de interacties tussen deze gebieden zijn nog niet helemaal duidelijk. Een manier om dit te onderzoeken is om veranderingen in neurale oscillaties te bestuderen. Niet alleen weerspiegelen deze oscillaties lokale veranderingen in doorlopende hersenactiviteit, ook is het zo dat synchronisatie van ritmische activiteit tussen hersengebieden mogelijk een efficiente interactie tussen hersengebieden bevordert. Omdat er slechts weinig studies over oscillaties in de context van taal bestaan, heeft dit proefschrift tot doel om neurale oscillaties te gebruiken om de neurobiologische mechanismen die betrokken zijn bij zinsverwerking te onderzoeken en zo nieuwe inzichten te verschaffen in hoe de hersenen werken.

In dit proefschrift heb ik neurale oscillaties gebruikt om beter te begrijpen hoe de hersenen taal begrijpen, door middel van gesynchroniseerde activiteit in een groot netwerk van hersengebieden. In onze dagelijkse communicatie begrijpen we taal met een ongelooflijke snelheid - de gemiddelde spreker produceert 160-260 woorden per minuut (Rodero, 2012; Tauroza & Allison, 1990), en we lezen ongeveer 200 - 400 woorden per minuut (Rayner, Schotter , Masson, Potter, & Treiman, 2016; Sereno, 2003; Staub & Rayner, 1998). Aangezien oscillaties een maat voor hersenactiviteit zijn met een precieze tijdsresolutie, zijn ze uitstekend geschikt om te onderzoeken hoe onze hersenen de snelheid van taal kunnen bijhouden om zo snel genoeg taal te kunnen begrijpen.

Samenvatting van de experimentele hoofdstukken

In **hoofdstuk 2**, heb ik de hersenactivieit van 102 proefpersonen met MEG gemeten terwijl zij luisterden naar zinnen (en woordenlijsten). Mijn belangrijkste vraag was of de ritmische synchronisatie van neuronale oscillaties op het ritme van spraak een robuust en betrouwbaar fenomeen is in zowel langzame (delta en theta) als snelle (gamma) frequenties. Ik heb de kruiscorrelatie tussen oscillaties en het spraaksignaal berekend, en vond dat de neurale oscillaties van in de pas gaan lopen met het ritme van spraak in de delta- en thetafrequenties, in de bilaterale bovenste en middelste temporale gyri, maar vond geen bewijs voor synchronisatie binnen de gamma frequentieband.

Voortbouwend op deze resultaten, heb ik getest of er individuele verschillen in synchronisatie bestaan. Ik liet zien dat proefpersonen verschilden in de frequentie waarin de synchronisatie tussen oscillaties en spraak maximaal was. Daarnaast vond ik, in tegenstelling tot het algemeen aanvaarde idee dat de rechterhemisfeer van de hersenen een voorkeur heeft voor trage ritmes (en de linkerhemisfeer voor snelle ritmes), dat bij de helft van de proefpersonen de synchronisatie van langzame frequenties is gelateraliseerd in de linkerhemisfeer en bij de andere helft in de rechterhemisfeer. Ik concludeerde dat de hersenen in staat zijn om spraak bij te houden met snelheden vergelijkbaar met de frequentie waarmee syllabische (theta) en prosodische (delta) informatie voorkomen in spraak, maar dat we het ritme van taal niet precies volgen en dat we geen voorkeur hebben om het ritme van taal te volgen in de rechterhersenhelft.

In **hoofdstuk 3**, testte ik de overheersende hypothese dat de doorlopende, intrinsieke, neurale oscillaties een noodzakelijke voorwaarde zijn voor de waargenomen synchronisatie. Hoewel dit het geval lijkt te zijn voor eenvoudige, herhaalde auditieve tonen of visuele stimuli, ontbreekt bewijs dat dit ook voor taal het geval is. Ik voorspelde dat als het waar is dat oscillaties ten grondslag liggen aan deze synchronisatie, de variatie in de frequentie waarin de synchronisatie maximaal is (te vinden in hoofdstuk 2) zou correleren met de variabiliteit in de frequentie van resting state oscillaties. Daarentegen zou een correlatie met de variabiliteit in piekfrequentie van het signaal in reactie op het begin en einde van gesproken zinnen (de zogenaamde evoked response) steun verschaffen voor het idee dat de temporele superpositie van evoked responses ten grondslag ligt aan de synchronisatie. Ik vond geen bewijs voor deze hypotheses. Ik heb wel aangetoond dat de spatiële distributie (topografie) van temporele superpositie van evoked responses in reactie op gesproken woordenlijsten vergelijkbaar is met de geobserveerde topografie in de originele coherentieanalyse. Dit suggereert dat (i) alleen de waarneming van activiteit in het frequentiedomein onvoldoende bewijs is voor oscillaties, en dat (ii) de superpositie van evoked responses niet mag worden genegeerd als een plausibele oorzaak van synchronisatie.

In **hoofdstuk 4** heb ik het lezen en begrijpen van zinnen onderzocht. Ik heb hiervoor de hersenactiviteit van 102 proefpersonen met MEG gemeten terwijl ze zinnen (met een zinvolle syntactische en semantische context) en woordenlijsten (met een niet-betekenisvolle context) lazen. Ik toonde aan dat bij het lezen van woorden in een betekenisvolle context oscillaties in de theta-, alfa-, bèta- en gammafrequenties gelijktijdig betrokken zijn, in meerdere hersengebieden die meer dan alleen het typische taalnetwerk omvatten. Deze frequenties (behalve gamma) werden ook gemoduleerd als gevolg van de positie van woorden in een zin (vroeg versus laat). Ik speculeerde dat de oscillerende activiteit geheugen-, predictie-, onderhouds- en integratieprocessen weerspiegelde die veranderen naarmate de lezer meer woorden van de zin leest.

In **hoofdstuk 5** keerde ik terug naar het thema van de individuele verschillen en gebruikte ik genetische informatie om de systematische biologische verschillen in het neurale systeem betrokken bij het lezen van zinnen te onderzoeken (waarbij ik zinnen met woordenlijsten vergeleek). Met behulp van het CNTNAP2-polymorfisme rs7794745 (met nucleobase A of T op elk chromosoom) heb ik AA-dragers vergeleken met T-dragers (AT- of TT-allel). De T-dragers vertoonden een groter verschil tussen de verwerking van zinnen vergeleken met woordenlijsten, in theta-oscillaties, in de linker inferieure frontale gyrus. Deze studie is een van de eerste die aantoont dat variabiliteit in met MEG gemeten oscillerende activiteit is gerelateerd aan genetische effecten van CNTNAP2, en dat MEG het potentieel heeft om relevante variabiliteit te identificeren in de neurale infrastructuur van taal.

PUBLICATIONS

Lam, N.H.L., Schoffelen, J.M., Uddén, J., Hultén, A., & Hagoort, P. (2016). Neural activity during sentence processing as reflected in theta, alpha, beta, and gamma oscillations. NeuroImage. http://doi.org/10.1016/j.neuroimage.2016.03.007

Fitneva, S. A.; **Lam, N.H.L.**, Dunfield, Kristen A. (2013). The development of children's information gathering: To look or to ask? Developmental Psychology, Vol 49(3), 533-542. http://dx.doi.org/10.1037/a0031326

Submitted

Hultén, A., Schoffelen, J.M., Uddén, J., **Lam, N.H.L.**, & Hagoort, P. (submitted) How the brain makes sense beyond the processing of single words – an MEG study.

Schoffelen, J.M., Hultén, A., **Lam, N.H.L.**, Marquand, A., Uddén, J., & Hagoort, P. (submitted) Frequency-specific directed interactions in the human brain network for language.

Uddén, J., Hultén, A., Schoffelen, J., **Lam, N.H.L.**, Harbusch, K., van den Bosch, A., Kempen, G., Petersson, K. M., & Hagoort, P. (Submitted).The supramodal syntactic complexity network in the human brain: Evidence from more than 200 participants.

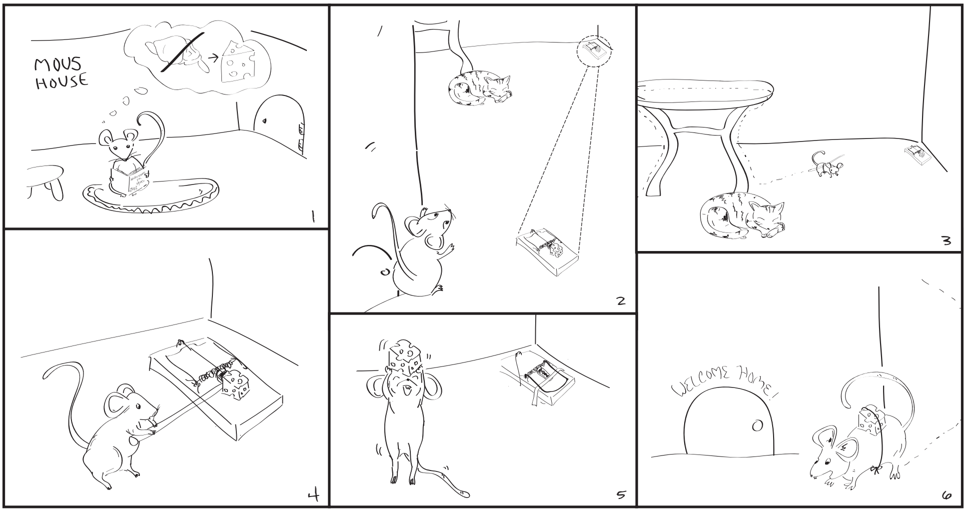
CURRICULUM VITAE

Nietzsche Lam (1989) has her roots in both Hong Kong and Canada, but considers herself to be a world citizen, having grown up and lived in 6 countries, speaking 8 languages.

At Queen’s University, Canada, she pursued a degree in Psychology where she became interested in Cognitive Science and Programming. Subsequently, she trekked over to the Netherlands to complete a master’s in Cognitive Neuroscience at the Radboud University Nijmegen under the support of a Canadian NSERC grant and a Dutch NUFFIC Scholarship. Here, she was introduced and enthralled into the world of neuronal oscillations and Magnetoencephalography. With much enthusiasm from her master’s she clambered aboard the PhD boat to join the largest multi-modal imaging neuroscience study on language, at the Donders Institute for Brain, Cognition and Behaviour, and the Max Planck Institute for Psycholinguistics. Here, under the support of a Max Planck Fellowship, she aimed to contribute a little bit more to our knowledge about how the brain allows us to comprehend language.

In parallel to her PhD, Nietzsche was a part of the FieldTrip Team - a MATLAB toolbox developed to help other neuroscientists analyze brain data. Together with the team, they squished many bugs and provided multiple analysis workshops in different countries. The latter years of her PhD was also focused on working as the English editor for the Donders Wonders - sharing the passion with a group of PhDs to teach neuroscience to the lay public, one blog post at a time.

Currently, Nietzsche is working as an associate medical publications manager at Excerpta Medica. In her spare time, with fellow Donderians, she is developing the Donders Teaching Kit – a non-profit project aimed to teach neuroscience to children in the Netherlands.



ACKNOWLEDGEMENTS

Gosh, I was really looking forward to writing the acknowledgements section. But now with the thesis written and approved, the cover designed, and the printing issues sorted, I'm stuck wondering how to write this. My first thoughts: I can write whatever I want! *hums a happy tune* I can be verbose, use too many adverbs, overlook grammatical agreement, mix up a hyphen and a dash, have run-on sentences… Faaaaantastic :D! Oh wait! That is not a good idea because I do want people to understand what I have to say. So much for free writing…
P.S. I was worried that this section would be too long, but Tom, Annelies and Lieneke said that I'm doing good☺.

5 years ago, a timid but eager student had no idea what a crazy project she'd gotten into... Luckily, she had Jan-Mathijs and Annika to show her the way. Now, and across the years, I am proud, and have openly gloated about this, to have the best supervisors in scientific history.

Jan-Mathijs Schoffelen, intimidating as you might be when one doesn't know you, I'd say that having Pino's gloves made you much more approachable ;) (sorry you lost them). Under your wing I gained a great set of skills, both in science and communication, but most importantly a friend. One who supported me (despite my occasional recklessness), gave me the pep talks I needed, regularly made fun of me, and was always ready to point out flaws in my logic/code and provide constructive feedback. I won't forget the countless times we popped by each other's office to complain about work. Of course, we also discussed the challenges with the project, stared at code, debugged it, and then complained some more. Oh, and to checked out which workout class the other was going to, less we accidentally end up in the same one again…

You have given me the confidence to believe in myself, to code, to lead a group, and to chatter on about MEG and oscillations (as if I knew what I was on about). Your generosity to teach me, let me absorb all the knowledge you had, and to adopt elegant coding habits will not be forgotten. You also gave me the opportunity to be in the spotlight, to learn to handle it, even when you deserved more credit. Thank you for everything.

Annika Hultén, we had 2.5 years together, short (in scientific terms) but sweet. Like a good scientific mother, you instilled discipline and care. MEG testing was done with the utmost rigour. So much so that after you left, aside from testing the other 100+ MOUS subjects, I became the MEG hotline when things went wrong in the lab. You never failed to check up on me even though I was at the DCCN and you at the MPI. For me, you always had X + n minutes. You cared about me scientifically and personally, and although our strong personalities would occasionally clash, we always worked it out. Now with Ebba, I'm sure you are busier than ever as a mom and scientist, can't wait to see how she grows. I should plan a trip over soon, preferably when there are more hours of daylight :D.

As a note, in the first few months of our project, Jan-Mathijs and Annika openly dubbed themselves as my "scientific mommy and daddy". This phrase rings true as I couldn't have been given better scientific family (thanks

Peter). Now, as I move on to the next chapter, I hope to have done you both proud, and look forward to sharing more beers (while staring at each other's shoes in silence) and stories in the future.

Peter Hagoort, the boss of it all ☺. You set the bar high and constantly challenged me. The regular frustration and disappointment was difficult, but you gave me the chance to make mistakes, and to ultimately prove that I had what it took to do research. Despite your many responsibilities, you took the time to help me with my writing, and thoroughly work through our manuscript, catching all errors, from conceptual mistakes to the missing comma. In addition, you gave me the freedom to pursue and hone other skills including teaching and management, which have proven to be very useful in the long run. Thank you Peter.

The MOUS project could not have been possible without the tears and sweat of the whole team. To the amazing people responsible for the fMRI and genetic sections: **Simon Fisher**, **Hubert Fonteijn**, **Julia Uddén**, **Andre Marquand** and **Karl- Magnus Peterson** thank you for bringing this project to life. To the army of Research Assistants, I cannot begin to express how grateful and appreciative I am of your time, effort and friendship: **Laura Arendsen, Manu Schuetze**, **Charlotte Poulisse** and **Maarten van den Heuvel**, thank you so much, and all the best with your PhDs/careers!

FieldTrip. The foundation to all things MEG/EEG. **Robert Oostenveld** and **Jan-Mathijs**, thank you for making so much of our research possible and doable. Without your generousity and motivation to create a software for data analysis, in parallel to doing research, much of the Donders would be wasting their time doing the wrong analysis or trying to write code from scratch. Just as inspiring are your wills to teach others (junior or senior) everything you know, and slowly build up our confidence to teach others. My experience squishing bugs, organizing and making tutorials, and teaching MEG theory and analysis has been priceless. In light of the current state of affairs, I and all other FT supporters hope to see the toolbox shine once more.

To my FT teammates, life would be boring without our discussions of which filter has optimal effects, how much smoothing to use, and the number of tapers to apply *ahem*. **Jörn Horschig**, **Jimmy Herring** (+Michelle +Dante), **Diego Lozano-Soldevilla**, **Roemer van der Meij**, **Eelke Spaak**, **Arjen Stolk**, **Lilla Magyari**, **Simon Homölle,** and **Johanna Zumer Leggett**, thank you for teaching and learning with me. Special shout out to **Tzvetan Popov** for being my co-tutor in Salzburg and giving guidance like an older brother ☺. Did you know we have 3 drummers on the FT team?

The Donders Centre for Cognitive Neuroimaging (DCCN) has been my scientific home for 5 years (Masters + PhD)

DCCN Admin and TG, goodness knows how any of us would function without your efficiency and amiable natures :). **Nicole Stekkinger**, **Ayse Öskan,** and **Sandra Heemskerk**, thank you for the lovely chats over the years, being the first friendly faces I see in the morning, and of course processing all our consent forms and finances.

Marek Tyc, **Eric van den Boogert**, **Uriel Plönes** , **Mike van Engelenburg, Rene de Bruin, Hurng-Chun Lee, Jessica Askamp**, and the rest of TG, thank you for giving me all the necessary (and bonus) technological infrastructure to allow my PhD to be completed in a timely and orderly manner. Aside from the adjustable standing desk (Yay for no back pain), managing the clusters, and keeping the labs in order, I also learned a lot more about IT and lab management, thank you!

Lucia Janssen, thank you for always coming into our offices to keep them organized and squeaky clean. My first office had a plant from Jan-Mathijs' PhD days, and today it is still growing happily thanks to your care! You always came into our office with a smile, and loved to have chat, thank you for making a difference to my time here.

Tildie Stijns, dearest Tildie, the gem of the DCCN. Like superwoman, you are known to tackle any issue big or small. In my eyes, you are the engine that keeps the DCCN running at all hours. The one who should be left to churn along steadily but is constantly bombarded by everyone, and doing more than expected. Your smile and energy are infectious, and you never failed to brighten up my day. Your stories are entertaining and I appreciate the time you took to reach out. May your forever reign supreme at the DCCN.

My extended scientific family and friends at the DCCN/DCC, you have provided much support and stimulating conversation. Whether we're discussing science (MEG/fMRI/TMS/<insert fav method or analysis technique>, publishing, scientific writing, how little time we have left...) or other issues (where we having dinner?, which movie is coming out?, the various political parties, the dystopian future...), it has been great!

My office mates over the years: **Flora Vanlangendonck**, **Ruud Berkers**, **Loek Brinkman**, **Payam Piray, Erik Lowet**, **Amber Heijne**, **Zahra Shams**, **Xu Gong** and **Janneke**, you've been great. I apologise for bursting into Disney tunes at random moments, or for coming into the office like a frustrated zombie.

To the more (less?) fortunate individuals who did not share an office with me, but were to be found at lunch, at talks or the Cultuur café, what awesomeness we had, and such sadness that our era has come to any end. Shout outs to **Tom Marshall, Iske Bakker, René Scheeringa, Wendy van Ginkel, Richard Kunert (my fellow defense and party buddy), Yuen Fang (it's been a while, hasn't it), Tim van Mourik, Anke Marit Albers, Simone Heideman (BIG Coffee coffee + Biomag 2014!), Izabela Mikuła, Alina Lartseva, Ruben van den Bergen, Ian Cameron, Elexa St. john-saaltink (Canadian Christmas!), Peter Badea** (honorary Donders/MPI, right?) **Daniel Sharoh, Linda de Voog, Isabela Wagner, Lonja Schuurman, Jacob Bellmund, Monja Froböse, Nils Müller, Ashley Lewis, Ricarda Braukmann, Peter Vavra, Catalina Ratala, Frauke van der Ven, Erik van Oort,** and **Caprice Sola**. Apologies if I forgot somebody, but please know you made a difference!

Donders Wonders, a blog that brought together people who are passionate about science and communication. What an awesome idea, and we are still going strong. Thanks for giving me the opportunity to train for a career in publishing by having me as your English editor and teacher. I learned a lot from every single blog, be it reading, editing or helping the writer. Thank you to **Lieneke Janssen**, **Jeroen van Baar**, **Annelies van Nuland**, **Kasia Sikora, Juliette Rando, Julian Tramper**, **Mahur Hashemi**, **Francie Manhardt**, **Romy Bakker**, and all of our other (past and present) members and (guest) bloggers.

Donders Teaching Kit (Oceana Programme) my latest endeavour. Here, we have the chance to educate children between the ages of 5 to 12 on neuroscience using puzzles, games, and comics. I know that our countless hours of translating from French to English, then English to Dutch, designing games, worrying about finances, collabs with others *pulls hair*… all of this will be worth it!

Leading this ambitious project is **Roselyne Chauvin** – une femme formidable! Je sais pas on trouvé les temps pour faire un doctorat et pour diriger le Donders Teaching Kit, c'est vraiment encroyable. J'aime travailler avec toi, tu as trop des idées et j'adore tes bandes dessinées!

Our team has only 4 members, small but capable! **Izabela Przezdzik** and **Sophie Akkermans**, it was great to have met you guys through this project. Your commitment and motivation are amazing, I enjoy working together, and I really do hope that this project succeeds ☺.

Peeps at the **Max Planck Institute for Psycholinguistics**, you've also been great. Thank you for being there: **Jolien ten Velden**, **Evelien Heyeselaar**, **Amie Fairs**, **Elliot Sollis**, **Sara Busquets-Estruch** (Tia, que tal a Cali? No oblido els moments de cantar i música), **Lisa Morano, Annika Nijveld, Gabriela Garrido**, **Lotte Schoot**, **Gwilym Lockwood**, **Lin Wang**, **Kevin Lam**, **Ina Grevel-Kadin,** and all other members of the **Neurobiology of Language** group.

Science takes its toll, and without sports, I don't think I'd have kept my sanity over the years. As such, I've become somewhat of an addict to sports. At the Radboud University Sports Center, not only did I get fitter and stronger, but also made several friends and acquaintances along the way.

Daan Roelofs, Samuel Zonneveld, Kelly Mostard, Roeland Smits, Louis, what great improvements the RSC has brought round. The fitness/gym are has had such a revamping! I also enjoyed all your classes, be it spinning, kettlebell, TRX, Next Level Outdoor, HIIT, the list goes on. Here, I have found other like-minded sports enthusiasts, and only come to love sports more. Thank you!

Daan, I can do the pull ups!! Thanks for improving my technique and checking on my form every now and then.

Bo Hermsen, calisthenics FTW! I waited 4 years and your class finally came along. Excited to meet another crazy who is always ready for pushups, burpees, pullups... Can't wait to see the sports photos and watch your business bloom.

Louis Jansen, TRX all the way! Training aside, thanks for all discussions on sports, gender differences (equality), life experiences and the occasional philosophy.

Astrid Creemers and **Frency Thijs**, your classes are brutal, but I love them. They always push me to the max. One tends to hate fatigue, but the feeling of satisfaction and happiness (yay for endorphins) always helped to clear my head of any PhD-related frustration/stress. Not to mention I could end the day feeling accomplish Thanks for being great (female) sport role models to me (and other ladies out there) ☺.

Within Nijmegen, I have made many friends outside of academia, thank you everyone!

Basketball. This word is largely, in my mind, associated with **Jonathan Roques** – merci beaucoup pour les premières années a Nijmegen. Était super bonne – basket-ball, band practise et la cuisine. Avec **Vitòria Piai** (good times working out at the gym!), vous avez organisé Friday bball, which at some point became Sunday bball. Here on, we have joined forces with other ball groups, and I've met many a good baller, and some good friends. Over the years, ball got more serious, and I was the only girl left playing with guys (ignorance + sheer will to improve). Amongst them were several guys who had confidence in me, and made me feel part of the team: **宋建康**, **汤志燃**，**肖烈和赵方舟**，很感谢你们跟我交朋友，每次打球或吃饭我都玩得很开心！ Also, **Enrique Urquijo** (muchas gracias por ayudarme con el mundo de los negocios, ahora tengo un nuevo trabajo!) **Toru, Constantin, Christian, Theodor Nadibaidze**, **Anchel Gonzalez**, **Philip Bassendowski**, **Sekou Keita**, **Marijn Lubbers**, **Jasper Beckermann**, and **Pol Melero Alcoy**, thanks for many good Sunday afternoon bball seshs.

Shout out to **Michael Marin** (Mike!) who saw the potential and let me train with the **university men's team – Heren 3**. Guys of Heren 3, the hussle was intense, and I struggled but thank you so much for having me ☺

The Band – Luxury Perfusion. I don't remember who came up with this name... **Jeff, Piet, Toru Hitomi, J Roques** and **Christian Hoffmann**. What a fabulous time we had! Soooo many good memories. Think at some point though, we got sick of each other – the week prior to our big performance at the Lux, we met every day to practise in the music room (basement of DCC, best kept secret, oh wait...). I loved singing and drumming with you guys, and perhaps one day we can have a reunion?

The Dierenambulance Nijmegen is an animal shelter for wild animals and some pets. Every day, we work 8 to 8 to look after animals in need. We also have an ambulance that goes around to pickup the sick ones, and release the recovered ones. Never have I seen more love for nature and life. Never have I felt more integrated into Dutch culture.
Sharon Gloudemans, ik ben zo zo blij dat we elkaar hebben ontmoet, I know you will go on to do great things! **Paul Deuning,** de papa van alle dieren, en de meester van de DAN! Ik heb zoveel van jullie beide geleerd over dierverzorging. Je oog voor detail, je aandacht voor de dieren, en je 200% inzet is indrukwekkend en

bewonderenswaardig. Ik herinner me de eerste keer dat ik de grond buiten met de hogedrukreiniger heb schoongemaakt, het was "fun" maar zo vies. Ook de eerste keer dat ik de babykonijntjes heb gevoed, en baby-egeltjes heb verzorgd. Heel hartelijk bedankt voor je geduld; ik weet dat ik niet de snelste ben met het Nederlands begrijpen and spreken, maar ik hoop dat ik het goed heb kunnen maken door de dieren te verzorgen.

Marthe Weijers en mijn klasgenoten bij Moving Matters. Ik heb echt een vet jaar met jullie hiphop gedanst. Jammer genoeg had ik het zo druk dat ik niet genoeg tijd had voor een tweede jaar. Marthe, je bent een enthousiast en geweldig meisje, elke vrijdag keek ik uit naar je lessen ☺ Ik heb zo ook veel meer woorden over bewegingen en richtingen geleerd. Thanks for making it so much fun!

Yulin Polman, hey girl! Who would that thought that we'd meet under the circumstances at G-Star? Super glad we met and became friends ☺

Certain friendships survive despite time and changes in (physical) space. My friends, although we're scattered across the continents, it's great to know you got my back

Jeffrey Neil Martin, where would I be today without you? I fear to consider that outcome. It cracks me up to think that we disliked each other when we first met. Since then, our friendship has gone through thick and thin, plus everything else in between. It's amazing to meet someone who grew up on a different continent, south of the equator, but who shares so much in common, even childhood TV shows! Your foresight, wit and intelligence has been the cause of much frustration but also much more happiness. Here is to a never-ending course of great memories to come. /chomp chomp/. By the way, I'm waiting for you to get an atom so we can go cruising.

Ruyan Teow (ruru), my eloquent friend, prolly the first female to really get me on every dimension. I hate that we're miles apart and that you prefer to stay stuck to our homeland, but hey, that's cool. You can live vicariously thru me, as you say. No really, get yourself over here asap! Much love!

Jonathan Wong (jonjon) my brother from another mother (and father) – 15 years of friendship, from culinary, to music, to science, you get it all :).

Raúl Tham Martinez, tio!! Also another ridiculous 15 years. Guitar-playing, walking home from school, hanging out in Alicante, the UK, and now hopefully in the Netherlands soon ☺.

Nicolle Domnik (+ Matt, +Kitties), my other food and science friend. What would I do without your long and hiliarious messages, food exchange, care packets from you and Ruru, and random cat posts?

Haris Saeed, **Sarah Notta**, **Joyce Li**, **Crystal Wong**, don't think I've forgotten you guys. Sweet days in undergrad, thanks for staying in touch over the years.

My Catalan siblings (escolta nens, sóc quasi catalana eh…), a more recent, wonderful addition to my life.
Joan Simó Padial, **Júlia Comes Barceló**, i **Ramon Gasulla Casamajo**, no em puc creure que nomes faci 2 anys que en vam conèixer ! Bueno, la Júlia va fer tard però no passa res. No hauria pogut sobreviure amb aquest dos nens sense tu. També m'agradaria donar les gràcies a les vostres famílies – **Adela**, **Joan**, **María**, **Ramon** i **l'avia del Ramon**, em veu acollir com i fos una mes de la familia, com la teva filla. Teniu cases moltes boniques on les cuines fan molt bona olor. He apres moltes coses de Catalunya i espero que continuem amb aquest intercanvi cultural.

Ramon, compaany, el professor de l'amor catala (hahahah) - t'agrada aquest títol, no? No podem fer un grup de 4 sense un enginyer (qui condueix?). El teu humour character relaxat em va ajudar a relaxer-me durant el meu phd. Recordo molt be els caps de setmana on esmorzavem al teu cafe preferit, anavem a comprar o jugavem a la play (jo, molt malament). I ara...qui fa la paella?

Júlia, soms com germanes. Tu ets una noia elegant and amazing, i la millor professora de la gramática catalana (ho sento nens però clearly la gramàtica catalana no es la vostra assignatura preferida). Tiaaa, m'entenc molt molt bé amb tu, i clar som millor que els unicorns. Els ultims 8 mesos del nostres PhD van ser molt durs. Quin estres, moltes emocions i moltes coses més... Ara, tenim cada una un doctorat eh ☺? Que farem després? Hem fet una llista i hem de comçenar de fer tics aviat. Espero que vinguis a viure a Amsterdam ;)

Joan: 'Nietz què faré sense tu?'
N: "No sé? No t'entenc, què vols dir…?"
J: "Sopetes... You know, like soup, like, not much"
N: "Ah, vale vale".
M'agraden molt aquestes frases catalanes, però m'agrada més que tenim una cosa especial. No oblidis, sisplau, que ets important per mi també! Que ràpid passa el temps, sembla ahir quan ens vam conèixer al bàsquet, i vam fer sopar al restaurant tailandiès, i com sempre vas perdre les claus! Soms molt diferents però ara ens entenem bé. Em fa molt feliç i sempre tens paciència amb mi. El PhD i els meus dies a Nij van ser pitjor sense tu. Ara nostres vides son separades, i unes vegades les dies son difícil… No sé que passarà en el futur, pero sé que anirà bé.'

Mijn paranymphen **Flora Vanlangendonck**, **Franziska Hartung**, and **Lorijn Zaadnoordijk**, I'm so glad we met. You have been such great friends over the years, thank you.

Flora, remember us as teeny tiny master students? We went from random (unconsciously planned) meet-ups at the library and the gym in our first years to being placed in the same office in our final PhD year. Having someone who was going through a similar research/PhD time line made things so much better. And of course, despite all our chatter and attempts to distract each other from work (i.e. mainly me), remember, we are the most quiet, concentrated office at the DCCN ;).

Franziska, small you may be, but feisty you sure are. I have always been impressed by the will and motivation with which you pursue your goals, may you continue to box away your obstacles! You and **Yves Ardelt**, have been the source of so many good evenings, parties, and even a vacation (Schiermoonikoog was a great, and much needed getaway). I look forward to visiting you guys in Pennsylvania, and hopefully we'll make that road trip!

Lorijn, (Lor-ee-geen, sorry :P),you brave girl for being the second student to join the MOUS project and working on fMRI resting-state connectivity! I love our coffee meet-ups, and being able to share all my (evil) thoughts with you. Omg, POTATO! Remember POTATO? :D Psst, I expect to see this word in your thesis when the time comes. Best of luck with your PhD, challenges have come hurtling your way, but I'm confident that you will bulldoze your way through! When is your tango performance btw? :P

My awesome family members in Hong Kong and Canada, you have supported me all these years. Thank you for all the love and generosity, it's always great to see you guys. 每次返嚟團敘食飯真係好開心。雖然我已經已經離開左十年但係心裡邊都掛住你哋同埋香港呢個美食天堂。你哋俾我個種溫暖及親切感其他人代替唔到。多謝咁多年嘅開心同關懷。我應承咗大舅父會三年內再見！

Mommy and Daddy! I am so grateful and blessed to have both of you. Quite sure I can't fit all my love for you both into these pages. 最近這五年，我慢慢開始明白和了解什麼是父母給孩子們的愛。 以前小時候我隻是想著自己，也許沒有好好珍惜你們。但現在我知道沒有你們一直的支持、愛 和 教導我不會有今天的成就。你們一直對我很有信心，特別是在 2016 這一年，雖然我們不住在一起，但感覺你們一直都在我身邊。 你們幫我考慮我的下一步，幫我進入商界，還有分享你們的生活經驗和你們對商界的體驗和想法。無論任何時候，你們都在支持我。謝謝這麼多年來的付出，我是世界上最幸福的女兒。

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DONDERS GRADUATE SCHOOL FOR COGNITIVE NEUROSCIENCE

For a successful research Institute, it is vital to train the next generation of young scientists. To achieve this goal, the Donders Institute for Brain, Cognition and Behaviour established the Donders Graduate School for Cognitive Neuroscience (DGCN), which was officially recognised as a national graduate school in 2009. The Graduate School covers training at both Master's and PhD level and provides an excellent educational context fully aligned with the research programme of the Donders Institute.

The school successfully attracts highly talented national and international students in biology, physics, psycholinguistics, psychology, behavioral science, medicine and related disciplines. Selective admission and assessment centers guarantee the enrolment of the best and most motivated students.

The DGCN tracks the career of PhD graduates carefully. More than 50% of PhD alumni show a continuation in academia with postdoc positions at top institutes worldwide, e.g. Stanford University, University of Oxford, University of Cambridge, UCL London, MPI Leipzig, Hanyang University in South Korea, NTNU Norway, University of Illinois, North Western University, Northeastern University in Boston, ETH Zürich, University of Vienna etc.. Positions outside academia spread among the following sectors: specialists in a medical environment, mainly in genetics, geriatrics, psychiatry and neurology. Specialists in a psychological environment, e.g. as specialist in neuro-psychology, psychological diagnostics or therapy. Positions in higher education as coordinators or lecturers. A smaller percentage enters business as research consultants, analysts or head of research and development. Fewer graduates stay in a research environment as lab coordinators, technical support or policy advisors. Upcoming possibilities are positions in the IT sector and management position in pharmaceutical industry. In general, the PhDs graduates almost invariably continue with high-quality positions that play an important role in our knowledge economy.

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ISBN 978-90-76203-80-5