

More than words

Neural and genetic dynamics of syntactic unification

Tineke M. Snijders

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**More than words:
neural and genetic dynamics of syntactic unification**

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Tineke Margreet Snijders

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Promotores:

Prof. dr. P. Hagoort
Prof. dr. G.A.M. Kempen (UL)

Manuscriptcommissie:

Prof. dr. J.M. McQueen
Prof. dr. P. Indefrey (Heinrich-Heine-Universität Düsseldorf)
Dr. S.E. Fisher (University of Oxford)

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Chapter 1

General introduction and outline

Introduction

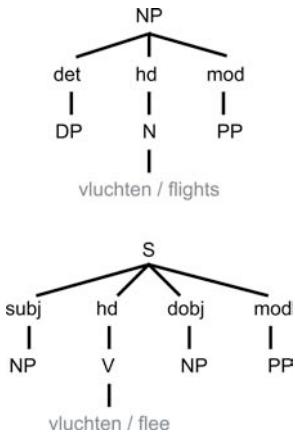
To understand what other people say (or write) is crucial for survival in our highly language-oriented society. An average person with reasonable education knows at least 50.000 words. These words can be combined into an infinite number of sentences, of which we hear and see many thousands each day. Although a large part of the words in our language are ambiguous, in most cases we smoothly interpret words in their sentence context and deduce the speaker's communicative intention.

In order to understand language we have to recognize the sound patterns or form of the words (phonology), the meaning of the words and phrases (semantics), and the way that words and phrases are put together to form grammatical sentences (syntax). Information we have learned about single words has been laid down in long-term memory, in what psycholinguists usually call the 'mental lexicon' (e.g. Levelt, 1992). Sentence comprehension requires the *retrieval* of the information about the single words from long-term memory, and the *combination* of the single-word information into a sentence or multiple-word representation, all the way up to a discourse or situation model. The process of combining the retrieved single word information into higher-level representations, has been called "integration" or "unification" (Marslen-Wilson, 1987; Hagoort et al., 1999; Sag and Wasow, 1999; Kempen and Harbusch, 2002). Both semantic (conceptual) and syntactic (structural) properties of words have to be retrieved and unified (Jackendoff, 2002).

This thesis discusses how sentence structure building (syntactic unification) occurs in the brain, and whether common variants in a certain gene (*CNTNAP2*) give rise to individual variability in sentence processing in the brain. As a starting point we take a computational model of parsing (to parse = '*to divide a sentence into parts and describe the grammar of each word or part*' (Hornby, 2000)), which will be described below. Next I will very briefly discuss the neurobiological basis of language processing, go into brain connectivity, discuss the time course of syntactic unification, and address individual variability. Finally, an outline of the thesis will be given.

Computational model

We take the computational model of syntactic parsing by Vosse and Kempen as a starting point to study syntactic unification in the brain (Vosse and Kempen, 2000). The advantage of using an explicit model is that well-defined predictions can be derived about how certain language input will be processed. According to the 'Unification Space' model, every incoming word retrieves one or more lexical frames from the 'Mental Lexicon' (ML). These lexical frames are elementary syntactic trees, specifying the possible structural environment of the particular input word. Figure 1.1 shows examples of lexical frames for a noun ("flights") and a verb ("flee"). This parsing account is 'lexicalist' in the sense that all syntactic information associated with a lexical item is retrieved from the ML rather than being supplied by grammatical rules (Vosse and Kempen, 2000).

**Figure 1.1.**

Lexical frames for the noun *vluchten* ‘flights’ and the verb *vluchten* ‘flee’. When encountering the word *vluchten*, the lexical frame of both the noun and the verb will be retrieved. In the Vosse and Kempen model, lexical frames consist of three-tiered treelets. The top-layer of a frame consists of a single phrasal node (e.g. NP). This ‘root’-node is connected to one or more functional nodes in the second layer (e.g. subject, head, direct object, modifier). Every functional node is linked to another phrasal node in the third layer. Each lexical frame is attached to one lexical item (the ‘anchor’, situated under the ‘head’ node). Word-class ambiguous lexical items function as anchor in more than one lexical frame.

Lexical frames that have been retrieved from memory will enter the ‘Unification Space’ one-by-one, as new input words arrive. Then, in the Unification Space, binding operations take place between lexical frames, resulting in an incrementally growing structural interpretation of the sentence. During the unification process lexical frames are linked, and agreement rules (number, gender, person, etc.) and word order constraints are applied. Unification links are dynamic, that is, the strength of the unification links varies over time until one stable phrasal configuration results. As language is intrinsically ambiguous, often several different unification possibilities exist. In the Unification Space model, selection among alternative unification links occurs via lateral inhibition (Vosse and Kempen, 2000).

Recently, a novel computer implementation of the Unification-Space parser (Vosse & Kempen 2000) has been developed, in the form of a localist neural network whose dynamics are based on interactive activation and inhibition (Vosse and Kempen, 2009). This new implementation has a higher level of neurocognitive plausibility. While the network is processing input word strings incrementally, the construction of syntactic trees is represented in the form of changing patterns of activation in nodes that code for syntactic properties of words and phrases, and for the grammatical functions they fulfill.

In this thesis I will use word-category ambiguous words (words that can be both a noun and a verb) to induce differential retrieval and unification demands (see Chapter 2 for an in-depth explanation hereof).

Neurobiological basis of syntactic unification

Large areas within left frontal and temporoparietal cortex are involved in language processing (e.g. Ojemann, 1991; Vigneau et al., 2006). The left temporal cortex plays a central role in the storage and retrieval of information about single words, information that has been encoded during language acquisition and stored in long-term memory. Hagoort (2003,2005) hypothesized that left posterior temporal cortex might be involved in the retrieval of lexical-syntactic information, including the lexical-syntactic frames that form the building blocks for syntactic unification. The left inferior frontal gyrus (LIFG) is associated with the ability to maintain information online, and to manipulate, select, and temporally integrate this information. These properties make LIFG an ideal candidate for a brain region

contributing to combinatorial (unification) operations in language (Hagoort, 2003, 2005a, b).

In Chapter 2 we use functional magnetic resonance imaging (fMRI, see Box 1), to test the hypothesis that the left posterior temporal cortex and the LIFG are involved in the retrieval of lexical syntactic information and the unification of this information, respectively.

BOX 1: Functional Magnetic Resonance Imaging (fMRI)

Functional neuroimaging tries to localize different mental processes to different parts of the brain. Magnetic resonance imaging (MRI) uses a strong magnetic field (expressed in Tesla) to make images of biological tissue (Huettel et al., 2004). With functional magnetic resonance imaging (fMRI) the blood-oxygenation-level dependent (BOLD) contrast is measured. Subjects lie down in an MRI scanner (see Figure) while performing cognitive tasks. The blood oxygenation level changes based upon the metabolic demands of neural activity. Thus, indirectly, the neural activity induced by mental processes is measured. The hemodynamic response assessed with fMRI lags behind the neural activity by about 4-6 seconds. A whole brain volume can be calculated only every 2-3 seconds. Thus, the temporal resolution of this technique is poor. However, the spatial resolution of fMRI is good, in the order of millimeters.



Huettel, S.A., Song, A.W., McCarthy, G., 2004. Functional Magnetic Resonance Imaging. Sunderland, MA, Sinauer Associates.

Brain connectivity

At the end of the 18th century Joseph Gall (1758-1828) pioneered the notion that the brain is the source of all mental activity, and different mental functions are located in different parts of the brain (Zola-Morgan, 1995). Although the claim that individual differences in mental capacities are reflected in differences of the thickness of the skull (phrenology) has since long been refuted, the idea of specialization of function within the brain is still valid today (see above). The mapping of the human brain with modern neuroimaging techniques such as functional MRI has also been called ‘neophrenology’, as it has often focused on localizing specific mental functions within the brain (Friston, 2002). Recently there has been a shift towards a more ‘network-based’ thinking: specific brain regions (such as prefrontal cortex) probably participate in a wide range of tasks, with specialized function emerging from the unique cooperation of a network of brain regions subserving domain-general mechanisms (Mesulam, 1998; Fuster, 2001; Marcus et al., 2003). Not only differences in the distribution of activations within a network, but also differences in the interaction among its components, can change the functional role of a network (Mesulam, 1981; Damasio, 1989; Mesulam, 1990, 1998; McIntosh, 2000; Friston, 2002).

In Chapter 3 I will discuss the connectivity of the different brain regions involved in syntactic unification. The modulatory effect of word-category ambiguity in sentences on the functional coupling of these regions of interest with other regions in the brain will be explored.

Time course of syntactic unification

As language is intrinsically ambiguous, often several different unification possibilities exist (i.e., different sentence structures are possible). Word-category ambiguous words in sentences might result in increased processing at the ambiguous word, and/or in increased processes in response to the resolution of the ambiguity (selection) at the disambiguating word.

In Chapter 5 we address the time course of syntactic unification during word-category ambiguity processing, using magnetoencephalography (MEG, see Box 2).

BOX 2: Magnetoencephalography (MEG)

Through magnetoencephalography (MEG) one can measure, outside of the skull, the magnetic field generated by small electric currents flowing in neurons. For a magnetic field to be present, hundreds of thousands of cells within the brain need to be simultaneously activated (Hämäläinen et al., 1993). The tiny magnetic field produced by the neurons, about a million times weaker than the earth's magnetic field, is picked up by super-conducting sensors outside the head that operate under very low temperatures. Event-related fields (ERFs) are averaged time epochs of the magnetic field evoked by a cognitive event (presentation of a stimulus). The magnetic field passes through tissues of the body with minimal distortion. Thus, the field does not get smeared out over the skull as much as happens with the electric potential (measured with the better-known technique of electroencephalography (EEG)). As a result, compared to EEG the spatial resolution of MEG is good. Compared to fMRI, MEG has a poor spatial resolution (in the order of one or a few centimeters). MEG has the same good temporal resolution as EEG, which is in the millisecond range.



Hämäläinen, M., Hari, R., Ilmoniemi, R.J., Knuutila, J., Lounasmaa, O.V., 1993. Magnetoencephalography - Theory, Instrumentation, and Applications to Noninvasive Studies of the Working Human Brain. *Reviews of Modern Physics* 65, 413-497.

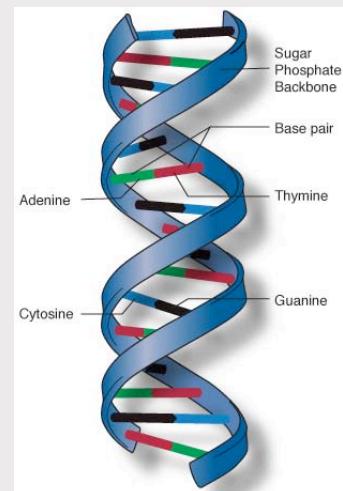
Individual variability mediated by genes

Do all individuals process language in a similar way, or are there individual differences in how the brain processes language? Of course, individual variability in language processing abilities exists (Just and Carpenter, 1992; Pakulak and Neville, 2009). Little is known about the genes that contribute to these individual differences, with the exception of rare mutations in the *FOXP2* gene causing a severe speech and language disorder (see Box 3 for some notes on genetic terminology). Genes that are responsible for normal individual differences in how language is processed might have an effect on brain activity in response to language. As of yet, there are no studies investigating, in the normal population, the effect of common polymorphisms in language-related genes on the activity of the brain in response to language.

Chapters 4 and 5 will address the influence of a specific common genetic variant of the *CNTNAP2* gene, a gene that is down-regulated by *FOXP2*, on sentence processing in the brain.

BOX 3: Some genetic terminology

Humans possess about 25000 different genes (Attia et al., 2009). *Genes* are pieces of *DNA* (deoxyribonucleic acid) that describe how to make proteins by putting the correct amino acids in the correct order. *Proteins* build cells, tissues, and enzymes, and are needed for the functioning of an organism. For production of proteins, DNA is first *transcribed* into messenger RNA, which is then *translated* into protein. In this way the genetic information at one gene (*genotype*) is converted into the protein that ultimately determines the *phenotype* (e.g. hair color). The building block of DNA is the *nucleotide*, a sugar with a phosphate group and a *base* (adenine: A, thymine: T, guanine: G, or cytosine: C). Each step of the staircase structure of DNA is formed by a pair of these bases (see figure). For more than 99%, the human *genome*, the entire collection of genetic information that a human possesses, is identical across people. However, as the human genome includes 3.3 billion base pairs, there are still more than 12 million potential *variations* between the genomes of two people. Differences that occur in less than one percent of the population are called *mutations*, whereas differences that occur more frequently are called *polymorphisms*. A single-base pair change is called a single-nucleotide polymorphism or *SNP* (pronounced ‘snip’). More than 12 million SNPs have been documented, with names as ‘rs7794745’ (with the prefix ‘rs’ standing for reference SNP). A minority of these SNPs are located in parts of the gene that are translated, of which *non-synonymous* SNPs lead to a change in the amino acid sequence of the resultant protein. Each variant that a gene may have is called an *allele*. In the case of non-synonymous SNPs the different alleles result in production of different forms of the protein for which the gene is responsible. An individual is *homozygous* at a gene location if he or she has two identical alleles at that location, and *heterozygous* if he or she has two different alleles (one on the maternal chromosome and one on the paternal) at that location.



Attia, J., Ioannidis, J.P.A., Thakkinstian, A., McEvoy, M., Scott, R.J., Minelli, C., Thompson, J., Infante-Rivard, C., Guyatt, G., 2009. How to use an article about genetic association: A: background concepts. *Jama-Journal of the American Medical Association* 301, 74-81.

Figure taken from <http://www.genome.gov/glossary/?id=140>.

Outline of the thesis

This thesis addresses the neural basis of sentence structure building, and the effect of a common polymorphism in *CNTNAP2* on sentence processing in the brain. First, we aim to disentangle the syntactic retrieval and unification processes and identify their respective neural correlates (Chapter 2). I proceed to discuss the communication between different brain regions during syntactic unification, using effective connectivity measures, in Chapter 3. Relatively little is known about the genetics of language processing. In Chapter 4 we report the effects of a common polymorphism in *CNTNAP2* on the brain response to sentence processing. The time course of syntactic unification in the brain is scrutinized in Chapter 5, and individual variability in syntactic processing routes mediated by *CNTNAP2* will be discussed. Finally, in Chapter 6, the results are summarized and I will give an integrative view on syntactic unification in the brain.

Chapter 2

**Retrieval and unification of syntactic
structure in sentence comprehension: an
fMRI study using word-category ambiguity**

Abstract

Sentence comprehension requires the retrieval of single word information from long-term memory, and the integration of this information into multi-word representations. The current fMRI study explored the hypothesis that the left posterior temporal gyrus supports the retrieval of lexical-syntactic information, while left inferior frontal gyrus contributes to syntactic unification. Twenty-eight subjects read sentences and word sequences containing word-category (noun-verb) ambiguous words at critical positions. Regions contributing to the syntactic unification process should show enhanced activation for sentences compared to words, and only within sentences display a larger signal for ambiguous than unambiguous conditions. The posterior left inferior frontal gyrus (LIFG) showed exactly this predicted pattern, confirming our hypothesis that LIFG contributes to syntactic unification. The left posterior middle temporal gyrus (LpMTG) was activated more for ambiguous than unambiguous conditions (main effect over both sentences and word sequences), as predicted for regions subserving the retrieval of lexical-syntactic information from memory. We conclude that understanding language involves the dynamic interplay between left inferior frontal and left posterior temporal regions.

This chapter is a slightly modified version of:

Snijders, T.M., Vosse, T., Kempen, G., Van Berkum, J.J.A., Petersson, K.M., Hagoort, P., 2009. Retrieval and unification of syntactic structure in sentence comprehension: an fMRI study using word-category ambiguity. *Cerebral Cortex* 19, 1493-1503.

Introduction

We hear and see thousands of words each day, and effortlessly interpret them in their context. To achieve this, several intricate processes are engaged by the brain. Whatever model of language comprehension one adheres to, all make the general distinction between retrieval and integration processes. Retrieval entails selecting the lexical representation of a word from memory. Information we have learned about single words has been laid down in long-term memory, in what psycholinguists usually call the ‘mental lexicon’ (e.g. Levelt, 1992). This information includes a word’s form, its syntactic properties (e.g. word class, gender), and the meaning of a lexical item. In order to understand single words we have to map the input signal onto word form representations in the mental lexicon (access) and select the corresponding lexical representation (Marslen-Wilson, 1987). In this way the information associated with the word form is retrieved. However, what makes language useful and creative is that words occur in all sorts of different contexts, with the varying combinations of words allowing for an infinite number of higher-level representations (von Humboldt, 1836). This process of combining the retrieved single word information into higher-level representations, has been called “integration” or “unification” (Marslen-Wilson, 1987; Hagoort et al., 1999; Sag and Wasow, 1999; Kempen and Harbusch, 2002). Both memory and unification processes occur in parallel at the semantic (conceptual) and at the syntactic (structural) level (Jackendoff, 2002). The current fMRI study focuses on the *syntactic* level. We aim to disentangle the syntactic retrieval and unification processes and identify their respective neural correlates.

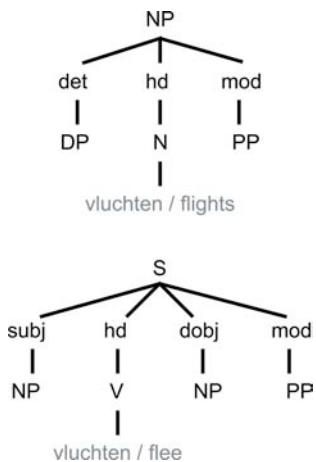
Computational model

Recently, in linguistic theories the separation between lexical items and traditional rules of grammar is fading. Increasing support has been found for lexicalist parsing models (Macdonald et al., 1994; Joshi and Schabes, 1997; Jackendoff, 2002). In lexicalist models syntactic properties of words needed for integration are retrieved from the lexicon (from memory), and the only remaining ‘rule’ is unification (Jackendoff, 2002).

A lexicalist model that is computationally explicit is the Unification Space Model of parsing by Vosse and Kempen (2000). This model accounts for a large series of empirical findings in the parsing literature and in the neuropsychological literature on aphasia. According to the Unification Space Model, every incoming word retrieves one or more lexical frames from the ‘Mental Lexicon’ (ML). These lexical frames are elementary syntactic trees, specifying the possible structural environment of the particular input word. See Figure 2.1 for examples of lexical frames for a noun (“flights”) and a verb (“flee”). This parsing account is ‘lexicalist’ in the sense that all syntactic information associated with a lexical item is retrieved from the ML rather than being supplied by grammatical rules (Vosse and Kempen, 2000; for a similar account, see Culicover and Jackendoff, 2005).

Lexical frames that are retrieved from memory will enter the ‘Unification Space’ in a sequential fashion, as new words arrive as input. Then, in Unification

Space binding operations between lexical frames are performed, resulting in an incremental structural interpretation of the sentence. During the unification process lexical frames are linked, and agreement features (number, gender, person, etc.) and word order constraints are applied. Unification links are dynamic, that is, the strength of the unification links varies over time until one stable phrasal configuration results. As language is intrinsically ambiguous, often several different unification possibilities exist. In the Unification Space model, selection among alternative unification links occurs via lateral inhibition (Vosse and Kempen, 2000; see Thompson-Schill, 2005 on selection).

**Figure 2.1.**

Lexical frames for the noun *vluchten* ‘flights’ and the verb *vluchten* ‘flee’. When encountering the word *vluchten*, the lexical frame of both the noun and the verb will be retrieved. In the Vosse and Kempen model, lexical frames consist of three-tiered treelets. The top-layer of a frame consists of a single phrasal node (e.g. NP). This ‘root’-node is connected to one or more functional nodes in the second layer (e.g. subject, head, direct object, modifier). Every functional node is linked to another phrasal node in the third layer. Each lexical frame is attached to one lexical item (situated under the ‘head’ node).

Brain regions

With the Unification Space Model as our theoretical framework, can we identify distinct neural systems subserving lexical-syntactic retrieval and syntactic unification? Large areas within left frontal and temporoparietal cortex are involved in language processing (e.g. Ojemann, 1991; Vigneau et al., 2006). Within the perisylvian cortex there is some evidence for a distribution of labor between lexical retrieval and unification operations over temporal and inferior frontal regions respectively (Hagoort, 2005a). The left temporal cortex plays a central role in the storage and retrieval of information about single words, information that has been encoded during language acquisition and stored in long-term memory. Information about the meaning of words is probably distributed over a number of brain regions, but there are indications that different parts of the left middle and inferior temporal gyri are most important for lexical-semantic processing (see e.g. Damasio et al., 1996; Saffran and Sholl, 1999; Hickok and Poeppel, 2000; Keller et al., 2001; Hickok and Poeppel, 2004; Indefrey and Cutler, 2005). Apart from extensive literature investigating the differential processing of nouns and verbs (see e.g. Caramazza and Hillis, 1991; Damasio and Tranel, 1993; Pulvermüller et al., 1999; Shapiro et al., 2006; Longe et al., 2007; Vigliocco et al., 2008), hardly anything is known about the brain regions involved in the lexical retrieval of a word’s *syntactic* properties (grammatical gender, syntactic frames, etc.). Based on a meta-analysis of syntactic processing (Indefrey, 2004), Hagoort (2003, 2005a, b) hypothesized that

left posterior temporal cortex might be involved in the retrieval of lexical-syntactic information, including the lexical-syntactic frames that form the building blocks for syntactic unification.

The left inferior frontal gyrus (LIFG) of the human brain might be particularly suitable for performing unification operations. The lateral prefrontal cortex – of which the LIFG is a part – plays a fundamental role in integration, in particular the integration of information in the temporal domain (Fuster et al., 2000; Fuster, 2001, 2002). The prefrontal cortex is capable of actively maintaining representations of various forms of information, through recurrent circuits between prefrontal cortex and posterior cortex (Durstewitz et al., 2000; Fuster, 2001; Miller and Cohen, 2001). Furthermore, in lateral prefrontal cortex these representations can be manipulated and flexibly updated. For instance, the left inferior frontal cortex is involved in selection among competing sources of information (Thompson-Schill et al., 1999; Thompson-Schill et al., 2005). The properties of LIFG (the ability to maintain information online, manipulate, select and temporally integrate this information) make it an ideal candidate for a brain region contributing to combinatorial (unification) operations in language (Hagoort, 2005a, b).

Thus, the hypothesis is that the left posterior temporal cortex and the LIFG are involved in the retrieval of lexical syntactic information and the unification of this information, respectively (Hagoort, 2003, 2005a). However, the evidence for this hypothesis is limited and indirect, coming from studies with widely varying design and stimulus materials. No study systematically manipulated both lexical-syntactic retrieval and syntactic unification. Here we set out to disentangle the retrieval and unification processes in sentence structure comprehension within one study, using the computationally explicit model by Vosse and Kempen (2000) as our starting point.

Ambiguity processing in sentences

In order to achieve this goal we exploited word-category (noun-verb) ambiguous words. These words can be interpreted as a noun or as a verb, such as the words ‘bike’ or ‘trains’. Behavioral and EEG studies have shown that multiple meanings of ambiguous words are transiently activated, even in a strongly disambiguating context. (see e.g. Swinney, 1979; Seidenberg et al., 1982; Duffy et al., 1988; Federmeier et al., 2000; Van Petten, 2002; Swaab et al., 2003). Relatively few neuroimaging studies have addressed the processing of lexical ambiguities within sentence comprehension (Stowe et al., 1994; Stowe et al., 1998; Rodd et al., 2005; Zempleni et al., 2007).

In an early PET study, Stowe and colleagues presented subjects with sentences containing a noun-verb ambiguous word in a neutral context. The sentence remained ambiguous for at least three words, and then was disambiguated into the least frequent (subordinate) meaning of the ambiguous word. The ambiguous sentences elicited more activity in the left inferior frontal gyrus than the unambiguous sentences (Stowe et al., 1994; Stowe et al., 1998).

More recently, Rodd and colleagues compared ‘high-ambiguity’ sentences that included several ambiguous words (e.g. “*the shell was fired towards the tank*”) with ‘low-ambiguity’ sentences (“*her secrets were written in her diary*”). Besides noun-noun ambiguities their materials included noun-verb ambiguities as well (e.g. *lock*, *beam*). Rodd and colleagues found increased activation for high-ambiguity relative to low-ambiguity sentences in left posterior inferior temporal cortex and bilateral inferior frontal gyri (Rodd et al., 2005).

Zempleni and colleagues showed participants sentences that contained noun-noun ambiguities of which one meaning was more frequent than the other (i.e. they were unbalanced). The final words of the sentence disambiguated the meaning to the dominant (most frequent), or the subordinate (less frequent) interpretation of the homograph. The sentences with a subordinate interpretation showed enhanced BOLD activation compared to sentences with a dominant interpretation in the left posterior and right anterior inferior frontal gyri and left posterior and right mid inferior/middle temporal gyri. Only the LIFG showed, in addition, more activity for the sentences with a dominant interpretation than for unambiguous sentences (Zempleni et al., 2007).

The above-mentioned studies can not yet unravel the relative contributions of the lexical retrieval and unification processes as part of ambiguity resolution. Sentences containing lexical ambiguities tax both retrieval and unification processes stronger than unambiguous sentences (see below). Thus, while these previous studies do indicate that left inferior frontal gyrus and left temporal gyrus are involved in retrieval and unification, they do not disentangle the two processes, nor do they target specifically the retrieval and unification of syntactic information. This is what we set out to do in the current study.

Design and predictions

To disentangle the lexical retrieval and unification processes related to syntactic information we presented subjects with (Dutch) sentences and with matched scrambled word sequences. In both sentences and word sequences the critical word was either word-class (noun/verb) ambiguous or unambiguous (see Table 2.1). The noun-verb ambiguous words were “balanced” in the sense that the noun and verb meaning had similar frequencies. The context preceding the ambiguous word was always neutral. For example, in the Dutch sentence beginning with *Beide vluchten* ..., the word *vluchten* can be either a noun (*flights*) or a verb (*flee*), resulting in continuations such as for example: *Beide vluchten werden geannuleerd* (‘both flights were cancelled’; disambiguation towards the noun reading for *vluchten*) or *Beide vluchten het behekste huis uit* (‘both flee the bewitched house’; disambiguation towards the verb reading). The logic of this design, formalized in terms of the computational model of Vosse and Kempen, is as follows.

Ambiguity effect: retrieval from mental lexicon. In a neutral context both noun and verb reading of a noun-verb ambiguous word are activated (Seidenberg et al., 1982; Duffy et al., 1988). That is, presentation of a noun-verb ambiguous word triggers the retrieval of both the noun and the verb version of the ambiguous word. As two

lexical frames are retrieved instead of one (see Figure 2.1), ambiguous words tax the lexical-syntactic retrieval process more heavily than unambiguous words. This ambiguity effect should occur in sentences as well as word sequences.

Grammaticality effect: unification process. While the factor Ambiguity manipulates the retrieval process, the Grammaticality factor is hypothesized to affect the unification process. When we compare sentences and word sequences, the sentences will require unification of the words into an overall sentence structure, while the word sequences do not. Thus, sentences will induce a higher Unification load.

Interaction: unification process. Given that the Grammaticality effect is not specific to syntactic unification (as there will be general semantic and phonological differences between sentences and word sequences as well), the crucial effect in our design is the interaction between Grammaticality and Ambiguity. In the sentence condition the two retrieved lexical frames (noun and verb) will compete for unification via lateral inhibition (the selection mechanism in our account). In the word condition no unification occurs, and the ambiguous words do not impose a higher unification load than their unambiguous counterparts. Thus, crucially, unification load will only be affected by ambiguity in the sentence condition, and not in the ‘random’ word condition.

Since we hypothesize LIFG to be contributing to the unification process, we expect that LIFG will be activated more for sentences than for word sequences, and within the sentences more for ambiguous than for unambiguous words. We predict the lexical-syntactic retrieval processes to occur in the left posterior temporal cortex. The ambiguous words will induce a higher lexical retrieval load than the unambiguous words in both word sequences and sentences. Hence, we expect the Ambiguity effect to identify the temporal area as subserving the retrieval of lexical frames.

Materials and Methods

Participants

Twenty-eight right-handed healthy volunteers (14 females, aged 18-35) participated in the experiment after having given written informed consent. Subjects were paid for their participation. All participants were native speakers of Dutch, without any history of neurological illness or head injury. Six additional subjects were scanned but excluded from analysis because of excessive movement in the MR scanner (2 subjects) or poor task performance (4 subjects, see below).

Stimulus material

The stimulus material consisted of 68 (Dutch) sentences (S) and 68 matched scrambled sequences of Dutch words (W). Both the Sentences and the Word sequences contained a critical word that was either word-class (noun/verb) ambiguous (A) or unambiguous (U). The critical word in the sentences was

disambiguated by the continuation of the sentence into either a noun (n) or a verb (v) reading. In total, this resulted in eight possible conditions: SAn, SAv, SUn, SUv, WAn, WAv, WUn, WUv (see Table 2.1 for examples). For the full set of experimental materials, see Appendix 1A.

Table 2.1.

Example of the experimental materials, with the critical word *bewijzen* (*evidence/to prove*).

SAn: Sentence Ambiguous (noun context)

Zodra jullie bewijzen_(n/v) leveren kunnen we beginnen.

As-soon-as you evidence_(n/v) provide can we start.

(As soon as you provide evidence_(n/v) we can start.)

SUn: Sentence Unambiguous (noun context)

Zodra jullie kopij_(n) leveren kunnen we beginnen.

As-soon-as you copy_(n) provide can we start.

(As soon as you provide copy_(n) we can start.)

SAv: Sentence Ambiguous (verb context)

Zodra jullie bewijzen_(n/v) dat hij erbij betrokken is arresteren we hem.

As-soon-as you prove_(n/v) that he in-it involved is arrest we him.

(As soon as you prove_(n/v) that he is involved we will arrest him.)

SUv: Sentence Unambiguous (verb context)

Zodra jullie beweren_(v) dat hij erbij betrokken is arresteren we hem.

As-soon-as you claim_(v) that he in-it involved is arrest we him.

(As soon as you claim_(v) that he is involved we will arrest him.)

WAn: Words Ambiguous (derived from SAn)

genoemd tegen bewijzen_(n/v) uit helaas gezeten jullie

named against proof/prove_(n/v) from alas seated you

WUn: Words Unambiguous (derived from SUn)

genoemd tegen kopij_(n) uit helaas gezeten jullie

named against copy_(n) from alas seated you

WAv: Words Ambiguous (derived from SAv)

in nogal bewijzen_(n/v) meestal maar dit in struikelen hem verschil opeens

in quite proof/prove_(n/v) mostly but this in stumble him difference suddenly

WUv: Words Unambiguous (derived from SUv)

in nogal beweren_(v) meestal maar dit in struikelen hem verschil opeens

in quite claim_(v) mostly but this in stumble him difference suddenly

Ambiguous critical words. Word-class ambiguous words were selected from the Dutch lexical databases CELEX (Baayen et al., 1993) and CLEF (Beek et al., 2001). Selected words had to be both a noun and a verb (and should not belong to any other word category). To ensure that both noun and verb meaning would be initially activated, all selected ambiguous words had a noun-ratio (noun frequency / summed frequency) between 0.25 and 0.75. We required that the two databases (CELEX and CLEF) agree on all criteria. In this way we got a highly reliable indication of frequency and noun-ratio. The average noun-ratio of the single ambiguous critical words was 0.51.

Ambiguous sentences. The ambiguous sentences were constructed such that both categories of the critical word fitted syntactically as well as semantically with the initial part of the sentences (up to and including the critical word); the sentences

were disambiguated by the subsequent part of the sentence (*after* the ambiguous word; see Table 2.1 for an example). A pre-test was conducted in order to assess the noun-ratio of the words in the sentence context. In this pre-test, subjects ($n=38$) had to complete sentences (e.g. “*Beide vluchten ...*”). For all items the ‘pre-test noun-ratio’ was defined as the percentage of subjects that completed the sentence in accordance with a noun interpretation of the ambiguous word. Only critical items with a ‘pre-test noun-ratio’ between 0.2-0.8 were selected. Based on the pre-test selection procedure, sixty-eight suitable ambiguous sentence-beginnings were selected, with an average noun-ratio of 0.46.

For every ambiguous item a noun and a verb sentence ending was constructed, with the same neutral sentence context preceding the critical word (SAn and SAv, see an example in Table 2.1). Noun and verb sentences were matched for average length. The sentences consisted of 6-12 words, with an average of 8.5 words per sentence. The critical word occurred on the second (34 sentences), third (27 sentences) or fourth (7 sentences) position of the sentence. None of the non-critical words in the sentences were balanced noun-verb ambiguous words.

Unambiguous sentences. For every ambiguous sentence item we constructed two suitable, unambiguous alternatives for the ambiguous critical word (a noun and a verb; see example SU_n and SU_v in Table 2.1) that fitted the remaining part of the sentence equally well as the ambiguous word. We selected part of the alternative words from the CLEF-corpus based on distributional similarity (Plas and Bouma, 2004). Words that are distributionally similar are words that share a large number of lexical-syntactic contexts, that is they form grammatical dependency relations with the same words (for example, *lemon* and *orange* can both be the direct object of *squeeze*). If for a critical word no such alternative could be found in the corpus, it was constructed by hand. Ambiguous and unambiguous words were matched for average length and (summed) word form frequency.

Word sequences. Word sequences were constructed from the sentences (WAn, WUn, WAv, WUv). For each sentence, every word (except the critical word) was substituted by a different corpus word belonging to the same syntactic category (noun, verb, adjective, rest), and with a similar length and frequency (the resulting average length for both sentences and word sequences was 42 characters, and the average CLEF/CELEX log frequency was 3.7 for sentences compared to 4.2 for word sequences). Subsequently the order of all words in the sequence (except the critical word) was randomized, with the constraint that two words could not be succeeding each other in the same way as in the original sentence. Sequences were checked on local grammaticality and were scrambled again if three or more consecutive words formed a coherent sentence fragment. We again made sure that none of the non-critical words in the sequence were balanced noun-verb ambiguous words.

Experimental lists. The stimuli were distributed over 4 lists. For every item, one of the following combinations occurred in each list: SAn+WUn; SAv+WUv; SU_n+WAn; SU_v+WAv; hence, no subject encountered the same critical word twice. This resulted in 34 items per subject per condition (SA, SU, WA, WU). The

pre-test noun-ratios, sentence lengths, and position and frequency of the critical words were all matched across the four lists. In addition, each list contained the same 28 sentence and 28 word sequence fillers, 36 of which (18 for each condition) contained a consonant string (e.g., *grpsd*) at various positions in the sentence/sequence (see Procedure).

Procedure

Stimuli were presented visually in serial presentation mode (word by word in the middle of the screen) using Presentation software (Version 9.13, www.neurobs.com). Every word remained on the screen for 300ms, with a 200ms inter-word-interval. Between sentences a visual fixation cross was presented for 5-8 seconds (low-level baseline). The participants were instructed to read each sentence/sequence carefully and attentively, and were told that after the experiment some questions concerning the experiment would have to be answered. The participants' task was spotting the consonant-strings (e.g., *cdslnl*), that were presented in 36 of the fillers. This simple control task was added to check whether subjects were paying attention. Subjects were defined as poor task performers if they made more than five errors (missing hits and false alarms) on the task, suggesting that these subjects did not pay enough attention to the stimuli.

Every subject saw 68 sentences and 68 word sequences (ambiguous/unambiguous; in noun/verb version), intermingled with 56 fillers (28 sentences and 28 sequences). Stimuli were presented in mini-blocks of three to four sentences or word sequences. All mini-blocks were shorter than 40 seconds. Before each block the label “Zinnen:” (“Sentences:”) or “Woorden:” (“Words:”) appeared on the screen (for 1.5 seconds) to indicate the condition of the following mini-block, which started after a fixation cross of 1-3 seconds. We expected the labels to encourage (“Sentences”) or discourage (“Words”) attempts to syntactically/semantically integrate the stimulus items in the upcoming mini-block. The ambiguous/unambiguous and verb/noun conditions were intertwined within the mini-blocks in a pseudo-randomised presentation order.

fMRI Data Acquisition

During the sentence/sequence presentation we acquired T2*-weighted EPI-BOLD fMRI data with a SIEMENS Trio 3T MR-scanner using an ascending slice acquisition sequence (volume TR = 2 s, TE = 35 ms, 90 degree flip-angle, 29 slices, slice-matrix size = 64 x 64, slice thickness = 3 mm, slice gap = 0.5 mm, FOV = 224 mm, isotropic voxel size = 3.5x3.5x3.0 mm). At the end of the scanning session, a structural MR image volume was acquired for which a high-resolution T1-weighted 3D MPRAGE sequence was used (TE = 3.93 ms, 8 degree flip-angle, 192 sagittal slices, slice thickness = 1.0 mm, voxel-size = 1 x 1 x 1 mm).

Data Analysis

Image preprocessing and statistical analysis were performed using Statistical Parametric Mapping (SPM2; www.fil.ion.ucl.ac.uk/spm). The first five image

volumes were discarded in order to avoid transient non-saturation effects. The functional EPI-BOLD images were realigned, slice-time corrected, and the subject-mean functional MR images were co-registered with the corresponding structural MR images using mutual information optimization. Subsequently, images were normalized onto a Montreal Neurological Institute (MNI)-aligned echo planar imaging template (based on 28 male brains acquired on the Siemens Trio at the Donders Centre for Cognitive Neuroimaging, Nijmegen) and resampled to an isotropic voxel size of 2 mm. Finally, the normalized images were spatially filtered by convolving the functional images with an isotropic 3D Gaussian kernel (10 mm full width at half maximum).

The fMRI data were proportionally scaled to account for various global effects, and analyzed statistically using the general linear model and statistical parametric mapping (Friston et al., 1995) in a two-step mixed design procedure. At the first-level, single-subject fixed effect analyses were conducted. The linear model included mini-block regressors to model the sentence/sequence presentation from the onset of the critical word to the offset of the sentence/sequence-final word. The beginnings of sentences/sequences and filler items were modeled together as a regressor of no interest (other words, OW), and the presentation of the fixation cross (FIX) was modeled as explicit baseline. We temporally convolved the explanatory variables with the canonical haemodynamic response function provided by SPM2. We included the realignment parameters for movement artifact correction and a temporal high-pass filter (cutoff 128s) to account for various low-frequency effects as effects of no interest. Temporal autocorrelation was modeled as a first-order plus white noise autoregressive process.

Region of Interest analysis. A meta-analysis (Bookheimer, 2002) suggests that activations related to syntactic processing in LIFG are centred in a 13 mm sphere around MNI coordinates [-44,19,14] (Petersson et al., 2004). This sphere was taken as the ROI of the relevant subpart of the LIFG (which henceforth we will simply refer to as LIFG). An average time course was calculated for LIFG (for every participant separately) using Marsbar (<http://marsbar.sourceforge.net/>). While we had a strong *a priori* hypothesis regarding the part of LIFG involved in syntactic unification, we did not have such a specifically defined region for the part of left posterior temporal cortex involved in lexical-syntactic retrieval. Thus, we specified a region of interest only for LIFG, and did not use an ROI for left temporal gyrus (LTG). For the ROI analysis at the second level a repeated measure ANOVA with the factors Grammaticality (S,W), Ambiguity (A,U), and Word class (n,v) was carried out on the subject contrast values using SPSS software (SPSS Inc., Chicago, IL, USA).

Whole brain analysis. For the second-level whole-brain analysis, we generated single-subject contrast images for the SAn, WAN, SUN, WUn, SAv, WAv, SUv, and WUv items relative to the baseline FIX, and used these in a one-way random effects repeated measures ANOVA (including the factors: condition (8) and subject

(28)). To correct for multiple comparisons, statistical inference was based on the cluster-size statistics from the relevant second-level SPM[T] volumes (Forman et al., 1995; Friston et al., 1996). SPMs were thresholded at $P < 0.002$ (uncorrected at the voxel level). To protect against false-positive results, only clusters of a size of 50 voxels or more are reported (unless otherwise specified). In this way SPM[T] volumes were generated to investigate the effect of grammaticality (i.e. sentences > words; words > sentences; Figure 2.3A; Table 2.2A/B) and the effects of ambiguity (ambiguous > unambiguous; unambiguous > ambiguous, Figure 2.3B, Table 2.3). Additionally, an SPM[T] volume was created for the effect of ambiguity within sentences only (SA>SU, Figure 2.3C, Table 2.4).

Anatomical inference. All local maxima are reported as MNI coordinates (Evans et al., 1993). Relevant anatomical landmarks were identified and Brodmann areas were defined using the Atlas of the Human Brain (Mai et al., 2004) and the Talairach Daemon (Lancaster et al., 2000).

Results

Control task

All 28 included participants made ≤ 3 errors (mean: 0.18 misses, 0.5 false alarms). Subjects that made more than 5 errors were excluded from analysis (4 subjects, see participants).

Region of Interest analysis

For the syntactic processing in the left inferior frontal gyrus (LIFG) we had a very specific region of interest (see Data Analysis). Figure 2.2 shows the ROI, and the mean contrast estimates of LIFG for SA, SU, WA and WU. LIFG was activated more strongly for sentences than for words ($F_{1,27} = 31.2$, $p < .001$), while only within sentences there was an effect of ambiguity (Ambiguity*Grammaticality: $F_{1,27} = 5.6$, $p = .025$; SA>SU: $T_{27} = 2.75$, $p = .005$). This activation pattern corresponds to the activation predicted for the Unification Space, supporting the hypothesis that the LIFG plays a role in syntactic unification operations during language comprehension.

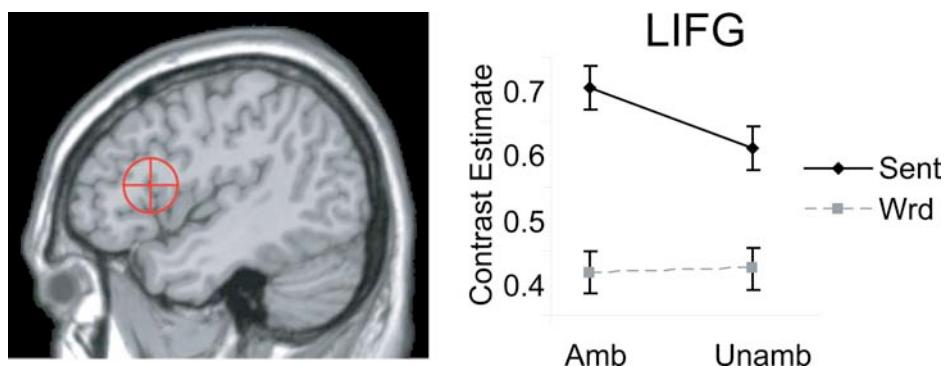


Figure 2.2.

ROI results. Mean contrast estimates for LIFG for SA, SU, WA, and WU. The ROI used is shown on the left (13 mm sphere around coordinates [-44,19,14]).

As mentioned in the Data Analysis section, we did not have an *a priori* specifically defined region of interest within the left posterior temporal cortex, so we used the whole brain analysis (ambiguity effect) to identify the part of the LTG involved in the retrieval of lexical-syntactic information.

Whole Brain analysis

Grammaticality effect. For the whole-brain comparison between sentences and word sequences a voxel-level threshold of $p = .05$ corrected for multiple comparisons based on random field theory (Worsley et al., 1996), and a cluster-size threshold of 20 voxels were used (Figure 2.3A, Table 2.2). As shown in Figure 2.3A, sentences

Table 2.2A

Sentences versus word sequences.

Region	BA	Cluster size	Voxel T^{189} value	x	y	z
Sentences > Words						
<i>L Temporal Gyrus, L IFG</i>						
L Temporal Pole	38		24.21	-54	18	-30
L anterior MTG	21		22.01	-56	-6	-16
L posterior MTG	21		18.77	-62	-44	-2
L IFG	47		17.13	-52	34	-8
L posterior STG	22		15.12	-58	-56	12
L IFG	45		15.04	-58	22	12
L posterior STG	39		14.22	-44	-58	18
L amygdala			10.66	-26	-6	-20
L ITG	20		9.56	-44	-16	-30
L culmen (cerebellum)			8.61	-26	-36	-26
L putamen			8.28	-18	2	4
<i>R Temporal Gyrus</i>						
R Temporal Pole	38		16.22	54	20	-32
R anterior MTG	21		13.39	56	8	-26
R middle MTG	21		10.24	52	-14	-16
R posterior MTG	21		6.96	62	-42	0
<i>R IFG</i>						
R anterior IFG	47		8.85	56	36	-10
R IFG	45		6.5	60	34	4
R posterior IFG	45		5.94	62	28	10
<i>L SFG / mOrbG</i>	11	328	10.85	-4	54	-20
<i>L anterior SFG</i>	9	227	13.01	-8	60	28
<i>L MFG</i>	6	208	7.55	-38	-2	-50
<i>L Lingual Gyrus</i>		79	5.35	-6	-62	2
<i>L posterior Cingulate Gyrus</i>		78	6.88	-12	-46	34
<i>R Culmen (cerebellum)</i>		62	6.01	30	-32	-32

Note: Significant activation peaks > 8 mm apart ($p < .05$ FWE corrected, cluster extent threshold 20 voxels). Multiple peaks within a single activation cluster are shown indented. BA = Brodmann's area; T^{189} value = T value for 189 degrees of freedom; x,y,z = the original SPM x,y,z coordinates in millimeters of the MNI space; STG = superior temporal gyrus; MTG = middle temporal gyrus; ITG = inferior temporal gyrus; SFG = superior frontal gyrus; MFG = middle frontal gyrus; IFG = inferior frontal gyrus; mOrbG = medial Orbital Gyrus

caused increased activation in comparison with word sequences in a large area in the perisylvian network, including LIFG, left middle temporal gyrus (LMTG) and both temporal poles (see Table 2.2A for a complete list). This is the network that we would indeed expect to see activated in sentence comprehension (e.g. Bavelier et al., 1997; Friederici, 2002; Indefrey and Cutler, 2005; Vigneau et al., 2006). For word sequences there was enhanced activation in the bilateral middle/superior frontal gyrus (M/SFG), the cingulate cortex, and supramarginal/angular gyrus (see Table 2.2B, Figure 2.3A). This network of areas is reminiscent of the “default mode” network described by Raichle and colleagues (Raichle et al., 2001). Indeed, inspection of the beta weights showed that both word sequences and sentences deactivate these areas compared to low-level baseline, but sentences gave rise to a larger deactivation than word sequences.

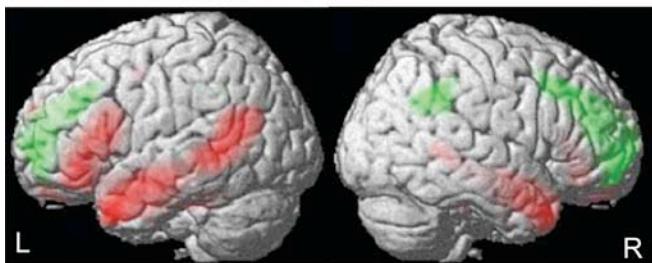
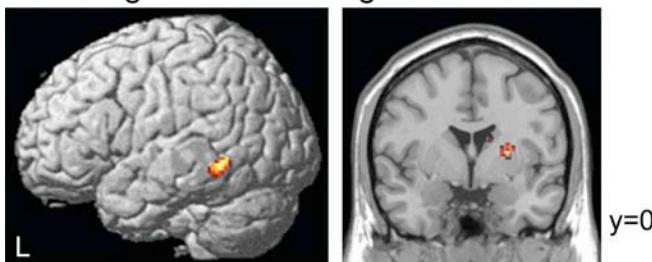
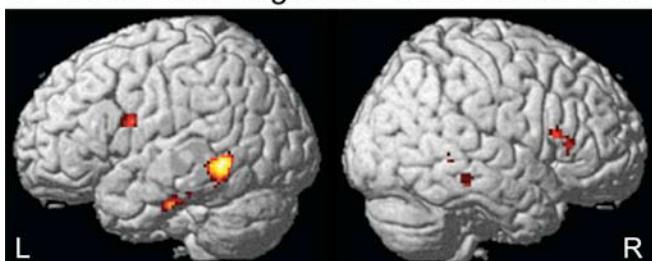
Ambiguity effect. Ambiguous words are expected to induce a larger load on the Mental Lexicon for both sentences and word sequences, as two lexical frames have to be retrieved from memory. We hypothesized these retrieval operations to take place in the left posterior temporal cortex. Indeed, we see an increased signal for

Table 2.2B

Word sequences versus Sentences.

Region	BA	Cluster size	Voxel T^{189} value	x	y	z
Words > Sentences						
<i>Bilateral M/SFG, CG</i>						
R anterior MFG	11		11.21	36	58	-12
R CG/ med SFG	32		11.15	4	36	30
R posterior MFG	9		10.88	40	26	42
L anterior MFG	10		10.61	-38	58	4
R anterior I/MFG	46		10.31	48	44	16
L MFG	9		10.25	-40	34	32
R Frontopolar G	10		10.25	24	64	4
L anterior M/SFG	10		9.24	-30	56	-4
R AC / Rostral G	32		8.43	8	46	-4
R anterior SFG	9		8.20	28	44	36
L AC / Rostral G	32		6.94	-8	40	0
R middle CG	23	1704	13.64	0	-24	30
R SMG	40	1280	12.25	58	-50	36
L Sup Parietal Lob	7	772	9.76	-10	-72	30
R Precuneus	7		9.07	-12	-62	34
<i>L angular G /SMG</i>						
L angular gyrus	40		7.19	-36	-50	36
L SMG	40		6.06	-44	-44	38
L SMG	40		5.24	-60	-38	40
Planum polare / Orbital G		82	6.69	32	22	-20
L posterior ITG		31	6.23	-58	-54	-20

Note: Significant activation peaks > 8 mm apart ($p < .05$ FWE corrected, cluster extent threshold 20 voxels). Multiple peaks within a single activation cluster are shown indented. AC = anterior cingulate; SMG = supramarginal gyrus; CG = cingulate gyrus; Sup Parietal Lob = superior parietal lobule; for additional abbreviations see Table 2.2A.

A Sentences vs. Word lists**B Ambiguous > Unambiguous items****C Sentence Ambiguous > Sentence Unamb****Figure 2.3.**

Whole brain analysis. Significant activations projected onto a rendered template brain surface in MNI stereotactic space.

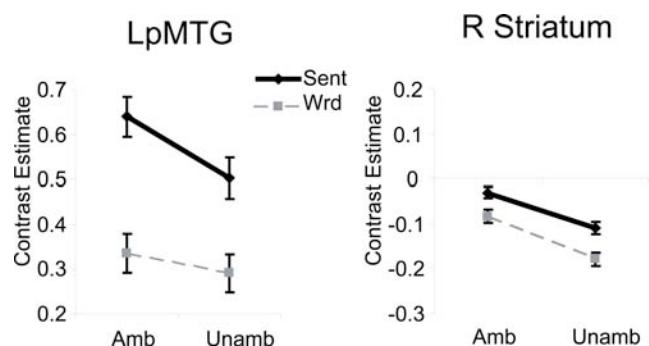
A: Effect of grammaticality. Enhanced activity within sentences is shown in red, increased signal for words is shown in green. (Activations shown at voxel-level $p_{FWE} < .05$, cluster-size threshold 20 voxels.)

B. Effect of ambiguity: enhanced activity for ambiguous as compared to unambiguous conditions. The right panel shows a coronal view of the brain at $y = 0$, displaying the ambiguity effect in the right striatum. (Activations shown at voxel-level $p_{uncorr} < .002$, cluster-size threshold 50 voxels.)

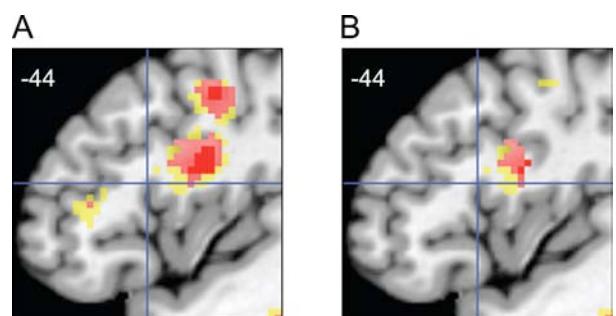
C. Effect of ambiguity within sentences: enhanced activity for ambiguous sentences as compared to unambiguous sentences. (Activations shown at voxel-level $p_{uncorr} < .002$, cluster-size threshold 50 voxels.)

Figure 2.4.

Mean contrast estimates for LpMTG and the right striatum (clusters identified by the whole-brain ambiguity effect) for SA, SU, WA, and WU.

**Figure 2.5.**

LIFG effect: comparison of ROI and whole-brain analysis (exploratory thresholds). Activations from the whole-brain analysis are displayed on a template (frontal cortex, sagittal view). Voxel-level p_{uncorr} : yellow $p < .01$; pink $p < .005$; red $p < .001$. Crosshair at [-44 19 14] (ROI). (A) Effect of ambiguity within sentences (SA>SU). (B) Effect of ambiguity within sentences (SA>SU), masked (inclusively) with the effect of grammaticality (sentences > words) at $p_{FWE} < .05$. Regions contributing to the syntactic unification process should show this pattern of activation.



the ambiguous compared to the unambiguous items in the left posterior middle temporal gyrus (LpMTG, see Figure 2.3B). Furthermore, enhanced activation for ambiguous items was seen in the striatum (Figure 2.3B), right posterior middle temporal gyrus (RMTG) and the right parahippocampal gyrus (see Table 2.3). There were no areas that showed larger activation for the unambiguous than for the ambiguous items. Figure 2.4 shows the mean contrast estimates for the activated cluster in LpMTG and the striatum (computed with Marsbar, <http://marsbar.sourceforge.net/>). It can be seen that the ambiguity effect in LpMTG was larger in the sentences than in the word sequences. An ANOVA on the mean contrast estimates in LpMTG showed a significant interaction between grammaticality and ambiguity, with the WA>WU comparison being marginally significant ($F_{\text{gram} \times \text{amb}}(1,27) = 6.98, p = .014$; SA>SU: $T_{27} = 4.72, p < .001$; WA>WU: $T_{27} = 1.40, p = .086$, see Figure 2.4). The effect of ambiguity in the striatum (the largest effect for this comparison, see Table 2.3) did not differ for sentences and word sequences ($F < 1$; see Figure 2.4).

Ambiguity effect in sentences. Additionally, we explored the effect of ambiguity within sentences only (SA > SU). The ambiguous sentences showed enhanced activation in the bilateral posterior MTG and the bilateral posterior IFG compared to the unambiguous sentences (see Table 2.4, Figure 2.3C). This is the same network of areas that was found previously in studies of lexical ambiguity in sentence processing (Rodd et al., 2005; Zempleni et al., 2007). The left inferior frontal

Table 2.3

Ambiguous versus Unambiguous conditions.

Region	BA	Cluster size	Voxel T^{189} value	x	y	z
Ambiguous > Unambiguous						
<i>R Striatum</i>		502				
R Putamen			3.96	24	0	8
R Caudate Body			3.94	14	8	16
R Putamen			3.83	26	-10	8
<i>L posterior I/MTG</i>		109				
L post MTG / ITS	37		3.82	-52	-50	-8
L posterior ITG	37		3.27	-46	-46	-14
L post MTG / ITS	37		3.11	-46	-54	-4
<i>R MTG</i>	37	72	3.57	48	-44	-6
<i>WM / PCL / CG</i>		56	3.61	-22	-38	34
<i>R parahippocampal gyrus</i>		50				
R paraHCG	36		3.28	22	-42	-6
R paraHCG / Occipital G			3.19	28	-48	-2

Unambiguous > Ambiguous: No significant activations

Note: Significant activation peaks > 8 mm apart ($p < .002$ uncorrected, cluster extent threshold 50 voxels). Multiple peaks within a single activation cluster are shown indented. ITS = inferior temporal sulcus; WM = white matter; PCL = paracentral lobule; CG= cingulate gyrus; paraHCG = parahippocampal gyrus; for additional abbreviations see Table 2.2A.

region we identified in this contrast (SA > SU) is overlapping with, but slightly posterior to, our region of interest. To explore whether other areas within LIFG (besides our ROI) might be involved, we show the whole-brain sentence ambiguity effect at lower thresholds in Figure 2.5 (frontal cortex). In Figure 2.5B this SA>SU activation is masked by the Grammaticality effect (Sentences>Words), as this is the pattern we were looking for in our ROI (unification). Although there is some activation in the anterior LIFG at a low threshold, most of the activation for SA>SU is situated posterior of [-44 19 14] (the center of our ROI). For the masked activation, we see activation only in posterior LIFG (Figure 2.5B).

Post-hoc Analysis on Context-Irrelevant associates

It is the case that word-category ambiguous words are semantically ambiguous as well. Therefore we conducted a post-test to investigate the semantic consequences of the ambiguity. The issue at hand is whether our results can be explained by a different amount of selection/inhibition of semantic information evoked by ambiguous and unambiguous words. A full description of the methods and results can be found in Appendix 2. First, in a normative study we determined the semantic associates of the sentence onsets (e.g. *Beide vluchten*). Of these associates we identified the ones that were context-irrelevant (i.e. inhibited in the remainder

Table 2.4

Ambiguous versus Unambiguous, separately for Sentence and Word sequence conditions:

Region	BA	Cluster size	Voxel T^{189} value	x	y	z
SA>SU						
<i>L posterior I/MTG</i>						
L post MTG / ITS	37	290	4.48	-52	-50	-8
L post MTG	21		3.42	-60	-44	-4
L post MTG / ITS	37		3.37	-46	-54	-4
<i>L mid ITG</i>						
L mid ITG	20	73	4.02	-50	-20	-28
L Fusiform Gyrus	20		3.80	-42	-24	-28
L mid ITG	20		3.18	-46	-30	-22
<i>R MTG</i>						
R ITS		65	3.54	48	-34	-14
R posterior MTG	37		3.31	50	-44	-4
<i>L IFG / PrG</i>	44/6/9	62	3.49	-44	0	22
<i>R IFG</i>						
R IFG	45	51	3.35	46	28	6
R IFG	44/45		3.24	44	18	14
R IFG	44/45		2.99	54	18	12

SU>SA; WA>WU; WU>WA: No significant activations

Note: Significant activation peaks > 8 mm apart ($p < .002$ uncorrected, cluster extent threshold 50 voxels). Multiple peaks within a single activation cluster are shown indented. SA = sentence ambiguous; SU = sentence unambiguous; WA = word-sequence ambiguous; WU = word-sequence unambiguous; ITS = inferior temporal sulcus; PrG = precentral gyrus; for additional abbreviations see Table 2.2A.

of the sentence). Then we compared the number of context-irrelevant semantic associates for ambiguous and unambiguous conditions. Statistical analysis indicated that there were more context-irrelevant associates for ambiguous than unambiguous items ($F_{1,43} = 46.16$, $p < .001$). To investigate whether this difference in context-irrelevance could explain our fMRI results, we included the context-irrelevance score for each sentence item as a covariate in the fMRI analysis (see Appendix 2). Context-irrelevance showed no effect in LIFG or LpMTG and the effect of word-category ambiguity was very similar, irrespective of whether the context-irrelevance regressor was included as a covariate in the statistical analysis or not. This shows that the difference in the amount of context-irrelevant information evoked by ambiguous and unambiguous items can not explain our fMRI results.

Discussion

The starting point of this study was the general distinction between retrieval and unification (integration) processes in language (Vosse and Kempen, 2000; Hagoort, 2005a). We explored the hypothesis that LIFG contributes to syntactic unification operations, while the left posterior temporal gyrus subserves the retrieval of lexical-syntactic information. To do this, we exploited word-category ambiguities in sentence and word sequence contexts. First, we predicted that the syntactic unification load should be larger for the sentence than for the word sequence condition, and larger for ambiguous than unambiguous items only within the sentences. This is exactly the activation pattern we found in the left inferior frontal gyrus, supporting the hypothesis that LIFG is involved in the unification process. Second, we expected retrieval of lexical-syntactic frames to be more demanding in the ambiguous than in the unambiguous condition in both sentences and word sequences. Indeed, left posterior middle temporal gyrus (LpMTG) showed a main effect of ambiguity, suggesting that LpMTG subserves the retrieval of lexical syntactic information from the Mental Lexicon. Thus, our study could confirm the role of posterior LIFG and LpMTG in syntactic unification and lexical-syntactic retrieval processes, respectively¹.

LIFG as the unification space for language

Evidence on the involvement of LIFG in unification/integration processes in language comprehension is accumulating (Hagoort, 2005a; Willem et al., 2007). Our study confirms the contribution of the posterior LIFG to the syntactic part of the unification process. However, we do not claim that the processing role of LIFG is restricted to syntax or even to language in general (see e.g. Decety et al., 1997; Kaan and Swaab, 2002; Hamzei et al., 2003; Patel, 2003). Nor do we claim that unification is the only function of the LIFG. A different but related proposal is that LIFG is associated with selection of information among competing alternatives

¹ The effect of ambiguity in sentences that we find could be an effect occurring at the ambiguous word (two lexical frames enter Unification Space and are competing) as well as an effect at the disambiguating word (one lexical frame wins and is selected). The low temporal resolution of fMRI does not permit us to distinguish between these two possibilities. Chapter 5 looks into this issue.

(Thompson-Schill et al., 2005). This is compatible with our results, as the outcome of the unification process is dependent on a selection mechanism that chooses between different unification options (Vosse and Kempen, 2000; Hagoort, 2005b). We prefer the term “unification” over “selection”, as we think “unification” is both a more general account of LIFG functioning and a computationally explicit process. For example, unification in LIFG occurs also for information that has no stable representation in long-term memory, and thus can not be selected (just like co-speech gestures, see Willems et al., 2007). Specific brain regions (such as LIFG) probably participate in a wide range of tasks, with specialized function emerging from the unique cooperation of a network of brain areas subserving domain-general mechanisms (Mesulam, 1998; Fuster, 2001; Marcus et al., 2003). Even if the processing role of LIFG as a whole is domain-general, due to the interplay with content specific areas there might emerge some specialization for unification ‘content’, with anterior LIFG being involved with semantic operations, and posterior LIFG with syntactic operations (see Hagoort, 2005a). In our case, syntactic unification might be the result of posterior LIFG working together with representational areas in the posterior temporal lobe.

Retrieval in LpMTG: sustained activation in dynamic interplay with LIFG

We found the left posterior middle temporal gyrus (LpMTG, on the border of the inferior temporal sulcus) to be activated more strongly for ambiguous than unambiguous conditions. This ambiguity effect is what we predicted for retrieval of lexical syntactic information from the Mental Lexicon. However, in LpMTG there was more activation for sentences than for words, and the ambiguity effect in LpMTG was larger in sentences than in word sequences (see Figure 2.4). Moreover, the ambiguity effect in the word sequences was only marginally significant. One possible interpretation of this pattern of results is that LpMTG plays a role in unification that is similar to that of LIFG. However, we favor an alternative interpretation: Sentence processing requires *sustained activation* of lexical frame information. During sentence comprehension, the lexical information has to be available for longer time intervals than during the processing of random word sequences. The lexical-syntactic information is most likely not ‘copied’ from the area necessary for its retrieval (Mental Lexicon) to the area necessary for unification (Unification Space). Instead, the sustained activation of lexical frame information could be triggered by feedback from the Unification Space to the Mental Lexicon (as implemented – for independent theoretical modeling reasons – in the recently revised Unification Space model, see Vosse and Kempen, 2009). The amount and/or duration of lexical frame activation is a function of the unification load imposed by the combinatorial operations necessary for unification. This explains why the lexical activation of the noun and verb frames has to be maintained longer in sentences as the unification load increases due to a word-class ambiguity.

How could the above-mentioned sustained activation and feedback be implemented neurally? LIFG has the neural machinery to provide feedback signals

to other areas in the brain (Miller and Cohen, 2001). Research has shown that the sustained activation of representations in posterior cortices is under the dynamic frontal top-down control (Tomita et al., 1999; Fuster, 2001; Curtis and D'Esposito, 2003; Miller and D'Esposito, 2005; Fiebach et al., 2006). For the present experiment, our interpretation is that the syntactic unification process requires the dynamic interplay between posterior LIFG and LpMTG. A similar reasoning can be found in Keller and others (2001), who manipulated lexical and syntactic factors (word frequency and syntactic complexity) and found a similar interaction pattern for both temporal and frontal regions. This interpretation is also in line with a recent fMRI study suggesting context-dependent interactions or feedback mechanism between LIFG and LpMTG (Gennari et al., 2007).

Our findings with regard to ambiguity resolution are consistent with earlier neuroimaging studies. The activation in LIFG is roughly comparable, but slightly more posterior, to the region that was identified in the studies by Rodd and Zempleni (Rodd et al., 2005; Zempleni et al., 2007). Striking is the fact that in these studies the coordinates for the activation peak in LpMTG for sentence ambiguous compared to sentence unambiguous conditions are very similar (this study: [-52 -50 -8], Rodd et al. 2005: [-52 -50 -10], Zempleni et al., 2007: [-50 -48 -12]). Although Rodd also included noun-verb ambiguities in her study, the focus of both these other studies was on noun-noun ambiguities. Thus, LpMTG might be involved in the retrieval of both semantic and syntactic properties of words. The more posterior locus of our LIFG activation fits well with the idea that there might be some specialization within subregions of LIFG for unification content, with the posterior LIFG contributing to syntactic unification, while semantic unification is subserved by a more anterior portion of LIFG (Hagoort, 2005a).

Other perspectives

An alternative interpretation of the interaction effects in LIFG and LpMTG might be a general attentional difference between the processing of sentences and word sequences, resulting in larger ambiguity effects for sentences. Sentences evoked more activation in perisylvian areas than word sequences. However, it is not the case that the ambiguity effect is larger in the sentences for all brain areas involved in ambiguity processing (see for example the activity in the striatum in Figure 2.4). Moreover, the fact that our participants were highly accurate in the control task (for both sentences and word sequences) argues against an attention interpretation.

A second alternative interpretation relates to semantic ambiguity. Word-category ambiguous words are intrinsically also ambiguous semantically. Thus, besides syntactic retrieval and unification differences, our ambiguity manipulation will also lead to semantic retrieval and unification differences. With our current experiment we can not entirely rule out the possibility that our fMRI results reflect semantic rather than syntactic processes. In order to address this issue we conducted a post-test to investigate the semantic consequences of the ambiguity. Each meaning of the ambiguous word can potentially activate a distinct set of

semantic associates. The post-test showed that for the word-category ambiguous condition more associates were “context-irrelevant” in that they had to be inhibited as a consequence of the ambiguity resolution. The left inferior prefrontal cortex is sensitive to difficulty in the selection of semantic information (e.g. Thompson-Schill et al., 2005). Thus, selection/inhibition of this semantic information during sentence processing might potentially drive the observed LIFG ambiguity effects, and possibly the observed LpMTG ambiguity effects as well. However, when we included the context-irrelevance score for each sentence item as a covariate in the fMRI analysis, this did not alter the results, suggesting that the difference in the amount of context-irrelevant information evoked by ambiguous and unambiguous items cannot explain our fMRI results. More importantly, when looking at the effect of context-irrelevance itself, there was absolutely no activation in LIFG or LpMTG, not even at very low threshold levels. In other words, the post-test strongly suggests that our fMRI results are not due to the diffuse semantic consequences (more context-irrelevant associates for ambiguous words) of the word-category ambiguity. Thus, the sentence ambiguity effect in LIFG is most likely due to the increased unification demands (competition between alternatives and/or selection of the correct syntactic structure, see note 1) resulting from our syntactic manipulation (word-category ambiguity).

Additionally involved brain regions

A striking effect that we did not expect beforehand is that, in addition to LpMTG, also the right striatum showed a large effect of ambiguity. The striatum is known to be involved in selection of behaviorally relevant stimuli and inhibition of competing alternatives (e.g. Cools et al., 2004; Cools et al., 2006). The left striatum has been found to be modulated by syntactic variables (e.g. Moro et al., 2001; Friederici and Kotz, 2003). Copland and colleagues have demonstrated the importance of the striatum in ambiguity processing, using semantic priming paradigms in patients with damage to the basal ganglia. Typically striatal dysfunction spares automatic activation of multiple meanings of ambiguous words, but disrupts later language processes that require inhibition of competing alternatives (Copland et al., 2000, 2001; Copland, 2003, 2006). Our study again stresses the importance of the striatum in ambiguity processing. The ambiguity effect we find in the striatum in both sentences and word sequences might reflect the selection of one meaning/lemma of the ambiguous word and/or the inhibition of the competing alternative.

Interestingly, when processing ambiguities in sentences, not only LIFG and LpMTG are activated, but also their right-hemisphere homologue areas (see Table 2.4 and Figure 2.3C). The involvement of the right hemisphere in language processing is more and more acknowledged, especially for the processing of complex, natural language (Faust and Chiarello, 1998; Kircher et al., 2001; Jung-Beeman, 2005). Our study again emphasizes the involvement of right perisylvian areas in language comprehension in ambiguous contexts. However, our results do not clarify whether the right hemisphere areas really contribute functionally to

unification processes in language, or whether the activations we find simply reflect interhemispheric connections between homologous areas (see also Rodd et al., 2005). The precise role of the striatum, RIFG, and RpMTG in language processing remains an issue for future research.

Conclusion

In conclusion, using the computational model of syntactic parsing by Vosse and Kempen (2000) as a starting point, this study disentangled syntactic unification and lexical-syntactic retrieval processes. Posterior LIFG plays a role in the unification of words into a sentence structure, while LpMTG is involved in the retrieval of lexical-syntactic information from memory. Although their specific contributions to the process may differ, syntactic unification in language requires the dynamic interplay between both brain regions.

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Chapter 3

Effective connectivity of cortical and subcortical regions during unification of sentence structure

Abstract

In a recent fMRI study we showed that left posterior middle temporal gyrus (LpMTG) subserves the retrieval of a word's lexical-syntactic properties from the mental lexicon (long-term memory), while left posterior inferior frontal gyrus (LpIFG) is involved in unifying (on-line integration of) this information into a sentence structure (Snijders et al., 2009). In addition, the right IFG, right MTG, and the right striatum were involved in the unification process. Here we report results from a psychophysical interactions (PPI) analysis in which we investigated the effective connectivity between LpIFG and LpMTG during unification, and how the right hemisphere areas and the striatum are functionally connected to the unification network. LpIFG and LpMTG both showed enhanced connectivity during the unification process with a region slightly superior to our previously reported LpMTG. Right IFG modulated right temporal activity in response to unification just as LpIFG was modulating left temporal activity. Furthermore, the striatum showed enhanced coupling to LpIFG and LpMTG during unification. We conclude that bilateral inferior frontal and posterior temporal regions are functionally connected during sentence-level unification. Cortico-subcortical connectivity patterns suggest cooperation between inferior frontal and striatal regions in performing unification operations on lexical-syntactic representations retrieved from LpMTG.

This chapter is a modified version of:

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Introduction

In order to comprehend language we have to retrieve information about single words from long-term memory (mental lexicon) and combine ('unify') this information into representations that span multiple words (Marslen-Wilson, 1987; Levelt, 1992; Hagoort, 2005a). Both memory and unification processes occur in parallel at the semantic (conceptual) and at the syntactic (structural) level (Jackendoff, 2002). Current syntactic theories tend to be lexicalist in nature: many properties relevant for structural integration are specified in the mental lexicon, rather than being computed by abstract syntactic rules. Thus, structured syntactic properties of words (treelets; including, for example, word class and gender information) are retrieved from the lexicon, and the only remaining 'rule of grammar' is the combinatorial process of unification ('Unify Pieces' in Jackendoff, 2002; somewhat similar to 'Merge' in Chomsky's Minimalist Program Chomsky, 1995).

In a recent fMRI study, we showed that the left posterior middle temporal gyrus (LpMTG) subserves the retrieval of lexical-syntactic information from the mental lexicon, while the left posterior inferior frontal gyrus (LpIFG) is involved in combining this information on-line into a sentence structure (Snijders et al., 2009, see Chapter 2). The lexical-syntactic information here specifies the possible structural environment of a lexical item (Vosse and Kempen, 2000). In the Snijders et al. study (2009), subjects read sentences and word sequences containing word-category (noun/verb) ambiguous words at critical positions. Regions contributing to the syntactic unification process should show enhanced activation for sentences compared to words, and increased activation for ambiguous compared to unambiguous conditions only when the target words are presented within a sentence, but not when presented in a random-word sequence. The LpIFG showed exactly this predicted pattern, indicating that it is involved in syntactic unification. Presentation of a noun-verb ambiguous word in a neutral context triggers the retrieval of both the noun and the verb version of the ambiguous word (Seidenberg et al., 1982; Duffy et al., 1988). Thus, regions subserving the retrieval of lexical-syntactic information from memory should show more activation for ambiguous than unambiguous conditions (i.e., main effect over both sentences and random-word sequences). This pattern was observed in the LpMTG, signaling its involvement in the retrieval process. The pattern of results suggested a dynamic interplay between these two regions in the unification process (Snijders et al., 2009). Additionally, we found activations in right inferior frontal gyrus (RIFG) and right mid-posterior middle temporal gyrus (RpMTG) for ambiguous compared to unambiguous conditions when presented in sentences but not when presented in word sequences. We also found an effect of ambiguity in the striatum (part of the basal ganglia, BG) in both word sequence and sentence contexts (for further details, see Chapter 2).

A number of studies, predominantly outside the language domain, have shown that the sustained activation of representations in posterior cortices is under the dynamic top-down control of frontal cortex (Tomita et al., 1999; Fuster, 2001;

Miller and Cohen, 2001; Curtis and D'Esposito, 2003; Miller and D'Esposito, 2005; Fiebach et al., 2006; Fuster, 2008). Furthermore, these representations can be manipulated, flexibly updated, and integrated over time in the frontal cortex (Thompson-Schill et al., 1997; Fuster, 2008). Syntactic unification might, therefore, be the result of LpIFG interacting with representational brain regions in the posterior temporal lobe (Snijders et al., 2009). This hypothesis was not directly tested in our previous fMRI study where we only examined the pattern of activation, rather than directly testing whether LpIFG and LpMTG were functionally connected during syntactic unification. If lexical-syntactic representations in LpMTG are modulated by frontal top-down processes, then we should observe evidence of "crosstalk" between LpIFG and LpMTG during language processing – evidence of effective connectivity - rather than mere co-activation of the two regions of interest. The aim of the current study, therefore, was to explicitly examine the connectivity between LpIFG and LpMTG during unification processes by testing for psychophysiological interactions (PPI) (Friston et al., 1997). We tested which brain areas showed enhanced coupling with LpIFG and LpMTG during sentence-level unification. We hypothesized that effective connectivity between LpIFG and LpMTG would be larger in ambiguous than in unambiguous sentences, and that the ambiguity effect would be absent for word sequences.

Classically, language processing has been localized in the left frontal and temporal brain regions. The role of right-hemisphere (RH) regions and the basal ganglia in language processing is still a matter of debate (RH e.g.: Faust and Chiarello, 1998; Kircher et al., 2001; Bookheimer, 2002; Jung-Beeman, 2005; BG e.g.: Copland et al., 2000; Lieberman, 2001; Friederici et al., 2003; Frisch et al., 2003; Ullman, 2004; Crosson et al., 2007). In the present study we also examined if the RIFG, RpMTG, and the striatum (regions showing an ambiguity effect in our previous study, see above) are functionally connected to the unification network. We were interested in whether 1) the right-hemispheric regions show connectivity patterns similar to their left-hemispheric counterparts, 2) the striatum shows enhanced connectivity to LpIFG and/or LpMTG during ambiguity processing, and 3) if this enhanced connectivity differs in a sentence versus a word-list context.

Thus, the goal of the current study was to identify how combinatorial processes in language modulate the connectivity between left frontal and temporal regions in the brain, and how the RH and the striatum are functionally connected to the unification network. More specifically, we investigated how word-category ambiguity in a sentence versus a word context alters the connectivity in cortical and subcortical networks.

Materials and Methods

Participants

Twenty-eight right-handed healthy volunteers (14 females, aged 18-35) participated in the experiment. All participants were native Dutch speakers with no

history of neurological illness or head injury. Subjects were paid for their participation. Six additional subjects were scanned but excluded from analysis because of excessive movement in the MR scanner (2 subjects) or poor task performance (4 subjects, see below). The study was approved by the local ethics committee and all participants gave written informed consent prior to the experiment in accordance with the Declaration of Helsinki.

Stimulus material

The stimuli consisted of 68 (Dutch) sentences (S) and 68 matched scrambled sequences of Dutch words (W). Both the Sentences and the Word sequences contained a critical word that was either word-class (noun/verb) ambiguous (A) or unambiguous (U). The critical word in the sentences was disambiguated by the continuation of the sentence into either a noun (n) or a verb (v) reading. In total, this resulted in eight possible conditions: SAn, SAv, SU_n, SUv, WAn, WAv, WU_n, WUv (see Table 3.1 for examples).

The ambiguous words were equibaised, that is, there was no strong preference for the noun over the verb interpretation or vice versa. This was brought out both by lexical frequencies as occurring in Dutch lexical databases (Baayen et al., 1993;

Table 3.1.

Example of the experimental materials, with the critical word *bewijzen* (*evidence/to prove*).

SAn: Sentence Ambiguous (noun context)

Zodra jullie bewijzen_(n/v) leveren kunnen we beginnen.
*As-soon-as you evidence*_(n/v) *provide can we start.*
*(As soon as you provide evidence*_(n/v) *we can start.)*

SUn: Sentence Unambiguous (noun context)

Zodra jullie kopij_(n) leveren kunnen we beginnen.
*As-soon-as you copy*_(n) *provide can we start.*
*(As soon as you provide copy*_(n) *we can start.)*

SAv: Sentence Ambiguous (verb context)

Zodra jullie bewijzen_(n/v) dat hij erbij betrokken is arresteren we hem.
*As-soon-as you prove*_(n/v) *that he in-it involved is arrest we him.*
*(As soon as you prove*_(n/v) *that he is involved we will arrest him.)*

SUv: Sentence Unambiguous (verb context)

Zodra jullie beweren_(v) dat hij erbij betrokken is arresteren we hem.
*As-soon-as you claim*_(v) *that he in-it involved is arrest we him.*
*(As soon as you claim*_(v) *that he is involved we will arrest him.)*

WAn: Words Ambiguous (derived from SAn)

genoemd tegen bewijzen_(n/v) uit helaas gezeten jullie
*named against proof/prove*_(n/v) *from alas seated you*

WU_n: Words Unambiguous (derived from SUn)

genoemd tegen kopij_(n) uit helaas gezeten jullie
*named against copy*_(n) *from alas seated you*

WAv: Words Ambiguous (derived from SAv)

in nogal bewijzen_(n/v) meestal maar dit in struikelen hem verschil opeens
*in quite proof/prove*_(n/v) *mostly but this in stumble him difference suddenly*

WUv: Words Unambiguous (derived from SUv)

in nogal beweren_(v) meestal maar dit in struikelen hem verschil opeens
*in quite claim*_(v) *mostly but this in stumble him difference suddenly*

Beek et al., 2001), as well as by a pre-test, on a different group of participants, where subjects had to complete sentence fragments ending with the ambiguity (e.g. “*Zodra jullie bewijzen ...*”). The ambiguous sentences were constructed such that both categories of the critical word fitted syntactically as well as semantically with the initial part of the sentences (up to and including the critical word); the sentences were disambiguated by the subsequent part of the sentence (*after* the ambiguous word; see Table 3.1 for an example). Word sequences were constructed from the sentences by substituting every word (except the critical word) by a different word, matched for length, frequency, and word category, and subsequently scrambling the order of the words in the sequence (except the critical word). For a full description of experimental materials, see Chapter 2 and Appendix 1A.

Procedure

Stimuli were presented using the serial visual presentation method (i.e. word by word in the middle of the screen) using Presentation software (Version 9.13, www.neuro-bs.com). Every word remained on the screen for 300 ms, with a 200 ms inter-word-interval. Between the sequences of words (sentences or random), a visual fixation cross was presented for 5-8 seconds (low-level baseline). The participants were instructed to read each sentence/sequence carefully and attentively, and were told that after the experiment some questions concerning the experiment would have to be answered. The participants' task was spotting the consonant-strings (e.g., *cdsn*l), that were presented in 36 of the fillers (18 sentences and 18 sequences). This simple control task was added to check whether subjects were paying attention. Subjects were defined as poor task performers if they made more than five errors (missing hits and false alarms) on the task, suggesting that these subjects did not pay enough attention to the stimuli.

Every subject saw 68 sentences and 68 word sequences (ambiguous/unambiguous; in noun/verb version), intermingled with 56 fillers (28 sentences and 28 sequences). No subject encountered the same critical word or context sentence/sequence more than once. Stimuli were presented in mini-blocks of three to four sentences or word sequences. All mini-blocks were shorter than 40 seconds. Before each block the label “Zinnen:” (“Sentences:”) or “Woorden:” (“Words:”) appeared on the screen (for 1.5 seconds) to indicate the condition of the following mini-block, which started after a fixation cross of 1-3 seconds. We expected the labels to encourage (“Sentences”) or discourage (“Words”) attempts to syntactically/semantically integrate the stimulus items in the upcoming mini-block. The ambiguous/unambiguous and verb/noun conditions were intertwined within the mini-blocks in a pseudo-randomised presentation order.

fMRI Data Acquisition

During the sentence/sequence presentation we acquired T2*-weighted EPI-BOLD fMRI data with a SIEMENS Trio 3T MR-scanner using an ascending slice acquisition sequence (volume TR = 2 s, TE = 35 ms, 90 degree flip-angle, 29

slices, slice-matrix size = 64 x 64, slice thickness = 3 mm, slice gap = 0.5 mm, FOV = 224 mm, voxel-size = 3.5 x 3.5 x 3.0 mm). At the end of the scanning session, a structural MR image volume was acquired for which a high-resolution T1-weighted 3D MPRAGE sequence was used (TE = 3.93 ms, 8 degree flip-angle, 192 sagittal slices, slice thickness = 1.0 mm, voxel-size = 1 x 1 x 1 mm).

Data Analysis

To enable comparisons with the published conventional analysis of this study (Snijders et al., 2009) we preprocessed the data in the identical manner. See Chapter 2 for the analysis and results of the conventional subtraction analysis. The group results of this analysis were used for choosing the regions of interest (ROIs) for the connectivity analysis.

Image preprocessing and statistical analysis were performed using Statistical Parametric Mapping (SPM2; www.fil.ion.ucl.ac.uk/spm). The first five image volumes were discarded in order to avoid transient non-saturation effects. The functional EPI-BOLD images were realigned, slice-time corrected, and the subject-mean functional MR images were co-registered with the corresponding structural MR images using mutual information optimization. Subsequently, functional images were normalized to a Montreal Neurological Institute (MNI)-aligned echo planar imaging template (based on 28 male brains acquired on the Siemens Trio at the Donders Centre for Cognitive Neuroimaging, Nijmegen) and resampled to an isotropic voxel size of 2 mm³. Finally, the normalized images were spatially filtered by convolving the functional images with an isotropic 3D Gaussian kernel (10 mm full width at half maximum).

Regions of interest (ROIs)

Regions of interest were chosen based on involvement in the syntactic unification process (Snijders et al., 2009). Seven regions of interest (ROIs) were specified for each individual: the left posterior inferior frontal gyrus (LpIFG), the left anterior inferior frontal gyrus (LaIFG), the left posterior middle temporal gyrus (LpMTGi), the right inferior frontal gyrus (RIFG), the right mid-posterior middle temporal gyrus (RpMTG), the right striatum (Rstriatum), and the left striatum (Lstriatum). Figure 3.1 illustrates the spatial location of these ROIs on a model brain. The ROIs were defined as 8-mm radius spheres with the origin at specific coordinates based on the group-analysis results of (Snijders et al., 2009, see Chapter 2). For LpIFG, RIFG, and RpMTG peak coordinates were taken from the sentence-ambiguous > sentence-unambiguous (SA>SU) contrast. For both the SA>SU contrast and the main effect of ambiguity (A > U) the peak voxel in LpMTG was at [-52 -50 -8], which was taken as ROI centre for LpMTG. As this ROI was located on the border of the inferior temporal sulcus, we will refer to it as LpMTGi from now on. The right striatum showed a main effect of ambiguity (Snijders et al., 2009), we used the peak voxel ([24 0 8]) for ROI definition. Additionally the left hemispheric counterpart of the right striatum ROI was added as ROI (Lstriatum). Furthermore we added a more anterior part of the LIFG as a control ROI (LaIFG, [-42 26 6]).

A meta-analysis (Bookheimer, 2002) suggests that activations related to semantic processing in LIFG are centered around these coordinates (Petersson et al., 2004). All ROIs are displayed in Figure 3.1; see the figure caption for MNI coordinates.

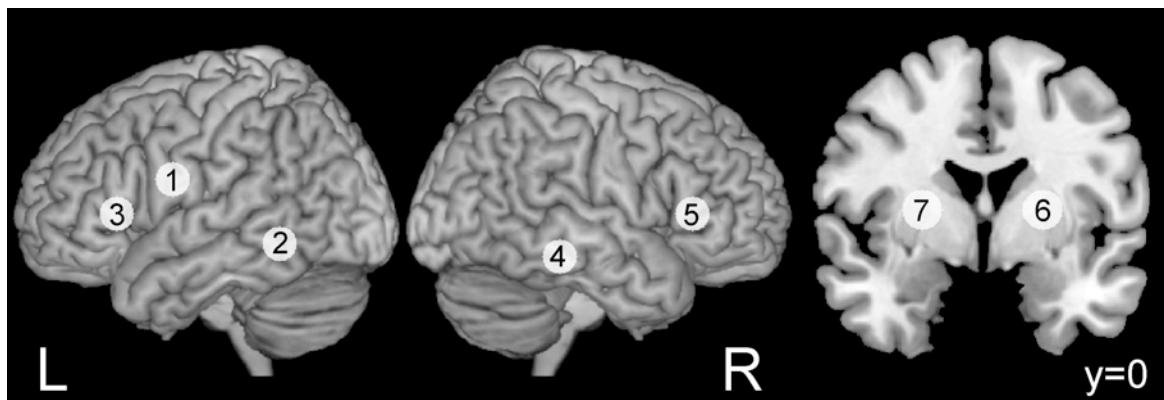


Figure 3.1.

Regions of interest (ROIs). Cortical ROIs projected onto a rendered template brain surface in MNI stereotactic space (left), and striatal ROIs displayed on a coronal view of the brain (right). All ROIs are 8 mm spheres around certain peak coordinates. (1) LpIFG [-44 0 22]; (2) LpMTGi [-52 -50 -8]; (3) LaIFG [-42 26 6]; (4) RpMTG [48 -34 -14]; (5) RIFG [46 28 6]; (6) Rstriatum [24 0 8]; (7) Lstriatum [-24 0 8].

Psychophysiological interactions analysis

In the current study we explored whether the ROIs show differential coupling with other brain regions depending on the experimental conditions, using the psychophysiological interactions (PPI) described by (Friston et al., 1997). The statistical model testing for psychophysiological interactions is a simple regression model of effective connectivity (Friston, 2002). Friston and colleagues define the contribution of a seed region to another region as the degree to which the activity in the second region can be predicted on the basis of activity of the first (that is, the activity of one region regressed on the activity of another region). A psychophysiological interaction reflects the *change* in this contribution depending on an experimental manipulation (Friston et al., 1997; Friston, 2002). Thus, a psychophysiological interaction expresses which brain regions (on a voxel-by-voxel basis) show an enhanced coupling (as evidenced by a steeper regression slope) with a region of interest (seed region) during one experimental condition compared to another condition (Friston et al., 1997). There are two possible interpretations of a PPI (see Friston et al., 1997): a condition change (in our case: ambiguity) modulates the degree to which activity in one region can be predicted on the basis of activity in the seed region, or, the seed region modulates the response of another region to the psychological factor (ambiguity).

For every ROI, two PPI analyses were performed: one looking for enhanced coupling of the seed region with other regions in the brain for sentence-ambiguous compared to sentence-unambiguous conditions (SA>SU), and one looking for enhanced coupling of the seed region with other regions in the brain for word-ambiguous compared to word-unambiguous conditions (WA>WU).

For each subject and for each ROI, the physiological activity of the seed regions was summarized as the first eigenvariates of the time series of all active voxels within an 8 mm radius sphere centered on the most significant voxel within the ROI. Significance of voxels was based on the following contrasts: for LIFG and RIFG we used the Sentences>Words contrast to identify active voxels, while for LpMTGi, RpMTG, and the striatum the Ambiguous>Unambiguous contrast was used (both $p < .05$ uncorrected). When there were less than 5 voxels in the ROI that met the above criteria, the statistical threshold was eased on an individual subject basis. To estimate underlying neuronal activity the physiological activity of the seed region was deconvolved (Gitelman et al., 2003).

The PPI regressor was obtained by multiplying the estimated neuronal activity from the seed region with a vector coding for effects of ambiguity within word lists or sentences (SA > SU: 1 for ambiguous-sentence condition, -1 for unambiguous-sentence condition; WA > WU: 1 for ambiguous-word condition, -1 for unambiguous-word condition). Just as for the more conventional subtraction analysis, for the PPI analysis the fMRI data were analyzed statistically using the general linear model and statistical parametric mapping (Friston et al., 1995) in a 2-step mixed-design procedure (Friston et al., 2007). At the first (single-subject) level, activity was modeled (on a voxel-by-voxel basis) using three predictor variables: the experimental contrast (SA > SU or WA > WU), the estimated neuronal activity from the seed region, and the interaction of the two (PPI regressor). We temporally (re)convolved the explanatory variables with the canonical hemodynamic response function provided by SPM2. We included the realignment parameters for movement artifact correction and a temporal high-pass filter (cut-off 128 s) to account for various low-frequency effects as effects of no interest. Temporal autocorrelation was modeled as a first-order plus white noise autoregressive process.

Then, for each seed region, individual PPI contrast images were entered into a one-sample t -test at the second (group) level. Whole brain family-wise error correction for multiple comparisons was applied by combining a significance level of $p < .005$, uncorrected at the voxel-level, with a cluster extent threshold of $p < .05$ corrected for multiple comparisons (Forman et al., 1995; Friston et al., 1996).

Anatomical inference

All local maxima are reported as MNI coordinates (Evans et al., 1993). Relevant anatomical landmarks were identified and Brodmann areas were defined using the Atlas of the Human Brain (Mai et al., 2004) and MRIcro (Rorden and Brett, 2000) using the AAL template (Tzourio-Mazoyer et al., 2002) and the Talairach Daemon (Lancaster et al., 2000).

Results

Left hemisphere

Seed region: LpIFG

We hypothesized the LpIFG would modulate the activity in the LpMTG in response to the unification process. Indeed, LpIFG showed an enhanced coupling during sentence-ambiguous compared to sentence-unambiguous conditions with a region in LpMTG, bordering the superior temporal sulcus (LpMTGs; see Figure 3.2A and Table 3.2). The activated region in LpMTGs was slightly superior to our region of interest in LpMTG (our ROI, LpMTGi, being located on the border of the inferior temporal sulcus). See Figure 3.3A for a comparison of the two regions. No regions showed larger connectivity with LpIFG for word-ambiguous compared to word-unambiguous conditions. Thus, only in a sentence context the LpIFG is modulating activity in LpMTGs more for ambiguous than unambiguous items.

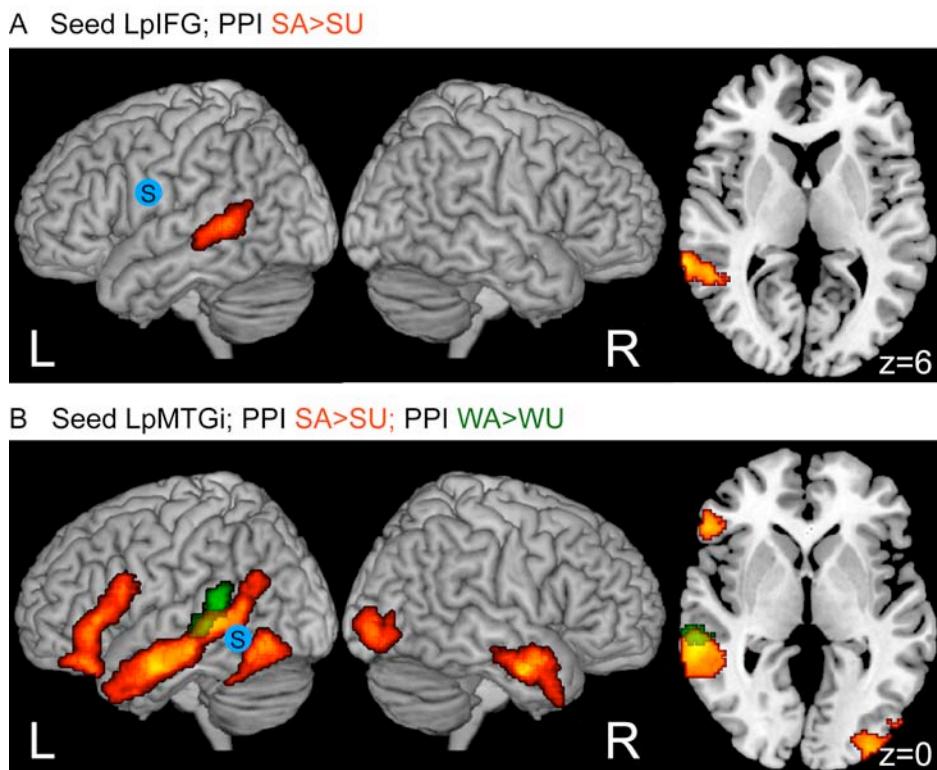


Figure 3.2.

PPI connectivity analysis results for left hemispheric cortical seed regions. Enhanced connectivity with the seed region (S, blue) for sentence-ambiguous (SA) compared to sentence-unambiguous (SU) conditions shown in yellow/red, and enhanced connectivity with the seed region for word-ambiguous (WA) compared to word-unambiguous (WU) conditions in green. Seed regions: (A) LpIFG; (B) LpMTGi. Significant activations projected onto a rendered template brain surface in MNI stereotactic space (left), and displayed on an axial view of the brain (right). Activations shown at voxel-level $P_{\text{uncorr}} < .005$, cluster-level $P_{\text{FWE}} < .05$.

Table 3.2. PPI connectivity results for left hemispheric cortical seed regions (LpIFG, LpMTGi, and LaIFG).

Seed	PPI	Region	BA	Cluster Size	Cluster p (corrected)	Voxel T^{27} value	x	y	z
LpIFG	SA>SU	<i>L posterior MTG/STS</i>		443	.002				
[-44 0 22]		L post-MTG/STS	22			4.76	-68	-40	6
BA 44/6/9		L post-MTG	21			3.91	-54	-50	6
		L mid-MTG	21			3.73	-68	-28	0
	WA>WU	<i>no significant clusters</i>							
LpMTGi	SA>SU	<i>LMTG</i>		2383	<.001				
[-52 -50 -8]		L mid-M/ITG	20/21			6.21	-56	-24	-14
BA 37/20		L ant-MTG	21			5.32	-56	-2	-24
		L mid/post-MTG	21/22			4.93	-62	-34	0
		<i>LIFG</i>		1005	<.001				
		L post-IFG(Oper)	44			4.54	-46	12	20
		L ant-IFG(Orb)	47			4.50	-38	36	-20
		L IFG(Tri)	45			4.46	-54	28	2
		<i>R anterior M/ITG</i>		679	<.001				
		R ant-M/ITG	20/21			5.99	52	-6	-26
		RMTG/TempPole	21			5.43	62	4	-18
		R mid-M/ITG	20/21			4.87	50	-16	-20
		<i>LpITG / LFuG</i>		573	.001				
		L ITG/IOcG/FuG	37			4.79	-44	-62	-10
		L FuG	37			4.51	-42	-56	-20
		L FuG	19/37			4.19	-40	-64	-18
		<i>ROcG</i>		439	.006				
		R IOcG	19			4.24	42	-82	-10
		R IOcG	18/19			4.20	36	-92	-4
		R OcG/post-ITG	19			3.77	52	-78	-2
	WA>WU	<i>L mid/post M/STG</i>		382	.013				
		L post-M/STG	22/42			4.25	-56	-38	12
		L mid-MTG	21			4.00	-60	-28	-4
		L mid-M/STG	21/22			3.28	-56	-30	4
LaIFG	SA>SU	<i>no significant clusters</i>							
[-42 26 6]	WA>WU	<i>no significant clusters</i>							
BA 45/47									

Note: Significant activation peaks > 8 mm apart (voxel-level $p < .005$ uncorrected, cluster-level $p < .05$ FWE corrected). Multiple peaks within a single activation cluster are shown indented. BA = Brodmann's area; T^{27} value = T value for 27 degrees of freedom; x,y,z = the original SPM x,y,z coordinates in millimeters of the MNI space; SA = sentence ambiguous; SU = sentence unambiguous; WA = word ambiguous; WU = word unambiguous; L = left, R = right, post = posterior; ant = anterior; I = inferior; M = middle; S = superior; TG = temporal gyrus; FG = frontal gyrus, Oper = pars opercularis; Orb = pars orbitalis; Tri = pars triangularis; TS = temporal sulcus; TempPole = temporal pole; FuG = fusiform gyrus; OcG = occipital gyrus.

Seed region: LaIFG

To explore whether other regions within LIFG are in a similar way modulating posterior regions during unification, we included another region of the LIFG, which was located more anterior than LpIFG, to serve as a control ROI (LaIFG, see methods). LaIFG showed no enhanced coupling with other brain regions for sentence-ambiguous compared to sentence-unambiguous conditions, nor for word-ambiguous compared to word-unambiguous conditions (see Table 3.2). Thus, the enhanced connectivity between LpIFG and LpMTGs is specific to the posterior part of LIFG.

Seed region: LpMTGi

LpMTGi showed more connectivity for sentence-ambiguous than for sentence-unambiguous conditions with left inferior frontal gyrus (LIFG), as well as with left middle temporal gyrus (LMTG, superior to ROI), right anterior middle temporal gyrus (RaMTG), left posterior inferior temporal gyrus (LpITG) and right occipital gyrus (ROcG; see Figure 3.2B and Table 3.2). The activated region in LpITG coincides with the so-called visual word form area (VWFA, see e.g. (McCandliss et al., 2003). For word-ambiguous compared to word-unambiguous conditions LpMTGi showed enhanced coupling with a region in left mid MTG / posterior STG (see Figure 3.2B (green) and Table 3.2).

Thus, for ambiguous sentences there is more connectivity between LpMTG and LIFG than for unambiguous sentences. The enhanced connectivity between LIFG and LpMTG as a result of word-category ambiguity (or ambiguity resolution) was only evident in the sentence, but not in the word sequence, condition. Both LpIFG and LpMTGi are modulating the activity of a region that is situated slightly posterior to our ROI in LpMTGi (see Figure 3.3A). Figure 3.3B displays the time-course of LpMTGi and the more superior LpMTGs for SA, SU, WA, and WU conditions. An ANOVA on the mean contrast estimates of LpMTGi and LpMTGs showed that LpMTGs was activated more strongly than LpMTGi for both word sequence and sentence conditions ($F_{\text{region}}(1,27) = 31.71, p < .001$, see Figure 3.3B). Furthermore, the grammaticality effect (Sentences > Word sequences) was larger in LpMTGs ($F_{\text{region} \times \text{gram}}(1,27) = 11.36, p = .002$; $F_{\text{LpMTGi: gram}}(1,27) = 50.72, p < .001$; $F_{\text{LpMTGs: gram}}(1,27) = 111.97, p < .001$), while the main effect of ambiguity was only significant in LpMTGi ($F_{\text{region} \times \text{amb}}(1,27) = 8.65, p = .007$; $F_{\text{LpMTGi: amb}}(1,27) = 13.38, p = .001$; $F_{\text{LpMTGs: amb}}(1,27) = 1.20, p = .283$). For both regions there was an ambiguity by grammaticality interaction ($F_{\text{region} \times \text{amb} \times \text{gram}} < 1$; $F_{\text{LpMTGi: amb} \times \text{gram}} = 6.98, p = .014$; $F_{\text{LpMTGs: amb} \times \text{gram}} = 7.47, p = .011$), with a significant effect of ambiguity in the sentence condition (SA>SU: LpMTGi: $T(27) = 4.72, p < .001$; LpMTGs: $T(27) = 2.53, p = .009$; WA>WU: LpMTGi: $T(27) = 1.40, p = .086$; LpMTGs: $T(27) = -1.18, p = .125$).

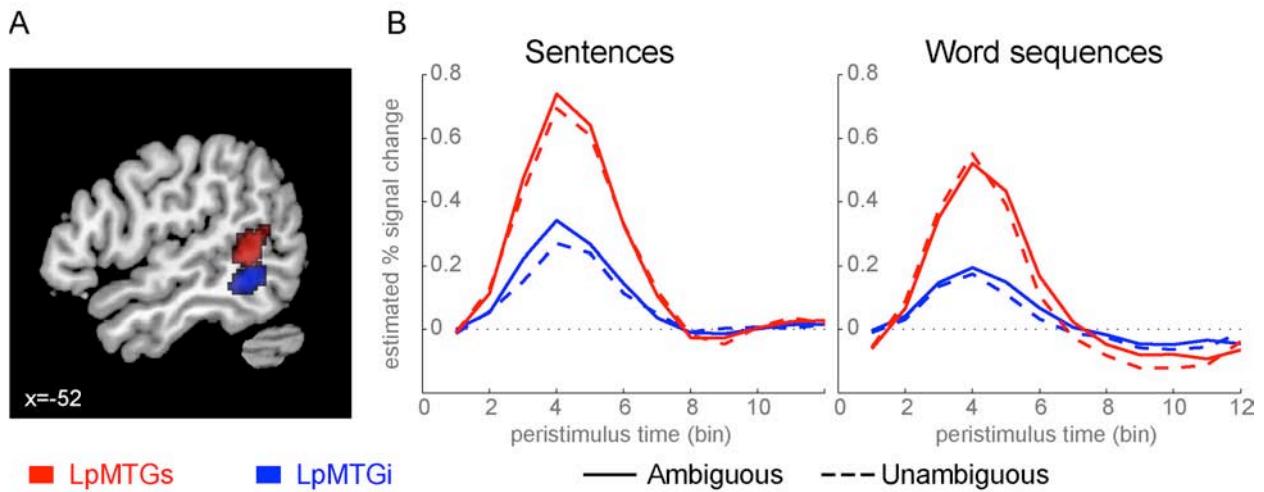


Figure 3.3.

Comparison of activations in LpMTGi and LpMTGs. (A) Main effect of ambiguity in LpMTGi is shown in blue (see Chapter 2). The region in LpMTGs that is modulated by LpIFG for sentence-ambiguous (SA) compared to sentence-unambiguous (SU) conditions is shown in red (see Figure 3.2A). Activations are displayed on a template, sagittal view, voxel-level $P_{\text{uncorr}} < .005$. (B) Peri-stimulus time histograms for LpMTGs (red) and LpMTGi (blue), showing Ambiguous (solid lines) and Unambiguous (striped lines) conditions in Sentence (left) and Word sequence (right) context. Peri-stimulus time histograms were extracted using a finite impulse response (FIR) method implemented in MarsBaR (<http://marsbar.sourceforge.net/>). Every time bin consists of 1 TR (2 seconds).

Right hemisphere

Seed region: RIFG

The RIFG showed more connectivity for sentence-ambiguous compared to sentence-unambiguous conditions with the precuneus, LpMTGs, RpMTGs, and R anterior/mid MTG (see Table 3.3 and Figure 3.4A). Note that the coupling between RIFG and LIFG was not modulated by sentence ambiguity. RIFG did not show larger connectivity to other brain regions for word-ambiguous compared to word-unambiguous conditions.

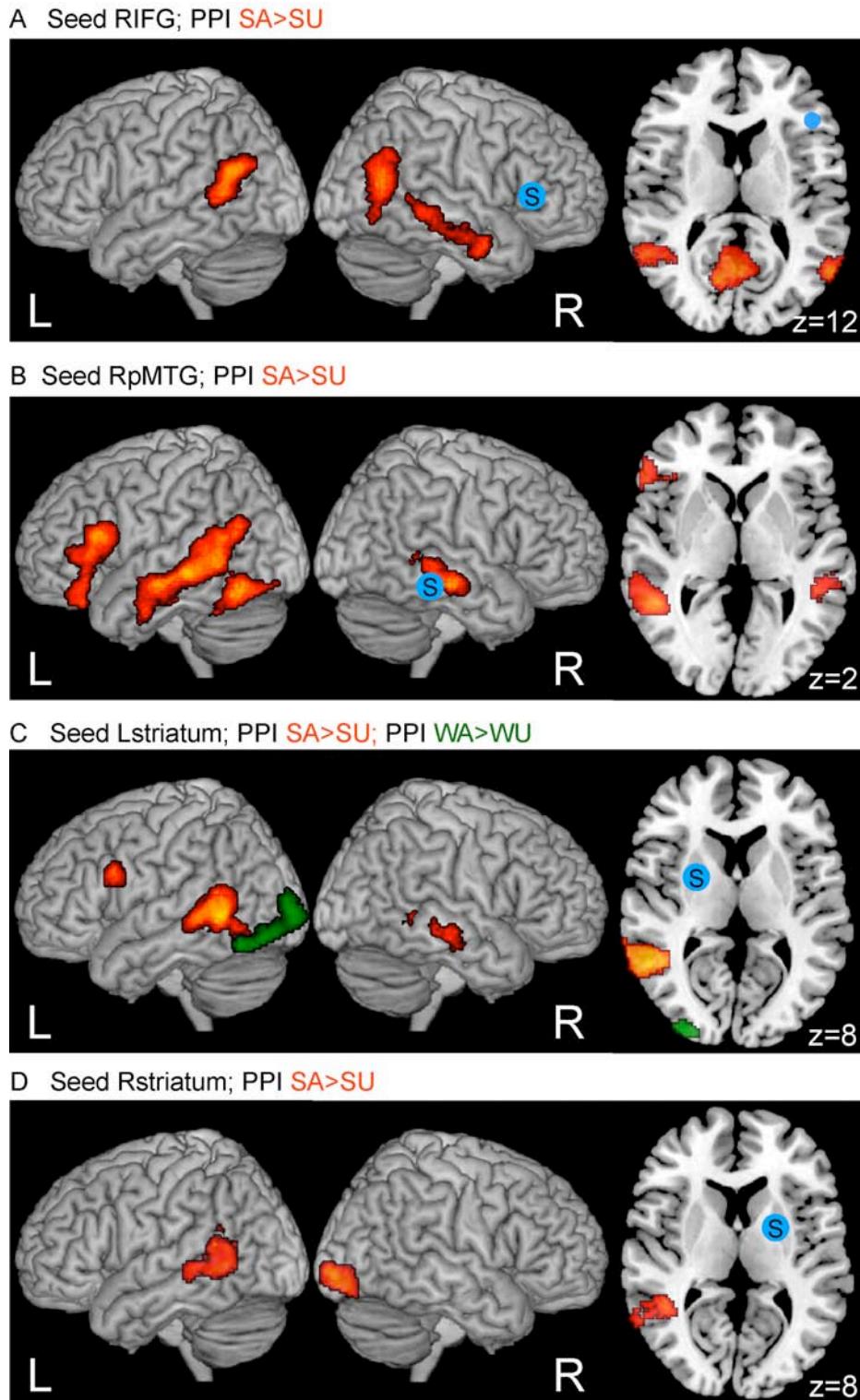
Seed region: RpMTG

RpMTG showed enhanced coupling for sentence-ambiguous compared to sentence-unambiguous conditions with LMTG, LIFG, the left fusiform gyrus (LFuG, VWFA), and R mid MTG (see Table 3.3 and Figure 3.4B). RpMTG showed no larger connectivity with other brain regions for word-ambiguous compared to word-unambiguous conditions.

Table 3.3. PPI connectivity results for right hemispheric cortical seed regions (RIFG, RpMTG)

Seed	PPI	Region	BA	Cluster Size	Cluster p (corrected)	Voxel T^{27} value	x	y	z
RIFG	SA>SU	<i>Calcarine Gyrus / Pcusn</i>		1299	<.001				
[46 28 6]		L CalcG	17/18			4.79	-12	-70	12
BA 45		Lingual G/CalcG	17			4.76	0	-64	10
		Pcun/CalcG	30/17/23			4.00	-4	-56	12
		<i>L posterior M/STG</i>		853	<.001				
		L post-MTG	39/21/37			4.37	-50	-60	20
		L post-MTG/STS	21/22			4.01	-52	-50	8
		L post-MTG/STS	21/37			3.98	-56	-54	14
		<i>R posterior M/STG</i>		541	.001				
		R post-M/STG	39			4.88	58	-66	22
		R post-MTG	37			4.67	58	-62	10
		R post-MTG/AngG	39			3.46	52	-72	26
		<i>R anterior/mid MTG</i>		346	.018				
		R ant-MTG	21			3.98	52	-2	-24
		R mid-MTG	20/21			3.75	68	-22	-18
		R ant-ITG	20/21			3.72	58	-6	-30
	WA>WU	<i>no significant clusters</i>							
RpMTG	SA>SU	<i>LMTG</i>		2232	<.001				
[48 -34 -14]		L mid-MTG	20			5.57	-50	-20	-16
BA 20		L mid/post-MTG	21			5.47	-56	-32	-6
		L post-MTG	21/37			4.96	-48	-48	2
		<i>LIFG</i>		1017	<.001				
		L post-IFG(Tri/Oper)	44/45			4.80	-44	22	18
		L post-IFG/FOp	44/45			3.96	-36	18	18
		L ant-IFG(Orb)	47			3.82	-42	36	-24
		<i>LFuG</i>		626	<.001				
		L FuG / L ITG	37			4.82	-46	-60	-18
		L IOcG	37/19			4.32	-48	-68	-14
		L FuG	37			3.90	-34	-56	-16
		<i>R mid MTG</i>		599	<.001				
		R mid-MTG	20/21			5.18	56	-22	-14
		R mid-MTG	20/21			4.22	48	-26	-10
		R mid-MTG	21/20/37			3.98	48	-34	-8
	WA>WU	<i>no significant clusters</i>							

Note: Significant activation peaks > 8 mm apart (voxel-level $p < .005$ uncorrected, cluster-level $p < .05$ FWE corrected). Multiple peaks within a single activation cluster are shown indented. Pcusn = precuneus; CalcG = calcarine gyrus; AngG = angular gyrus; FOp= frontal operculum; for additional abbreviations see Table 3.2.

**Figure 3.4.**

PPI connectivity analysis results for subcortical and right hemispheric cortical seed regions. Enhanced connectivity with the seed region (S, blue) for sentence-ambiguous (SA) compared to sentence-unambiguous (SU) conditions shown in yellow/red, and enhanced connectivity with the seed region for word-ambiguous (WA) compared to word-unambiguous (WU) conditions in green. Seed regions: (A) RIFG; (B) RpMTG; (C) Lstriatum; (D) Rstriatum. Significant activations projected onto a rendered template brain surface in MNI stereotactic space (left), and displayed on an axial view of the brain (right). Activations shown at voxel-level $P_{\text{uncorr}} < .005$, cluster-level $P_{\text{FWE}} < .05$.

*Subcortical regions**Seed regions: Striatum*

The PPI results for the L+R striatum can be seen in Table 3.4 and Figure 3.4C/D. Both right and left striatum showed enhanced coupling with several brain regions for ambiguous compared to unambiguous conditions.

For sentence-ambiguous compared to sentence-unambiguous conditions Rstriatum showed a larger connectivity with LpMTGs and ROcG, while the enhanced coupling with LIFG did not survive multiple comparisons correction. Lstriatum showed a larger connectivity with LpMTGs, RMTG, and LpIFG for sentence-ambiguous compared to sentence-unambiguous conditions. For word-ambiguous compared to word-unambiguous conditions, connectivity was significantly enhanced between Lstriatum and LOcG/LpITG only (see Table 3.4 and Figure 3.4C).

Table 3.4. PPI connectivity results for subcortical seed regions (Rstriatum, Lstriatum).

PPI	Region	BA	Cluster	cluster P (corrected)	Voxel T^{27}	x	y	z
			Size		value			
R striatum [24 0 8]	SA>SU	<i>LpMTG / STS</i>	910	<.001				
		L post-STS	39/21		5.31	-40	-50	16
		L post-STS	21		4.31	-44	-44	8
		L post-MTG	37/21		4.18	-44	-52	0
		<i>ROcG</i>	468	.001				
		R IOcG	18		4.67	30	-94	-4
		R IOcG	19		4.37	44	-86	-10
		R IOCG/Lingual G	18		4.35	28	-90	-12
	WA>WU	<i>no significant clusters</i>						
L striatum [-24 0 8]	SA>SU	<i>L posterior MTG</i>	1244	<.001				
		L post-MTG	21/37		5.38	-54	-52	0
		L post-MTG	21/37		5.14	-46	-50	2
		L post-MTG/STS	21		4.57	-50	-52	12
		<i>R mid/posterior MTG</i>	417	.005				
		R mid-MTG	20/21		4.77	50	-22	-10
		R mid-M/ITG	20/37		4.27	46	-30	-14
		R post-MTG	21		3.76	50	-46	-2
		<i>L posterior IFG</i>	337	.015				
		L post-IFG(Oper)	44		4.72	-38	10	28
		L post-IFG(Oper/Tri)	44		3.93	-46	12	28
	WA>WU	<i>L OcG / L posterior ITG</i>	627	.001				
		L IOcG	18/19		4.36	-38	-88	-10
		L IOcG/FuG	19		4.34	-44	-82	-12
		L FuG/post-ITG	37/19		4.23	-42	-62	-18

Note: Significant clusters (voxel-level $p < .005$ uncorrected, cluster-level $p < .05$ FWE corrected).

For abbreviations see Table 3.2.

Discussion

The main goal of the current study was to identify whether unification processes in language modulate the connectivity between left frontal and temporal brain regions. We hypothesized that in word-category ambiguous sentences the effective connectivity between LIFG and LpMTG would be larger than in unambiguous sentences, while this ambiguity effect would not be present in word sequences. Our results showed that this was the case. For sentence ambiguous compared to sentence unambiguous conditions, LpIFG showed larger connectivity to LpMTGs, while LpMTGi showed larger connectivity to LIFG (and several other regions in the sentence processing network). No such enhanced coupling with ambiguity was observed between LIFG and LMTG in the context of word sequences. Thus, our results support the hypothesis of enhanced connectivity between left frontal and temporal regions during the unification process. However, we did not see direct effective connectivity between LpIFG and LpMTGi; instead both regions were modulating a separate brain region slightly superior to LpMTGi: LpMTGs (see Figure 3.3). As Figure 3.3B shows, LpMTGs was highly activated for words and even more so for sentences. Interestingly, in addition to the seed regions in LpIFG and LpMTGi, LpMTGs also showed enhanced coupling with the seed regions in RIFG, RpMTG, and the striatum for sentence ambiguous compared to sentence unambiguous words (see Figure 3.4 and Tables 3.3-3.4). Therefore, this region seems to serve as a hub in the language processing network.

The roles of LpMTGi and LpMTGs

Both LpMTGi and LpMTGs are known to be involved in the activation of meanings of words stored in long-term memory² (e.g. (Vandenbergh et al., 1996; Gold and Buckner, 2002; Bedny et al., 2008a). Frequently studies have found LpMTGs involvement when the preceding sentence or discourse context results in increased semantic unification load of a word (e.g. (Ni et al., 2000; Kuperberg et al., 2003; Xu et al., 2005; Willems et al., 2007; Ferstl et al., 2008; Willems et al., 2008), see (Hagoort et al., 2009) for a review). This LpMTGs involvement in semantic unification might be the result of the conceptual representation of the individual words in LpMTGs being constantly maintained and updated by LIFG when new words come in (see also Humphries et al., 2007). While LpMTGi has been implicated in the processing of (semantic) ambiguity in sentences (Rodd et al., 2005; Davis et al., 2007; Zempleni et al., 2007), LpMTGs seems to be especially involved when different sources of information converge on a common conceptual memory representation (Beauchamp et al., 2004; Hein et al., 2007; Hagoort et al., 2009; Willems et al., 2009).

Furthermore, LpMTGs is involved in the processing of syntactically complex sentences, which has been attributed to the integration of lexical-semantic and

² Other functions such as theory of mind, processing of faces and biological motion, and audiovisual integration have been attributed to LpMTGs/STS as well (see Hein and Knight, 2008 for a review). STS might serve different functions depending on variable network co-activations with other brain regions.

syntactic information during sentence comprehension (Friederici et al., 2009). Note that here also different sources of information converge on a common memory representation.

Both LpMTGi and LpMTGs are activated more for verbs than for nouns (both: Grossman et al., 2002; Davis et al., 2004; Bedny et al., 2008b; LpMTGi: Warburton et al., 1996; LpMTGs: Shapiro et al., 2006) and more for mental verbs than for motion verbs (Grossman et al., 2002). Furthermore, LpMTGi is activated more for verbs with multiple verb arguments (den Ouden et al., 2009). This verb effect might be related to either the more difficult semantic (event) structure or the more complex lexical-syntactic information of (mental) verbs (Bedny et al., 2008b). For example, mental verbs such as *believe* often carry embedded S-nodes (*X believes that Y*), and are thereby syntactically more complex than e.g. action verbs. We hypothesize that LpMTGi activation reflects the retrieval of lexical-syntactic frames associated with different word categories (noun, verb, determiners, etc.). Results of Davis and colleagues indicate that in LpMTGs the syntactic word-class effect is presumably more dependent on the semantic rather than syntactic properties of the experimental items (Davis et al., 2004). LpMTGi and LpMTGs might cooperate for retrieval of lexical-syntactic information and activation of appropriate word meanings.

The left hemisphere unification network

Our interpretation of the present PPI results is as follows: when a word-category ambiguous word is presented, lexical-syntactic information (syntactic templates for noun and verb) is retrieved from memory. This process is subserved by LpMTGi (Snijders et al., 2009). LpMTGi and LpMTGs work in concert for activating the conceptual representation of the word (both in sentence and word sequence context). If the ambiguous word is presented in a sentence context, the lexical-syntactic information given by LpMTGi is used by LpIFG for syntactic unification. During this process, the conceptual representation in LpMTGs is updated and maintained by feedback from inferior frontal gyrus. Future studies will need to give evidence about the precise division of labor for LpMTGi and LpMTGs between activating lexical-syntactic versus conceptual representations.

Both LIFG and LpMTG activation has been described in response to syntactically complex sentences (Keller et al., 2001; Fiebach et al., 2005), even if stimuli were matched for lexical content (Peelle et al., 2010). One possible interpretation of this pattern of results is that LpMTG plays a role in unification that is similar to that of LIFG. However, we favor an alternative interpretation: Sentence processing requires sustained activation of lexical-syntactic information (Snijders et al., 2009). The lexical-syntactic information is most likely not ‘copied’ from the area necessary for its retrieval (LpMTG) to the area necessary for unification (LIFG). Instead, the sustained activation of lexical-syntactic information could be triggered by feedback from the LIFG to the LpMTG (see Vosse and Kempen, 2009 for a computational implementation hereof). The amount and/or duration of lexical-syntactic activation is a function of the

unification load imposed by the combinatorial operations necessary for unification. Although we suggest a certain division of labor between LpMTG and LIFG in the retrieval and unification of lexical-syntactic information respectively, we hypothesized that the continuous interplay between these regions is needed for successful syntactic unification (Snijders et al., 2009). The current study found direct evidence for LIFG and LpMTG working in concert during syntactic unification processes.

Right hemisphere and the unification network

Second, in an exploratory fashion, we investigated how RIFG and RpMTG are functionally connected to the unification network. Both RH regions get involved in sentence processing when confronted with a word-category ambiguity. For word-ambiguous compared to word-unambiguous conditions RIFG and RpMTG did not show enhanced connectivity to other brain regions. For sentence-ambiguous compared to sentence-unambiguous conditions, RpMTG showed differential connectivity to the left-hemispheric language processing network. RIFG modulated the response of RpMTGs to sentence ambiguity, in a similar way as LpIFG modulated the response of LpMTGs. This suggests that, at least for RIFG, involvement of right hemisphere regions in the unification process is not solely due to interhemispheric connections between homotopic regions. The results are in agreement with data suggesting that the right hemisphere gets involved with sentence processing when context is needed for the disambiguation of alternative interpretations (see e.g. Faust and Chiarello, 1998; Kircher et al., 2001; Bookheimer, 2002; Grindrod and Baum, 2005; Menenti et al., 2009; Tesink et al., 2009b)

Striatum and the unification network

Third, we investigated how the striatum is functionally connected to the unification network. Does the striatum show enhanced connectivity to LIFG and/or LpMTG during ambiguity processing, and does this enhanced connectivity differ in a sentence versus a word-list context? Although in the subtraction analysis there was no difference in striatal ambiguity effect for sentence and word sequence conditions (Snijders et al., 2009; see Chapter 2), the connectivity analysis showed very different results for the striatum in the context of sentences versus words. For word-ambiguous compared to word-unambiguous conditions the striatum modulated activity in low-level visual regions only. However, for sentence-ambiguous compared to sentence-unambiguous conditions also regions in left and right MTG and in LIFG showed enhanced coupling with the striatum (see Table 3.4 and Figure 3.5). Thus, the PPI analysis revealed that the striatum is functionally connected to cortical regions for word and sentence-level ambiguities, but, importantly, to a *different* network of cortical regions depending on whether the context is a sentence or a sequence of words.

Syntactic unification requires the maintenance and on-line integration of lexical-syntactic representations over time, and the flexible and selective updating

of these representations (selecting among competing alternatives, see Hagoort, 2005a). In the context of working memory (WM) research, the focus has traditionally been on the role of the prefrontal cortex (PFC) in maintenance and updating of information. Recently also the striatum has been found to play a role in the updating of representations (Frank et al., 2001; Gruber et al., 2006; Cools, 2008; McNab and Klingberg, 2008). The basal ganglia (BG) might provide a dynamic gating mechanism for WM by momentarily inhibiting or disinhibiting the PFC, thus enabling (but not directly causing) e.g. lexical-syntactic information to be actively relayed to PFC (Hazy et al., 2007). This is much like the BG involvement in gating the selection of actions in motor operations (Mink, 1996) and in agreement with interpretations of BG contribution to language processing (e.g., Crosson et al., 2007).

How can we explain our results in the light of existing knowledge on the basal ganglia? Salient events (such as in our case ambiguous words) elicit dopamine release (Schultz et al., 1993; Zink et al., 2006), thereby reducing the BG threshold for facilitating/suppressing a cortical command in response to particular stimuli (Frank, 2005), and thus providing a relevance signal for cortical areas involved in word processing and unification. In word sequences, the saliency of ambiguous lexical-syntactic representations is only relevant for lower-level word processing regions, which results in higher connectivity of the striatum to LpITG/LOcG (coinciding with the visual word form area, McCandliss et al., 2003). The unification operations on the lexical-syntactic representations are essential only in a sentence context. Thus, inferior frontal and striatal regions may cooperate for performing unification operations on lexical-syntactic representations retrieved from LpMTG only in this type of context. Evidence that the striatum can modulate information transfer between cortical regions comes from a recent study using dynamic causal modeling (den Ouden et al., in press).

Obviously, cortico-striatal loops function as an integrated system, where it is difficult to segregate functional roles of nodes in the system. Whether during sentence unification the striatum is directly or indirectly modulating activity in LpIFG, LpMTG, or the connection between these regions, remains a question for further research.

Conclusion: the unification network in the brain

In this study we investigated the unification brain network using psychophysiological interactions. The results show that bilateral inferior frontal and posterior temporal gyri are functionally connected during unification. Furthermore, the striatum is functionally connected to the cortical unification network. Connections between LIFG and the striatum might control the extraction of lexical-syntactic information from left posterior temporal regions in the service of the unification operations subserved by LIFG (see also O'Reilly and Frank, 2006; Dayan, 2008). RIFG and RpMTG get involved in unification when context is needed for the disambiguation of alternative interpretations.

Although language in the brain has been studied since the 19th century, the study on network interactions during sentence comprehension has only just begun (Hampson et al., 2002; Homae et al., 2003; Prat et al., 2007; Chow et al., 2008; Tyler and Marslen-Wilson, 2008). The current study adds important insights to this emerging field, and provides important input for further studies on unification dynamics, for example using dynamic causal modeling (Friston et al., 2003).

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Chapter 4

Effects of a common CNTNAP2 polymorphism on functional and structural brain measures related to language processing

Abstract

Little is known as yet of the genes that are involved in language processing. Rare mutations in the *FOXP2* gene cause a severe speech and language disorder. In the current study we investigated the effect of a common polymorphism (rs7794745) in *CNTNAP2*, a gene that is down-regulated by *FOXP2*, on the brain response to language comprehension in the normal population. *CNTNAP2* is a cell-adhesion molecule that influences the properties of neural networks. Fifty-one participants, divided in two *CNTNAP2* genotype groups based on their rs7794745 genotype (AA vs. AT/TT), read sentences and word sequences in the MRI-scanner. While the overall network of brain regions involved in sentence processing was similar, a difference in activation and connectivity patterns in frontal and temporal brain regions was observed for the two genotype groups. In addition, a group of 309 subjects showed increased grey matter volume for the AA group in right prefrontal cortex. The results suggest that the common rs7794745 polymorphism in *CNTNAP2* results in different neurocognitive processing routes for sentence processing. A tentative interpretation of our findings is that subjects with an AA genotype process sentences in a more context-driven way, while T-carriers (who have a slightly increased risk for autism) are more lexically driven in their processing styles. The results give an indication of the plasticity of the language processing system in the brain. It is an open question whether *CNTNAP2* mainly affects language, or whether its effect on language is mediated through other high-level cognitive processes such as cognitive flexibility.

This chapter is a modified version of:

Snijders, T.M., Rijpkema, M., Franke, B., Brunner, H.G., Dediu, D., Folia, V., Udden, J., Fernandez, G., Petersson, K.M., Hagoort, P., submitted. A common *CNTNAP2* polymorphism affects functional and structural aspects of language-relevant neuronal infrastructure.

Introduction

The current study investigates the influence of genetic factors on individual differences in language processing in the brain. Numerous investigations into the genetic foundations of language and speech, using a variety of methods such as twin and adoption studies, have consistently found moderate to high heritability scores of both pathological and normal variation in language ability (for reviews, see Stromswold, 2001; Ramus and Fisher, 2009). It is certainly not the case that one gene is responsible for language processing, but instead a whole ensemble of genes works together subserving the ability to produce and comprehend a language (Fisher and Marcus, 2006).

However, despite the large genetic component reflected by heritability estimates, not much is known about the specific genes and mechanisms involved in language processing. The most promising candidate to date is represented by *FOXP2*, a gene coding for a forkhead transcription factor, a regulator of gene-expression (Carlsson and Mahlapuu, 2002; Lai et al., 2003). Its disruption determines a complex pathology, *developmental verbal dyspraxia*, which includes difficulties with learning and producing sequences of oral movements relevant for speech, as well as impairments in language production and comprehension, including grammar (Lai et al., 2001; Watkins et al., 2002a; MacDermot et al., 2005; Feuk et al., 2006; Shriberg et al., 2006). In the current study we investigated the effect of a common polymorphism in *CNTNAP2*, a gene that is down-regulated by *FOXP2* (Vernes et al., 2008, see below), on the brain response to language comprehension.

Neuroimaging studies of the British KE family - half of whose members have a truncating *FOXP2* mutation leading to the original discovery of this gene (Lai et al., 2001) - demonstrated structural and functional abnormalities in brain regions related to motor and language processing (Vargha-Khadem et al., 2005). Voxel-based morphometry (VBM) studies showed reduced grey matter volume in the bilateral caudate nucleus, inferior frontal gyrus, precentral gyrus, and the cerebellum in affected family-members, while there was an increase in grey matter in the posterior portion of the superior temporal gyrus, the angular gyrus and the putamen (Watkins et al., 2002b; Belton et al., 2003; Vargha-Khadem et al., 2005). Functional neuroimaging experiments using verb generation, showed a left-dominant activation for unaffected family members, and a more bilateral activation pattern for affected family members, with reduced activation in bilateral inferior frontal gyri, left precentral gyrus, and putamen (Liegeois et al., 2003). Thus, *FOXP2* might be important for the development of putative frontostriatal and frontocerebellar networks (Vargha-Khadem et al., 2005).

FOXP2 is highly conserved across species. The human protein differs at only three amino-acid positions from the mouse form, and at two positions from the common chimpanzee, gorilla, and rhesus macaque orthologues (Enard et al., 2002; Zhang et al., 2002). In many different vertebrates (e.g. humans, monkeys, mice, rats, birds, zebrafish), *FOXP2* is expressed in brain circuits involving the cortex, basal ganglia, thalamus and cerebellum (Fisher and Scharff, 2009). Introducing the

human version of the *FOXP2* gene into mice results in alterations in their ultrasonic vocalizations, as well as increased synaptic plasticity and dendrite length of medium spiny neurons of the striatum (Enard et al., 2009). A whole-genome analysis has identified several genes differentially regulated by the human and chimp version of *FOXP2* (Konopka et al., 2009), suggesting possible mechanisms for its human-specific effects.

Recently it has been found that *FOXP2* down-regulates the expression of the gene coding for contactin-associated protein-like 2 (*CNTNAP2*) (Vernes et al., 2008). The protein encoded by *CNTNAP2*, also known as Caspr2, is a member of the neurexin superfamily of transmembrane proteins involved in mediating cell-cell interactions in the nervous system (Poliak et al., 1999; Nakabayashi and Scherer, 2001). In general, contactin-associated proteins have been linked to neuron-glia interactions (Poliak et al., 2001), and *CNTNAP2* in particular is concerned with neuronal recognition, cell adhesion, and localization and maintenance of voltage-gated potassium channels (Inda et al., 2006; Fisher and Scharff, 2009). Recently a role of *CNTNAP2* at the level of the synapse has been suggested (Zweier et al., 2009).

Gene-expression analyses in the developing human brain identified *CNTNAP2* transcripts as enriched in frontotemporal-subcortical circuits (i.e. frontal lobes and anterior temporal lobes, striatum, and dorsal thalamus) (Alarcon et al., 2008). *CNTNAP2* expression is lowest in cortical layers of the developing human cerebral cortex with the highest *FOXP2* levels (Vernes et al., 2008). Interestingly, *CNTNAP2* expression is enriched in frontal cortical areas in human, but not in mouse or rat (Abrahams et al., 2007).

Mutations and polymorphisms of *CNTNAP2* have been linked to several neurodevelopmental disorders, such as epilepsy (Strauss et al., 2006), schizophrenia (Friedman et al., 2008), Gilles de la Tourette syndrome (Verkerk et al., 2003), mental retardation (Zweier et al., 2009), specific language impairment (SLI, Vernes et al., 2008), and especially autism spectrum disorders (ASD), characterized by impaired communication, deficits in social interactions and rigid and repetitive behaviors (Abrahams and Geschwind, 2008; Alarcon et al., 2008; Arking et al., 2008; Bakkaloglu et al., 2008; Rossi et al., 2008).

Importantly, several studies link *CNTNAP2* to language abilities. A mutation of this gene in children with focal epilepsy causes severe language regression (Strauss et al., 2006), while in SLI an association between *CNTNAP2* and non-word repetition has been found (Vernes et al., 2008). Furthermore, *CNTNAP2* has been associated with language delay (age at which subjects spoke their first word) in autism (Alarcon et al., 2008), and a mutation of *CNTNAP2* in a boy with autism and developmental speech delay has been described (Poot et al., 2010).

Genes that are responsible for individual differences concerning language processing might have an effect on the neural architecture for language processing. As of yet, there are no studies investigating the effects of common polymorphisms in language-related genes on patterns of language-related brain activity and brain

structure in the normal population. This is what we set out to do in the current study.

We looked at the effect of a common polymorphism in *CNTNAP2* (rs7794745) on brain activity in response to sentence and word processing. Subjects read sentences and scrambled word sequences. Both the sentences and the word sequences could contain word-category (noun/verb) ambiguous words, resulting in increased lexical-syntactic retrieval demands. Additionally, word-category ambiguous words presented in sentence contexts caused more difficulty in integrating (unifying) the lexical-syntactic information into a sentence structure (see Chapter 2 for details). Genotype dependency of both the effect of grammaticality (sentences versus word sequences) and the effect of ambiguity (ambiguous versus unambiguous items) will be described below. We will also report genotype effects on grey matter volume in the brain.

We investigated the common *CNTNAP2* single nucleotide polymorphism (SNP) rs7794745 (A>T). This particular *CNTNAP2* SNP is associated with autism susceptibility (carriers of the T-allele have an increased risk, see Arking et al., 2008).

Materials and Methods

Participants

Fifty-one European Caucasian neurologically healthy volunteers (aged 18-35, 26 females) participated in the experiment. Nineteen of the participants (aged 20-35, 10 females) participated in the study reported in (Snijders et al., 2009) and were genotyped (test-group 1). Thirty-two of the participants (aged 18-34, 16 females) have been newly recruited for the current study (test-group 2). All participants were right-handed native speakers of Dutch. Subjects were paid for their participation. The study was approved by the local ethics committee and all participants gave written informed consent prior to the experiment in accordance with the Declaration of Helsinki. Eleven additional subjects were scanned but excluded from analysis because of excessive movement in the MR scanner (4 subjects), poor task performance (1 subject, see below), failure to collect saliva (1 subject), failure to complete the fMRI experiment (2 subjects), and 3 subjects proved to be non-Caucasian.

Participants in structural MRI

Structural MRI was performed in a large sample participating in the Brain Imaging Genetics (BIG) study at the Donders Centre for Cognitive Neuroimaging and the Department of Human Genetics of the Radboud University Nijmegen (Medical Centre). Three-hundred-nine (309) right-handed European Caucasian subjects participated in this part of the study (153 females, aged 18-35). Subjects had no self-reported neurological or psychiatric history.

Stimulus material

The stimuli consisted of 68 Dutch sentences (S) and 68 matched scrambled sequences of Dutch words (W). Both the sentences and the word sequences contained a critical word that was either word-class (noun/verb) ambiguous (A) or unambiguous (U). The critical word in the sentences was disambiguated by the continuation of the sentence into either a noun (n) or a verb (v) reading. In total, this resulted in eight possible conditions: SAn, SAv, SU_n, SU_v, WAn, WAv, WU_n, WU_v (see Table 4.1 for examples).

Table 4.1.

Example of the experimental materials, with the critical word *bewijzen* (*evidence/to prove*).

SAn: Sentence Ambiguous (noun context)

Zodra jullie bewijzen_(n/v) leveren kunnen we beginnen.
*As-soon-as you evidence*_(n/v) *provide can we start.*
*(As soon as you provide evidence*_(n/v) *we can start.)*

SUn: Sentence Unambiguous (noun context)

Zodra jullie kopij_(n) leveren kunnen we beginnen.
*As-soon-as you copy*_(n) *provide can we start.*
*(As soon as you provide copy*_(n) *we can start.)*

SAv: Sentence Ambiguous (verb context)

Zodra jullie bewijzen_(n/v) dat hij erbij betrokken is arresteren we hem.
*As-soon-as you prove*_(n/v) *that he in-it involved is arrest we him.*
*(As soon as you prove*_(n/v) *that he is involved we will arrest him.)*

SU_v: Sentence Unambiguous (verb context)

Zodra jullie beweren_(v) dat hij erbij betrokken is arresteren we hem.
*As-soon-as you claim*_(v) *that he in-it involved is arrest we him.*
*(As soon as you claim*_(v) *that he is involved we will arrest him.)*

WAn: Words Ambiguous (derived from SAn)

genoemd tegen bewijzen_(n/v) uit helaas gezeten jullie
*named against proof/prove*_(n/v) *from alas seated you*

WU_n: Words Unambiguous (derived from SUn)

genoemd tegen kopij_(n) uit helaas gezeten jullie
*named against copy*_(n) *from alas seated you*

WAv: Words Ambiguous (derived from SAv)

in nogal bewijzen_(n/v) meestal maar dit in struikelen hem verschil opeens
*in quite proof/prove*_(n/v) *mostly but this in stumble him difference suddenly*

WU_v: Words Unambiguous (derived from SU_v)

in nogal beweren_(v) meestal maar dit in struikelen hem verschil opeens
*in quite claim*_(v) *mostly but this in stumble him difference suddenly*

The ambiguous words were equibaised, that is, there was no strong preference for the noun over the verb interpretation or vice versa. This was brought out both by matching the words' lexical frequencies as occurring in Dutch lexical databases (Baayen et al., 1993; Beek et al., 2001), as well as by matching words on the results of a pre-test, on a different group of participants, where subjects had to complete sentence fragments ending with the ambiguity (e.g. "Zodra jullie *bewijzen* ..."). The ambiguous sentences were constructed such that both categories of the critical word fitted syntactically as well as semantically with the initial part of the sentences (up to and including the critical word); the sentences were disambiguated by the

subsequent part of the sentence (*after* the ambiguous word; see Table 4.1 for an example). Word sequences were constructed from the sentences by substituting every word (except the critical word) by a different word matched for length, frequency, and word category, and subsequently scrambling the order of the words in the sequence (except the critical word). For a full description of experimental materials, see Chapter 2 and Appendix 1A.

General procedure

Test-group 2 (32 subjects) participated in two scanning sessions: a first session of half an hour in which a resting state and a DTI scan were performed (described elsewhere), and, after a short break, a second session consisting of the fMRI experiment (see below). On a separate day, subjects participated in behavioral testing (see below).

Test-group 1 (19 subjects) only participated in the fMRI experiment (data described by Snijders et al., 2009), and not in the resting state/DTI scans or behavioral experiments.

fMRI procedure

Stimuli were presented using the serial visual presentation method (i.e. word by word in the middle of the screen) using Presentation software (Version 9.13, www.neuro-bs.com). Every word remained on the screen for 300 ms, with a 200 ms inter-word-interval. Between the sequences of words (sentences or random), a visual fixation cross was presented for 5-8 seconds (low-level baseline). The participants were instructed to read each sentence / word sequence carefully and attentively, and were told that after the experiment some questions concerning the items would have to be answered. The participants' task was spotting the consonant-strings (e.g., *cdsnl*), that were presented in 36 filler-items (18 sentences and 18 sequences). This simple control task was added to check whether subjects were paying attention. Subjects were defined as poor task performers if they made more than five errors (misses and false alarms) on the task, suggesting that these subjects (n=1) did not pay enough attention to the stimuli.

Every subject saw 68 sentences and 68 word sequences (ambiguous/unambiguous; in noun/verb version), intermingled with 56 fillers (28 sentences and 28 sequences). No subject encountered the same critical word or context sentence/sequence more than once. Stimuli were presented in mini-blocks of three to four sentences or word sequences. All mini-blocks were shorter than 40 seconds. Before each block the label “Zinnen:” (“Sentences:”) or “Woorden:” (“Words:”) appeared on the screen (for 1.5 seconds) to indicate the condition of the following mini-block, which started after a fixation cross of 1-3 seconds. We expected the labels to encourage (“Sentences”) or discourage (“Words”) attempts to syntactically/semantically integrate the stimulus items in the upcoming mini-block. The ambiguous/unambiguous and verb/noun conditions were intertwined within the mini-blocks in a pseudo-randomised presentation order.

fMRI data acquisition

During the sentence/sequence presentation we acquired T2*-weighted EPI-BOLD fMRI data with a SIEMENS 3 Tesla MR-scanner (test-group 1: Trio; test-group 2: Trio Tim) using an ascending slice acquisition sequence (volume TR 2 s, TE 35 ms, 90 degree flip-angle, 29 slices, slice-matrix size 64 x 64, slice thickness 3 mm, slice gap 0.5 mm, FOV 224 mm, voxel-size 3.5 x 3.5 x 3.0 mm). At the end of the scanning session, a structural MR image volume was acquired for which a high-resolution T1-weighted 3D MPRAGE sequence was used (TE 3.93 ms (test-group 1), TE 3.03 ms (test-group 2), 8 degree flip-angle, 192 sagittal slices, slice thickness 1.0 mm, voxel-size 1 x 1 x 1 mm).

sMRI data acquisition

For the structural imaging part, all images were acquired at 1.5T Siemens Sonata and Avanto scanners (Siemens, Erlangen, Germany) using small variations to a standard T1-weighted 3D MPRAGE sequence (TR 2300 ms, TI 1100 ms, TE 3.03 ms, 192 sagittal slices, FOV 256 mm). These variations included TR/TI/TE/slices of 2730/1000/2.95/176, 2250/850/2.95/176, 2250/850/3.93/176, 2250/850/3.68/176, and the use of GRAPPA parallel imaging with an acceleration factor of 2. All scans covered the entire brain and had a voxel size of 1x1x1 mm.

Genetic analysis

DNA was isolated from saliva using the Oragene system (DNA Genotek Inc., Kanata, Ontario, Canada). DNA-isolation and genotyping were performed in a CCKL-accredited laboratory at the Department of Human Genetics of the Radboud University Nijmegen Medical Centre in Nijmegen. The *CNTNAP2* polymorphism (rs7794745, A>T) was genotyped using Taqman analysis (assay ID: rs7794745: Taqman assay C_2661558_10, reporter 1: VIC-A-allele, forward assay; Applied Biosystems, Nieuwerkerk a/d IJssel, The Netherlands). Genotyping was carried out in a volume of 10 µl containing 10 ng of genomic DNA, 5 µl of Taqman Mastermix (2x; Applied Biosystems), 0.125 µl of the Taqman assay and 3.875 µl of MilliQ. Amplification was performed by an initial denaturation at 95°C for 12 min, followed by 40 cycles of denaturation at 92°C for 15 seconds and annealing/extension at 60°C for 1 minute. This was carried out on a 7500 Fast Real-Time PCR System, and genotypes were scored using the algorithm and software supplied by the manufacturer (Applied Biosystems). Generally, 5% blanks as well as duplicates within and between plates were taken along as quality controls during genotyping.

For further analysis, carriers of at least one T allele were grouped together and compared to carriers of the AA homozygous genotype.

Behavioral testing

Ambiguity test

On a separate day after the fMRI experiment, subjects of test-group 2 filled in a sentence completion task. Here, subjects saw the first part of experimental

sentences up to and including the ambiguous word (e.g. “*Zodra jullie bewijzen ...*”, see Table 4.1). The four versions of this sentence completion task mirrored the fMRI experimental versions, such that subjects had seen the ambiguous words of the sentence completion task only in the word sequence condition, and not in the sentence condition, of the fMRI experiment. Every version consisted of 34 experimental items and 35 fillers. Subjects had to complete the sentence four times. For all four sentence completions we scored whether the subject had interpreted the ambiguous word as a noun or a verb. For every item the noun-ratio was calculated as the amount of noun interpretations divided by the total number of answers for that item (mostly four). If subjects would be totally unbiased, they would give two noun-interpretations and two verb-interpretations for every item, resulting in a noun-ratio of 0.5. ‘Bias’ was defined as the difference of the noun-ratio (for one particular item) from 0.5. For every subject a mean bias-score was calculated over all 34 items.

Next to the ambiguity sentence completion task, several behavioral tests were administered to test-group 2: a reading span task, a verbal fluency task, a non-word repetition task, a digit span task, a spatial memory span task, an artificial grammar learning task, and autism questionnaires. These behavioral tests will not be discussed in the current paper, as the sample size is too small to detect genetic influences on behavior, and there were no straightforward significant effects of genotype on the behavioral tests.

fMRI data analysis

Image preprocessing and statistical analysis were performed using Statistical Parametric Mapping (SPM5; www.fil.ion.ucl.ac.uk/spm/software/spm5). The first five image volumes were discarded in order to avoid transient non-saturation effects. The functional EPI-BOLD images were realigned, slice-time corrected, and the subject-mean functional MR images were co-registered with the corresponding structural MR images using mutual information optimization. Subsequently, functional images were normalized to a Montreal Neurological Institute (MNI) aligned echo planar imaging template (based on 28 male brains acquired on the Siemens Trio at the Donders Centre for Cognitive Neuroimaging) and resampled to an isotropic voxel size of 2 mm³. Finally, the normalized images were spatially filtered by convolving the functional images with an isotropic 3D Gaussian kernel (10 mm full width at half maximum).

The fMRI data were proportionally scaled to account for various global effects, and analyzed statistically using the general linear model and statistical parametric mapping (Friston et al., 2007) in a 2-step mixed design procedure. At the first-level, single-subject fixed effect analyses were conducted. The linear model included mini-block regressors to model the sentence/sequence presentation from the onset of the critical word to the offset of the sentence/sequence-final word. The beginnings of sentences/sequences and filler items were modeled together as a regressor of no interest (other words, OW), and the presentation of the fixation cross (FIX) was modeled as explicit baseline. We temporally convolved the

explanatory variables with the canonical hemodynamic response function provided by SPM5. We included the realignment parameters for movement artifact correction and a temporal high-pass filter (cut-off 128 s) to account for various low-frequency effects as effects of no interest. Temporal autocorrelation was modeled as a first-order plus white noise autoregressive process.

For the second-level whole-brain analysis, we generated single-subject contrast images for the SAn, WAn, SU_n, WU_n, SA_v, WA_v, SU_v, and WU_v items relative to the baseline FIX, and used these in a one-way random effects repeated measures ANOVA (including the factors: genotype [2], condition [8], and subject [51]). Test-group (1 vs 2) was added as a covariate. SPM[T] volumes were generated to investigate the effect of grammaticality (i.e., sentences > words, for both groups combined and for the separate genotype groups, Table 4.2), the effects of ambiguity (ambiguous > unambiguous, for both groups combined and for the separate genotype groups), and the interactions between genotype groups and grammaticality ((sentences-words)AA > (sentences-words)AT/TT; (sentences-words)AT/TT > (sentences-words)AA; Table 4.3, Figure 4.1) and between genotype and ambiguity ((ambiguous-unambiguous)AA > (ambiguous-unambiguous)AT/TT; (ambiguous-unambiguous)AT/TT > (ambiguous-unambiguous)AA). Additionally, SPM[T] volumes were created for the effect of ambiguity within sentences only (SA > SU, for both groups combined (Table 4.4) and for the separate genotype groups), and its interaction with genotype ((SA-SU)AA > (SA-SU)AT/TT); (SA-SU)AT/TT > (SA-SU)AA).

For brain regions showing a significant grammaticality by genotype interaction, an average time course was calculated, separately for every participant, using Marsbar (<http://marsbar.sourceforge.net/>). As a post-hoc test, for both genotype groups a repeated measures ANOVA with the factors Grammaticality (S,W), Ambiguity (A,U), and Word class context (noun,verb; see Table 4.1) was carried out on the subject contrast values using SPSS software (SPSS Inc., Chicago, IL). Also, correlations between grammaticality effect (sentences-words) and the behavioral measures were computed in these brain regions.

Statistical inference

To correct for multiple comparisons, statistical inference was based on the cluster-size statistics ($p < .05$) from the relevant second-level SPM[T] volumes (Forman et al., 1995; Friston et al., 1996). SPMs were thresholded at $p < .001$ (uncorrected at the voxel level). For the whole-brain comparison between sentences and word sequences (Table 4.2), we used a voxel-level threshold of $p < .05$ corrected for multiple comparisons based on random field theory (Worsley et al., 1996). Only clusters of size > 10 voxels are reported.

Effective connectivity analysis

After having identified differences in the grammaticality effect between genotypes in the left posterior middle temporal gyrus, bordering the superior temporal sulcus (LpMTGs, medial to LpMTGs showing enhanced connectivity with LpIFG for

sentence ambiguous compared to sentence unambiguous conditions in Chapter 3), we tested for a difference in effective connectivity between LpIFG and LpMTGs for the two genotype groups.

Thus, we explored whether differences between genotype groups existed in effective connectivity of the seed region LpIFG depending on ambiguity in sentences, using psychophysiological interactions (PPI) described by (Friston et al., 1997). A PPI expresses which brain regions (on a voxel-by-voxel basis) show an enhanced coupling (as evidenced by a steeper regression slope) with a region of interest (seed region) during one experimental condition compared to another condition (Friston et al., 1997), see also Chapter 3. The seed region for the PPI analysis was the left posterior inferior frontal gyrus (LpIFG). The ROI was defined as a 8-mm sphere with the origin at MNI coordinates [-44 0 22], based on the group-analysis results (SA>SU) reported in Chapter 2. For each subject, the physiological activity of seed region LpIFG was summarized as the first eigenvariate of the time series of all active voxels within an 8 mm sphere centered on the most significant voxel within the ROI. Significance of voxels was based on the Sentences>Words contrast to identify active voxels ($p < .05$ uncorrected). When there were less than 5 voxels in the ROI that met the above criteria, the statistical threshold was eased on an individual subject basis (not different between genotype groups). To estimate underlying neuronal activity the physiological activity of the seed region was deconvolved (Gitelman et al., 2003).

First, a PPI analysis for each subject was performed at the first level, looking for enhanced coupling of LpIFG with other regions in the brain for SA compared to SU conditions. Then, individual PPI contrast images were entered into a two-sample t -test at the second (group) level. Contrasts were used to compare the PPI of AA and AT/TT genotype groups.

Anatomical inference

All local maxima are reported as MNI coordinates (Evans et al., 1993). Relevant anatomical landmarks were identified and Brodmann areas were defined using the Atlas of the Human Brain (Mai et al., 2004) and MRIcro (Rorden and Brett, 2000) using the AAL template (Tzourio-Mazoyer et al., 2002) and the Talairach Daemon (Lancaster et al., 2000).

sMRI data analysis

The structural MRI analysis was performed using SPM5 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm5/>) and VBM5.1 Toolbox version 1.19 (<http://dbm.neuro.uni-jena.de/vbm/>). Raw DICOM MR imaging data were converted to NIFTI format using the conversion implemented in SPM5. Normalizing, bias-correcting, and segmenting into grey matter, white matter, and cerebrospinal fluid was performed using the VBM toolbox in SPM using priors (default settings). This method uses an optimized VBM protocol (Ashburner and Friston, 2000; Good et al., 2001) as well as a model based on Hidden Markov Random Fields (HMRF) developed to increase signal-to-noise ratio (Cuadra et al.,

2005). Total volume of grey matter, white matter, and cerebrospinal fluid was calculated by adding the resulting tissue probabilities. Brain volume was defined as the sum of white matter and grey matter volume.

Voxel-based morphometry preprocessing was carried out in the following way. Diffeomorphic image registration was performed using the DARTEL toolbox in SPM (Ashburner, 2007). First, all images were realigned to templates created from 556 in-house datasets. Second, Jacobian scaled ('modulated') images were calculated and subsequently transformed to MNI space using affine transformation. Finally, all data were smoothed with an 8 mm FWHM Gaussian smoothing kernel. Data analysis was performed in SPM using the grey matter images. After grouping all datasets to genotype, images with poor quality or artifacts were identified using the sample homogeneity check implemented in the VBM toolbox. Images that showed a deviation of more than 1.5 times the interquartile range from the median were discarded from further analysis ($n=13$).

Statistical analysis was performed using a GLM approach in SPM. A full-factorial ANCOVA was applied using genotype (AA vs. T-carriers) as factor. The age, sex, total brain volume, and scan protocol of each participant were added to the model as covariates. *t*-tests were performed assessing the difference between AA and T-carriers. Cluster statistics were corrected for non-stationarity. In this exploratory analysis of local grey matter volume differences SPMs were thresholded at $p < .001$ (uncorrected at the voxel level). For illustrative purposes, volume differences are shown at voxel-level $p_{\text{uncorr}} < .005$, with a cluster-level $p_{\text{FWE}} = .005$ (Figure 4.5).

Results

Behavioral results

Ambiguity test

The mean bias-score of the 32 participants in test-group 2 was 0.29. The bias-score did not differ significantly between the two genotype groups (mean AA: 0.28, mean AT/TT: 0.29, $T = -0.37$, $p = .71$)

Control task functional MRI experiment

All 51 included participants made ≤ 4 errors on the control task performed during the functional MRI experiment (mean: 0.29 misses, 0.52 false alarms). Subjects that made more than 5 errors were excluded from analysis (1 subject in test-group 2, see participants).

Functional imaging experiment

Genotyping

Fifty-one participants were genotyped successfully for rs7794745. Twenty-six subjects (13 males, 13 females) were homozygous for the A allele (AA group), and twenty-five subjects (12 males, 13 females) were carrier of at least one T allele (AT/TT group: 22 AT, 3 TT). The genotype distribution was according to Hardy-Weinberg equilibrium (HWE, $p = .55$).

Table 4.2A. Sentences versus Word sequences

Region	BA	Cluster Size	Voxel T^{343} value	x	y	z
<i>L temporal gyrus, L IFG</i>		12845				
L ant-MTG	20		26.87	-56	-10	-20
L ant-MTG/TempPole	21		26.48	-54	10	-28
L post-MTG	21		21.56	-60	-44	-2
L IFG(Orb)	47		21.35	-54	28	2
L IFG(Tri)	45		20.47	-56	26	6
L post-MTG/STS	21/37		20.29	-56	-56	12
L amygdala	20		13.83	-26	-16	-20
L FuG	37		11.26	-26	-34	-22
L tectum			11.05	-8	-32	-4
L pallidum			8.99	-14	2	6
L CalcG	17		7.00	-4	-58	10
L thalamus			6.87	-6	-12	2
<i>R temporal gyrus</i>		3165				
R TempPole	38		16.71	50	16	-32
R ant-MTG	21		15.70	58	0	-22
R mid-MTG	20		15.55	54	-10	-20
R para-HCG	36		9.47	22	-8	-24
R post-MTG	22		7.03	66	-46	8
R FuG	37		6.84	28	-30	-28
<i>L PrG</i>	6	502	12.46	-44	0	50
<i>L medial SFG</i>	32/10/9	420	15.70	-12	58	26
<i>R IFG</i>		134				
R IFG(Tri)	45		7.61	56	32	4
R IFG(Tri)	45		7.10	58	24	8
R IFG(Orb)	47		6.93	52	34	-6
<i>L gyrus rectus</i>	11	43	9.63	-4	50	-24
<i>R calcarine gyrus</i>	17/18	21	5.12	16	-98	2
<i>L SMA</i>	32/6	12	5.57	-6	14	50

Note: Significant activation peaks > 8 mm apart (voxel-level $p < .05$ FWE corrected, cluster extent threshold 10 voxels). Multiple peaks within a single activation cluster are shown indented. BA = Brodmann's area; T^{343} value = T value for 343 degrees of freedom; x,y,z = the original SPM x,y,z coordinates in millimeters of the MNI space; L = left; R = right; ant = anterior; post = posterior; I = inferior; M = middle; S = superior; TG = temporal gyrus; TS = temporal sulcus; FG = frontal gyrus; Orb = pars orbitalis; Tri = pars triangularis; TempPole = temporal pole; FuG = fusiform gyrus; CalcG = calcarine gyrus; para-HCG = parahippocampal gyrus; PrG = precentral gyrus; SMA=supplementary motor area.

Table 4.2B. CNTNAP2 AA genotype: Sentences versus Word sequences

Region	BA	Cluster Size	Voxel T^{343} value	x	y	z
<i>L temporal gyrus, L IFG</i>		10024				
L ant-MTG/TempPole	21		20.29	-54	10	-28
L mid-MTG	20		17.10	-56	-14	-18
L IFG(Orb)	38/47		15.69	-52	28	-8
L post-MTG/STS	37		15.48	-56	-60	12
L post-MTG	21		14.96	-58	-48	0
L IFG(Tri)	45		14.06	-56	24	6
L hippocampus	20/34/36		11.34	-26	-8	-20
L para-HCG	30/35		10.12	-20	-24	-14
L tectum			9.41	-8	-30	-6
L FuG	20/37		8.38	-34	-32	-26
L pallidum			7.82	-14	2	6
L thalamus			5.88	-6	-12	2
<i>R temporal gyrus</i>		2423				
R M TempPole	38/21		13.11	52	14	-30
R ant-MTG	21		12.42	56	8	-26
R mid-MTG	20/21		10.50	56	-10	-18
R para-HCG	35		7.83	22	-12	-22
R post-MTG	22		6.68	66	-44	4
R FuG	20		5.98	36	-20	-26
<i>L medial SFG</i>	10/9/32	417	13.06	-10	58	26
<i>L PrG</i>	6	350	10.02	-44	-2	50
<i>L lingual gyrus</i>	17/18	317	6.36	-2	-66	4
<i>R IFG</i>		178				
R IFG(Tri)	45		7.03	56	32	4
R IFG(Tri)	45		6.70	58	24	8
R IFG(Orb)	47		6.42	52	34	-6
<i>L gyrus rectus</i>	11	25	7.81	-4	50	-24
<i>L SMA</i>	32/6	13	5.44	-6	10	52

Note: Significant activation peaks > 8 mm apart (voxel-level $p < .05$ FWE corrected, cluster extent threshold 10 voxels). Multiple peaks within a single activation cluster are shown indented. For abbreviations see Table 4.2A.

Table 4.2C. *CNTNAP2* AT/TT genotype: Sentences versus Word sequences

Region	BA	Cluster Size	Voxel T^{343} value	x	y	z
<i>L temporal gyrus, L IFG</i>		8008				
L mid-MTG	20		21.51	-56	-10	-20
L M TempPole	38/21		17.88	-52	14	-32
L post-MTG	21		17.19	-60	-42	-2
L post-MTG	21/37		15.45	-56	-52	6
LIFG(Orb)	47/38		15.11	-50	30	-12
LIFG(Tri)	45		15.07	-56	26	6
L post-MTG/STS	39		12.46	-42	-60	20
L hippocampus/para-HCG	20/36		8.77	-26	-16	-20
L FuG	37/30		8.66	-26	-34	-20
L hippocampus/amygadala	36/20		6.51	-32	-2	-24
L tectum			6.44	-8	-30	-4
L FuG	37		5.67	-40	-44	-24
<i>R temporal gyrus</i>		1198				
R ant/mid-MTG	20/21		11.96	54	-8	-22
R M TempPole	38/21		10.78	50	16	-32
R mid-MTG	20/21		7.18	48	-30	-10
R mid-MTG	20		7.13	50	-24	-12
<i>L PrG</i>	6	271	7.90	-46	2	48
<i>L (medial) SFG</i>	10/9/32	198	10.64	-14	58	26
<i>L CalcG</i>		125				
L lingual gyrus/CalcG	17		5.78	-12	-50	4
L precuneus/CalcG	30/17		5.19	-6	-56	10
<i>L pallidum</i>		51	5.33	-16	4	4
<i>R para-HCG</i>	35	48	5.75	22	-10	-26
<i>L gyrus rectus</i>	11	14	6.13	-2	50	-24

Note: Significant activation peaks > 8 mm apart (voxel-level $p < .05$ FWE corrected, cluster extent threshold 10 voxels). Multiple peaks within a single activation cluster are shown indented. For abbreviations see Table 4.2A.

Table 4.3. CNTNAP2 genotype x Grammaticality (Sentences versus Word sequences) interaction

Region	BA	Cluster Size	Cluster p (corrected)	Voxel T^{343} value	x	y	z
AA > AT/TT							
<i>RIFG(Orb)</i>		511	.002				
R ant-IFG(Orb)	47			4.55	42	32	-4
R ant-IFG(Orb)	47			3.85	44	24	-8
R S TempPole	38/45/47			3.83	52	16	-8
<i>medial SFG</i>		279	.023				
L medial SFG	10/9/32			5.43	-2	52	30
L medial SFG	10			4.52	-4	60	22
R medial SFG	10			3.23	6	62	16
AT/TT > AA							
<i>L posterior MTG/STS</i>		257	.031				
L post-MTG/STS/AngG	39			4.38	-38	-50	18
L post-MTG/MoCg	39/37			3.48	-36	-62	18
L post-MTG	21/37			3.35	-44	-50	8

Note: Significant activation peaks > 8 mm apart (voxel-level $p < .001$ uncorrected, cluster-level $p < .05$ FWE corrected). Multiple peaks within a single activation cluster are shown indented. AngG = angular gyrus; OcG = occipital gyrus; for additional abbreviations see Table 4.2A.

Table 4.4. Sentence Ambiguous versus Sentence Unambiguous conditions

Region	BA	Cluster Size	Cluster p (corrected)	Voxel T^{343} value	x	y	z
<i>L IFG (Oper)</i>							
L IFG(Oper)		276	0.024				
L IFG(Oper)	44			3.82	-42	10	22
L IFG(Oper)	6/44			3.50	-46	8	14
L PrG	6			3.42	-50	2	34

Note: Significant activation peaks > 8 mm apart (voxel-level $p < .001$ uncorrected, cluster-level $p < .05$ FWE corrected). Multiple peaks within a single activation cluster are shown indented. Oper = pars opercularis; for additional abbreviations see Table 4.2A.

Grammaticality effect

Since both genotype groups consisted of highly-educated subjects without language impairment, it would be highly surprising if the brain response to sentence processing of the two groups would be completely different. Indeed, the two groups (AA and AT/TT) showed a similar brain response for sentences compared to word sequences (see Table 4.2, where A: both groups combined; B: AA genotype group; C: AT/TT genotype group). As expected, in both genotype groups sentences activated the sentence comprehension network (see Snijders et al., 2009) consisting of perisylvian regions, including left inferior frontal gyrus (LIFG) and bilateral middle temporal gyri (see Table 4.2 for a complete list). In addition, the AA genotype group showed a grammaticality effect in right inferior frontal gyrus (RIFG, see Table 4.2).

CNTNAP2 Genotype x Grammaticality interaction

Although the main activation pattern for sentences compared to word sequences was highly similar, in a number of brain regions a grammaticality x genotype interaction could be observed (see Figure 4.1 and Table 4.3). Subjects homozygous for AA showed a larger grammaticality effect (sentences > word sequences) in the triangular/orbital part of the right inferior frontal gyrus (RIFG(Orb), cluster extending into the Temporal Pole) and the bilateral medial superior frontal gyrus (mSFG). Subjects with AT/TT genotype, on the other hand, showed a larger grammaticality effect (sentences > word sequences) in a region in left posterior middle temporal gyrus, bordering on the superior temporal sulcus and the middle occipital gyrus (LpMTGs).

For the activation clusters showing a genotype x grammaticality interaction (RIFG(Orb), mSFG, and LpMTGs), mean contrast estimates are shown in Figure 4.2.

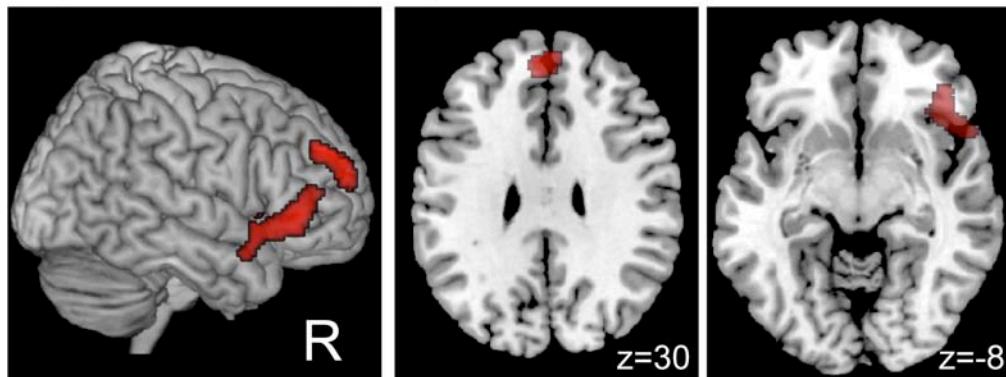
RIFG(Orb)

Figure 4.2 shows that while there was no difference between genotypes in RIFG(Orb) for word sequences, AT/TT genotype subjects showed a decrease in RIFG(Orb) response for sentences compared to word sequences ($F_{1,24} = 8.02$, $p = .009$), while AA genotype subjects did not ($F_{1,25} = 1.09$, $p = .307$).

RIFG(Orb) and Ambiguity test

The grammaticality effect in RIFG(Orb) was negatively correlated with the bias-score (the tendency to stick to a certain (noun or verb) interpretation) of the ambiguous sentence completion task ($r = -.384$, $p = .030$). The grammaticality effect in RIFG(Orb) was only present in the AT/TT genotype group (see above and Figure 4.2). Indeed, when testing the groups separately (see Figure 4.3), there was no significant correlation between grammaticality effect in RIFG(Orb) and mean bias score in the AA genotype group ($r = -.317$, $p = .250$), while there was a significant correlation in the AT/TT genotype group ($r = -.495$, $p = .043$). Thus, AT/TT subjects who were more biased towards a noun or verb interpretation (and

A (Sentences-Words)AA > (Sentences-Words)AT/TT



B (Sentences-Words)AT/TT > (Sentences-Words)AA

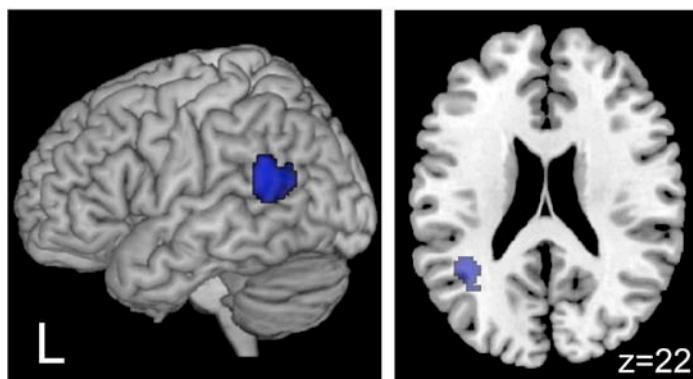


Figure 4.1.

CNTNAP2 Genotype x Grammaticality interaction.

(A) AA>AT/TT. Enhanced activity for AA compared to AT/TT genotype groups for sentences versus word sequences is shown in red. (B) AT/TT > AA. Enhanced activity for AT/TT compared to AA for sentences versus word sequences is shown in blue. Significant activations projected onto a rendered template brain surface in MNI stereotactic space (left), and displayed on an axial view of the brain (right). Activations shown at voxel-level $p_{\text{uncorr}} < .001$, cluster-level $p_{\text{FWE}} < .05$.

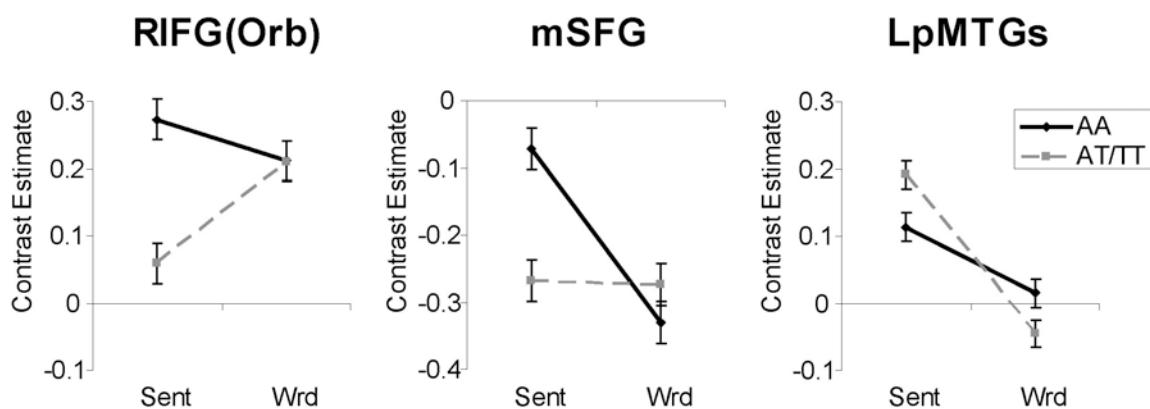
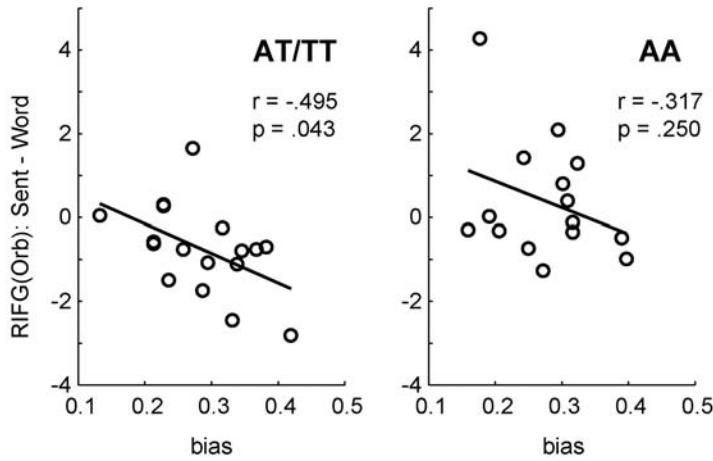


Figure 4.2.

Mean contrast estimates for RIFG(Orb), mSFG, and LpMTGs (clusters identified by the whole-brain grammaticality by genotype interaction effect) for sentences (Sent) and word sequences (Wrd) for AA (solid black) and AT/TT (striped grey) genotype groups.

**Figure 4.3.**

Correlation between grammaticality effect (sentences – word sequences) in RIFG(Orb) and bias (as measured by the ambiguity sentence completion task), for AT/TT (left) and AA (right) genotype groups.

did not revise their initial interpretation), showed a larger decrease for sentences compared to words in RIFG(Orb) than AT/TT subjects who were less biased.

mSFG

As depicted in Figure 4.2, mSFG is deactivated for both sentences and word sequences compared to baseline. For AA genotype subjects, this decrease in activation is less for sentences than for word sequences ($F_{1,25} = 20.59$, $p < .001$), while there was no difference between sentences and word sequences in the AT/TT genotype group ($F < 1$).

LpMTGs

The third brain region that showed an interaction between grammaticality and genotype was LpMTGs ($F_{1,49} = 5.85$, $p = .019$). LpMTGs was activated more for sentences than for word sequences in both AA and AT/TT genotype groups, but this effect was larger for AT/TT ($F_{1,24} = 34.89$, $p < .001$), than for AA ($F_{1,25} = 5.83$, $p = .023$, see Figure 4.2).

Ambiguity effect

No main effect of ambiguity survived multiple comparisons correction, and no brain regions differed in ambiguity effect between *CNTNAP2* genotype groups.

Ambiguity effect in sentences

Here we tested for word-class ambiguity effects in sentence contexts only. LpIFG was activated more in sentence ambiguous than in sentence unambiguous conditions, for both genotype groups combined (see Table 4.4). There was no significant difference for AA versus AT/TT genotype groups in the ambiguity effect in sentences.

Effective connectivity

Effective connectivity was tested by means of a PPI analysis. In an earlier study, we found that LpIFG shows enhanced coupling for sentence ambiguous compared to sentence unambiguous conditions to LpMTGs (see Chapter 3), a region slightly lateral to the LpMTGs region that showed a differential grammaticality effect between genotypes. Thus, we were interested whether there would be differential effective connectivity between LpIFG and LpMTGs for the two genotype groups. Indeed, the AA group showed more connectivity than the AT/TT group between LIFG and LpSTG for sentence ambiguous compared to sentence unambiguous conditions (see Figure 4.4). Small volume correction taking the peak voxel in LpMTGs from Chapter 3 (MNI coordinates [-68 -40 6]) resulted in a significant cluster peaking at MNI coordinates [-64 -42 12] (AA>AT/TT, $p = .018$ corrected).

Figure 4.4.

PPI connectivity analysis results. Differences between genotypes (AA > AT/TT) in enhanced connectivity with seed region LpIFG (S, blue) for sentence ambiguous (SA) compared to sentence unambiguous (SU) conditions (shown in red). Activations projected onto a template brain surface in MNI stereotactic space. Activations shown at voxel-level $p_{uncorr} < .001$.

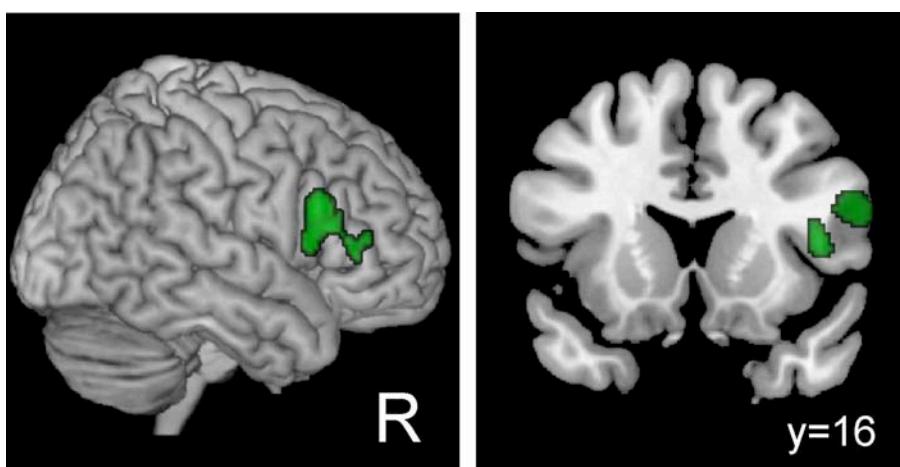
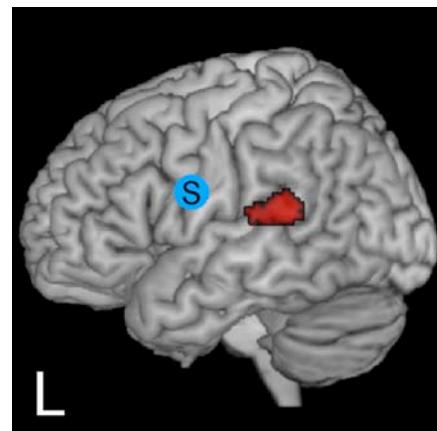


Figure 4.5.

Structural MRI results. Larger grey matter volume for AA compared to AT/TT genotype groups is shown in green. Grey matter volume differences projected onto a rendered template brain surface in MNI stereotactic space (left), and displayed on a coronal view of the brain (right). Grey matter volume differences shown at voxel-level $p_{uncorr} < .005$, cluster-level $P_{FWE} = .005$.

Structural imaging analysis

In a group of 309 subjects with rs7794745 genotype data, we looked for differences in local grey matter volume. Of these subjects, 145 (70 males, 75 females) were homozygous for the A allele (AA group), and 164 (86 males, 78 females) were carrier of at least one T allele (AT/TT group: 125 AT, 39 TT), with no deviation from HWE ($p = .14$). Testing for structural differences between *CNTNAP2* genotype groups revealed the grey matter volume in the opercular/triangular part of right inferior frontal gyrus (RIFG, BA44/45) to be significantly larger in the AA than in the AT/TT genotype group (Figure 4.5).

Discussion

We investigated the effect of a common polymorphism in *CNTNAP2* on brain activity in response to sentence and word reading. Although the main sentence-processing network was activated in a similar way for the two genotype groups, some differences existed as well. Thus, for the first time, an association has been observed between the brain response to language processing and a common genetic variant. The results showed a larger grammaticality effect (sentences > words) for the AA than for AT/TT genotype groups in RIFG(Orb) and mSFG, while the AT/TT genotype group showed a larger grammaticality effect in LpMTGs. Additionally, an effective connectivity analysis indicated that for the AA group there was more connectivity than for the AT/TT group between LpIFG and LpMTGs for sentence ambiguous compared to sentence unambiguous conditions. Finally, a VBM analysis on a large set of subjects (521) showed that AA subjects had more grey matter in RIFG than AT/TT subjects did.

Both genotype groups activated a network of brain regions known to be involved in language processing. Within this network, the two genotype groups showed a different balance in activation patterns of these brain regions. Interestingly, regions showing an effect of *CNTNAP2* genotype are overlapping with regions affected by *FOXP2* in the KE-family (Vargha-Khadem et al., 2005). Can we say anything about the individual nodes within the network that are modulated by *CNTNAP2* genotype?

The RIFG showed differences between *CNTNAP2* genotype-groups both in grey matter volume (BA 44/45) and in activation for sentences compared to words (BA 47/45). Subjects with an AT/TT genotype showed a decreased response for sentences compared to words in RIFG(Orb), while AA subjects did not. Classically, language processing has been localized to left frontal and temporal brain regions. However, the right hemisphere is known to be especially recruited for language processing in context (text, discourse) (Faust and Chiarello, 1998; Kircher et al., 2001; Bookheimer, 2002; Grindrod and Baum, 2005; Rodd et al., 2005; Menenti et al., 2009; Tesink et al., 2009b, see also Chapters 2 and 3). Functional MRI research suggests that the RIFG is involved in the forming and updating of a situation model, that is, a mental representation of the situation described in the sentence or discourse, constructed through interactions between

incoming information and background world knowledge (van Dijk and Kintsch, 1983; Graesser et al., 1997; Ferstl et al., 2005; Ferstl et al., 2008; Menenti et al., 2009). During word and sentence processing, individual differences might exist in how often the situation model is updated. For word sequences, the words do not form a coherent discourse and it will be difficult to construct a situation model. For sentences, a situation model can be constructed and updated with incoming information. Interestingly, AT/TT subjects that were more biased towards either a noun or a verb interpretation of ambiguous words (and did not revise their initial interpretation as shown in the ambiguity sentence completion task), showed a larger decrease for sentences compared to words, than AT/TT subjects who were less biased (see Figure 4.3). Thus, subjects who are less keen to update their situation model in sentence comprehension, show a decrease in activation in RIFG(Orb) for sentences.

How can we relate this to the *CNTNAP2* genotype dependent structural grey matter volume differences in RIFG? Considering the mechanism of action of *CNTNAP2*, it is unlikely that only RIFG is a target of *CNTNAP2* action. A more plausible interpretation is that the structural brain differences are the effect of long-term differential functional recruitment of RIFG. Thus, an increased use of RIFG for sentence processing by AA subjects, might lead to increases in grey matter volume (see e.g. Maguire et al., 2003; Draganski et al., 2004; Mechelli et al., 2004).

It is interesting to note that individuals with autism spectrum disorders (ASD), for which carriers of the T-allele of the SNP of the current study have a slightly increased risk (see introduction and Arking et al., 2008), also use RIFG in language processing differentially from controls (Wang et al., 2006; Mason et al., 2008; Tesink et al., 2009a). People with ASD have language difficulties especially with regard to pragmatic language aspects, i.e. the ability to comprehend and use language in context (Tager-Flusberg et al., 2005).

Medial superior frontal gyrus (mSFG, also called medial prefrontal cortex, MPFC) shows a grammaticality effect (sentences > words) for the AA genotype group, but not for the AT/TT genotype group. MPFC has been implicated in mentalizing tasks, requiring the ability to take someone else's perspective (Amodio and Frith, 2006; Frith and Frith, 2006; Buckner et al., 2008; Mitchell, 2009). In language experiments the MPFC is, for example, involved in tasks that require establishing connections between successively presented sentences (Ferstl and von Cramon, 2002), or that require integration of the content of a message with speaker characteristics (e.g. someone with an upper-class accent saying '*I have a big tattoo on my back*', Tesink et al., 2009a). Thus, the MPFC seems to be involved in the interpretation of somebody else's plans and motivations, for example of a protagonist within a text (Mason and Just, 2006). In our experiment, sentences often invite participants to take perspective by the usage of person pronouns (e.g., '*Ook lichten we de brandweer in na het ongeval*'-'*We also alert the fire brigade after the accident*', see also Table 4.1). An explanation of the results would be that AA

genotype subjects, while reading sentences, might take the protagonist perspective to a larger extent than AT/TT genotype subjects do.

Finally, a relatively medial part of LpMTGs showed a larger grammaticality effect (sentences > words) for the AT/TT genotype than for the AA genotype group. LpMTGs plays an important role in word and sentence processing, and is especially involved when different sources of information converge on a common conceptual memory representation (Beauchamp et al., 2004; Hein et al., 2007; Hagoort et al., 2009; Willems et al., 2009, see also Chapter 3). Apparently the balance in activation pattern of brain regions involved in language processing is different for the two genotype groups, with AA subjects using RIFG(Orb) and mSFG more in sentence comprehension, and AT/TT subjects using LpMTGs more. In very general terms, one could call the AA subjects more context-driven and the AT/TT subjects more lexically-driven in their processing styles. Interestingly, individuals with ASD, associated with the rs7794745 T allele, show a tendency to use context to a lesser extent than controls (Happe and Frith, 2006).

While no effect of *CNTNAP2* genotype on the ambiguity effect in the brain could be detected, an effective connectivity analysis indicated that for the AA group there was more connectivity than for the AT/TT group between LpIFG and a more lateral part of LpMTGs, for sentence ambiguous compared to sentence unambiguous conditions. One way to interpret these results would be that, as AT/TT subjects are already using part of LpMTGs for sentence processing more than AA subjects, they need less interplay between left inferior frontal and posterior temporal regions for the processing of ambiguous sentences. The results fit well with the interpretation of more lexically-driven processing style of AT/TT genotype subjects. Again remarkable similarities to autism research can be noted: people with ASD show less connectivity between brain regions involved in sentence comprehension (Just et al., 2004).

What could be the functional consequence of the different brain activity for the different *CNTNAP2* genotype groups? So far we did not see any clear behavioral differences between the two groups, but, the sample size for behavioral testing was too small to detect possible differences in behavioral output mediated by genotype (test-group two: 32 subjects). Generally, differences at the behavioral level are much harder to detect than differences at the neural level, as people can use different strategies and are well able to compensate (Tesink et al., 2009a). The results suggest that people with differing genotypes might use different neurocognitive processing routes, with (within the measurement limits of the present study) similar behavioral output (see also Koten et al., 2009). In a recent MEG study we confirmed the involvement of the currently studied *CNTNAP2* variant in mediating inter-individual variability as to which processing route is used for sentence comprehension (see Chapter 5).

What might be the potential relevance of this finding? Probably the most important implication is that the results give an indication of the plasticity of the language processing system. Studies on aphasic patients have already suggested multiple-route plasticity: when confronted with brain damage people can switch to

a different processing route (Kolk, 2000; Hagoort et al., 2003). Our study indicates that people have a genetic predisposition to use a certain neurocognitive processing route. This might give rise to differential options of plasticity in the case of brain damage. Further research is needed to elucidate this issue.

How could a common polymorphism in *CNTNAP2* result in different neurocognitive processing routes? As discussed above, *CNTNAP2* is a cell-adhesion molecule expressed during development, and is probably also involved at the level of the synapse (Alarcon et al., 2008; Zweier et al., 2009). Such synaptic cell-adhesion molecules shape the properties of neural networks by specifying synaptic functions (Südhof, 2008). Thus, variation in synaptic connections might very well have an influence on high-level cognitive and social processes (such as language) that require the involvement of complex neural networks. Consequently, differential functional recruitment of specific regions within a neural network might result in structural brain changes (see above). In addition, structural and functional alterations in synaptic connections could lead to different neurodevelopmental disorders that have been found affected by *CNTNAP2* (c.f. Betancur et al., 2009; Bourgeron, 2009). It is an open question whether *CNTNAP2* mainly affects language, or whether its effect on language is mediated through the role of this gene in high-level cognitive processes such as cognitive flexibility. As mentioned above, genes with an effect on synaptic functioning will probably affect multiple high-level processes requiring complex neural networks.

Probably the currently studied SNP, which lies in an intron of *CNTNAP2*, is only a marker for the functioning of the gene, and itself not directly related to language. Future studies need to answer the question whether other *CNTNAP2* SNPs show similar, complementary, and/or stronger effects. A good candidate to scrutinize in further analyses would be SNP rs17236239, the *CNTNAP2* SNP that was associated with nonsense-word repetition in children with SLI (Vernes et al., 2008). Also, genes functioning in ways similar to *CNTNAP2* (other genes coding for neurexins and neuroligins), and genes that are regulated by the human specific amino acids of FOXP2 (see Konopka et al., 2009) would be interesting targets for future research.

Conclusion

In conclusion, this study is the first to show an effect of a common genetic polymorphism on the brain response to language processing. A common polymorphism in *CNTNAP2* (rs7794745) results in different neurocognitive processing routes, as revealed by a different balance in activation patterns of brain regions recruited for sentence processing.

Acknowledgements

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Chapter 5

Temporal dynamics of word-category

ambiguity resolution depend on *CNTNAP2*

genotype: an MEG study

Abstract

In a recent fMRI study, using word-category (noun/verb) ambiguous words in a sentence or word-list context, we showed left inferior frontal and posterior temporal brain regions to be associated with syntactic unification processes (Snijders et al., 2009, see Chapter 2). Due to the low time resolution of fMRI, it remained unresolved whether this is due to competition processes at the ambiguous word, or to the resolution of the ambiguity (selection) at the disambiguating word. We used the superior temporal resolution of magnetoencephalography (MEG) to resolve this issue. Enhanced event-related fields (ERFs) were observed over bilateral frontotemporal regions for words in sentences compared to words in random word lists. Additionally, word-category ambiguities within sentences resulted in increased response over left frontotemporal regions at the disambiguating word (400-700 ms). Thus, the left frontotemporal brain activation is related to the selection part of the unification process (ambiguity resolution). At the word-class ambiguous word, opposite effects were identified for subjects with differing genotypes of a common *CNTNAP2* polymorphism (rs7794745, A>T; previously associated with sentence processing in the brain; see Chapter 4). While subjects with an AA genotype showed enhanced ERFs over left temporal regions for sentence-ambiguous compared to sentence-unambiguous conditions, T allele carriers showed reduced ERFs for sentence-ambiguous conditions. This means that a common polymorphism in *CNTNAP2* mediates inter-individual variability as to which syntactic processing route is used in the face of word-category ambiguity.

This chapter is a modified version of:

Snijders, T.M., Piantoni, G., Kempen, G., Vosse, T., van Berkum, J.J.A., Rijkema, M., Franke, B., Fernandez, G., Oostenveld, R., Hagoort, P., in preparation. Temporal dynamics of word-category ambiguity resolution depend on *CNTNAP2* genotype: an MEG study.

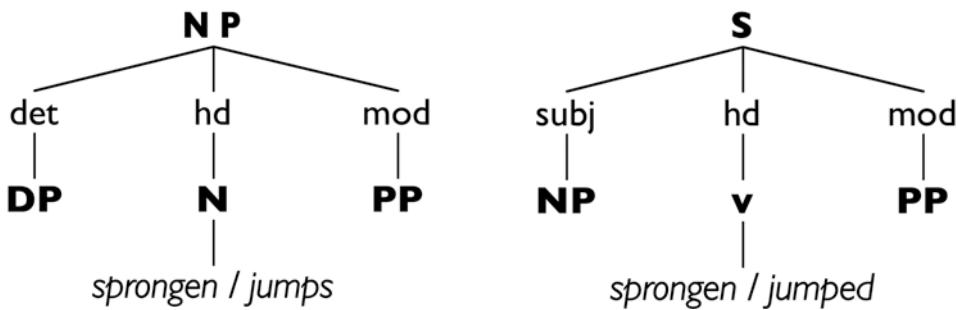
Introduction

Understanding the language we hear or read requires the retrieval of information about single words from long-term memory (mental lexicon) and the combination ('unification') of this information into representations spanning multiple words (Marslen-Wilson, 1987; Vosse and Kempen, 2000; Hagoort, 2005a). Both semantic (conceptual) and syntactic (structural) properties of words have to be retrieved and unified (Jackendoff, 2002). According to modern 'lexicalist' syntactic theories most, if not all, properties relevant for structural integration are specified in the mental lexicon, rather than being computed by abstract syntactic rules. Thus, structured syntactic properties of words (see below) are retrieved from the lexicon, and the only remaining 'rule of grammar' is the combinatorial process of unification.

In a recent fMRI study, we showed that the left posterior middle temporal gyrus (LpMTG) subserves the retrieval of lexical-syntactic information from the mental lexicon, while the left posterior inferior frontal gyrus (LpIFG) is involved in combining this information on-line into a sentence structure (Snijders et al., 2009, see Chapter 2). In the current study we looked at the *time course* of syntactic unification processes in the brain. We employed the high temporal resolution of magneto-encephalography (MEG), using similar materials as in (Snijders et al., 2009).

In order to investigate the time course of the syntactic unification process, we take the computational model of syntactic parsing by Vosse and Kempen (2000) as a starting point. This 'Unification Space' model is based on a lexicalist grammar that is computationally explicit. The model accounts for essential empirical findings in the psycholinguistic and neuropsychological literature on human syntactic processing. According to the Unification Space model, every incoming word retrieves one or more lexical frames from the mental lexicon. These lexical frames are elementary syntactic trees, specifying the possible structural environment of the particular input word (Vosse and Kempen, 2000; for a similar account, see Culicover and Jackendoff, 2005). Figure 5.1 shows examples of lexical frames for a noun ("jumps") and a verb ("jumped").

Lexical frames that have been retrieved from memory will enter the Unification Space one-by-one, as new input words arrive. Then, in the Unification Space, binding operations take place between lexical frames, resulting in an incrementally growing structural interpretation of the sentence. During the unification process lexical frames are linked, and agreement rules (number, gender, person, etc.) and word order constraints are applied. Unification links are dynamic, that is, the strength of the unification links varies over time until one stable phrasal configuration results. As language is intrinsically ambiguous, often several different unification possibilities are pursued in parallel. In the Unification Space model, selection among alternative unification links occurs via lateral inhibition (Vosse and Kempen, 2000). Recently, a novel computer implementation of the Unification-

**Figure 5.1.**

Lexical frames for the noun *spongén* ‘jumps’ and the verb *spongén* ‘jumped’. When encountering the word *spongén*, the lexical frame of both the noun and the verb will be retrieved. In the Vosse and Kempen model, lexical frames consist of three-tiered treelets. The top-layer of a frame consists of a single phrasal node (e.g. NP). This ‘root’-node is connected to one or more functional nodes in the second layer (e.g. subject, head, direct object, modifier). Every functional node is linked to another phrasal node in the third layer. Each lexical frame is attached to one lexical item (the “anchor”, situated under the ‘head’ node). Word-class ambiguous lexical items function as anchor in more than one lexical frame.

Space parser (Vosse & Kempen 2000) has been developed, in the form of a localist neural network whose dynamics are based on interactive activation and inhibition (for details on this model, nicknamed SINUS, see Vosse and Kempen, 2009, and see discussion).

In the (Snijders et al., 2009) study, participants read sentences and word sequences containing word-category (noun/verb) ambiguous words at critical positions. According to the Unification Space model, presentation of a noun-verb ambiguous word triggers the retrieval of both the noun and the verb version of the ambiguous word (in both sentences and word sequences). Hence, ambiguous words tax the lexical-syntactic retrieval process more heavily than unambiguous words, as two (or more) lexical frames are retrieved instead of one (see Figure 5.1). Sentences require unification of the words into an overall structure, whereas the word sequences do not. Furthermore, in the sentence condition, the two retrieved lexical frames (noun and verb) in the ambiguous condition compete for unification via lateral inhibition (selection). No unification takes place in the word condition, and the ambiguous words do not impose a higher unification load than their unambiguous counterparts.

Brain regions contributing to the syntactic unification process should show enhanced activation for sentences compared to words, and increased activation for ambiguous compared to unambiguous conditions only when the target words are presented within a sentence, i.e. not when presented in a random-word sequence. The LpIFG showed exactly this predicted pattern, indicating that it is involved in syntactic unification. Regions subserving the retrieval of lexical-syntactic information from memory, on the other hand, should show more activation for ambiguous than for unambiguous conditions, in sentences as well as in random word strings. This pattern was observed in the LpMTG, signaling its involvement in the retrieval process. The pattern of results suggested a dynamic interplay

between these two regions in the unification process (Snijders et al., 2009). A subsequent functional connectivity study confirmed the existence of enhanced functional coupling between left inferior frontal and left posterior temporal regions during sentence-level unification (Snijders et al., submitted-a, see Chapter 3).

The effect of ambiguity in sentences in frontotemporal regions found in Chapter 2 could be an effect occurring at the ambiguous word (two lexical frames entering the Unification Space and starting a competition) as well as an effect at the disambiguating word (one lexical frame wins and is selected). Given the low temporal resolution of fMRI, we could not distinguish between these two possibilities. The high temporal resolution of MEG allowed us to resolve this question with the present MEG study.

In general, psycholinguistic models do not pay much attention to inter-individual differences. However, individual variability in language processing abilities certainly exists (Just and Carpenter, 1992; Pakulak and Neville, 2009). Recently we have shown that a common polymorphism in the *CNTNAP2* gene, a gene that is down-regulated by *FOXP2*, is a source of inter-individual variability in language processing (Snijders et al., submitted-b). *CNTNAP2* is a cell-adhesion molecule expressed during development, and is probably also active at the level of the synapse. Variance in synaptic connections might very well have an influence on high-level cognitive and social processes such as language. Our fMRI study showed that a common genetic variant in *CNTNAP2* leads to differential functional recruitment of brain areas in the sentence processing network (Snijders et al., submitted-b, see Chapter 4). Would this difference also be reflected in a differential time course for syntactic processing in the brain?

In the present study we investigated the time course of the syntactic unification process. Is the activity in left frontotemporal regions induced by increased unification demands for ambiguous sentences, as identified in the fMRI study by (Snijders et al., 2009), caused by competition processes at the ambiguous word or by ambiguity resolution at the disambiguating word? Which syntactic processing routes are used in the face of word-category ambiguity? Furthermore, we were interested in individual variability in syntactic processing routes. Are individual differences in the time course of syntactic unification processes mediated by common genetic variation in the *CNTNAP2* gene?

Materials and Methods

Participants

Thirty-two native Dutch speakers (16 females, aged 18–25) recruited through the subject database of the Donders Centre for Cognitive Neuroimaging, Nijmegen, participated in the study. Participants were right-handed without any history of neurological disease or language-related impairment. Participants provided written consent according to the Declaration of Helsinki and they were paid for their collaboration. Six additional participants were measured but discarded because of machine failure (three occasions) and excessive head movement.

Stimulus Material

The stimuli consisted of 80 Dutch sentences (S) and 80 matched scrambled sequences of Dutch words (W). Both the Sentences and the Word sequences contained a critical word that was either word-class (noun/verb) ambiguous (A) or unambiguous (U). The critical word in the sentences was disambiguated to either a noun (n) or a verb (v) reading by the immediately following word. In total, this resulted in eight possible conditions: SAn, SAv, SU_n, SUv, WAn, WAv, WU_n, WUv (see Table 5.1 for examples).

The ambiguous words were equibaised, that is, there was no strong preference for the noun over the verb interpretation, or vice-versa. This was brought out both by matching the words' lexical frequencies as occurring in Dutch lexical databases (Baayen et al., 1993; Beek et al., 2001), as well as by matching words on the results of a pre-test, on a different group of participants, where subjects had to complete sentences (e.g. "*Want deze sprongen ...*"). The ambiguous sentences were constructed such that both word-classes of the ambiguous word fitted syntactically as well as semantically with the initial part of the sentences (up to and including the critical word); the sentences were disambiguated by the word following the ambiguous word (see Table 5.1 for an example). Word sequences were constructed from the sentences by substituting every word (except the critical word) by a different word matched for length, frequency, and word-class, and subsequently scrambling the order of the words in the sequence (except the critical (ambiguous/unambiguous) word). For a full description of experimental materials, see Chapter 2. These original experimental materials were extended from 68 to 80 items. In the original materials the disambiguation could also occur later in the sentence, so we adapted these materials such that the disambiguating word always followed the ambiguous word immediately. For the full set of materials of the present experiment see Appendix 1B.

Experimental Lists

Experimental lists were assembled consisting of three parts (blocks). For the first two blocks, the 80 experimental items were distributed over four lists, matched for pretest noun-ratios, sentence lengths, and position and frequency of the critical words. For every item, one of the following combinations occurred in each list: SAn+WUv; SAv+WU_n; SU_n+WAv; SUv+WAn; hence no critical word was repeated in the first two blocks. To increase the number of trials per condition, the critical items from the first block were repeated in the third block, swapping the condition pairs to minimize any possible priming or memory effect. For instance, if subjects had seen SAn and WUv of an experimental item in the first block, they would encounter WAn and SUv in the third block (see Table 5.1 for an example item). Consequently, both ambiguous and unambiguous items were repeated, but the critical word was never seen more than once in a sentence or a word context, and the context itself was never repeated. This resulted in 8 different experimental lists, with 60 items per subject per condition (SA, SU, WA, WU). Every experimental list was assigned to two male and two female participants.

Table 5.1.

Example of the experimental materials, with the critical word *sprongen* (*jumps/jumped*).

SAn: Sentence-ambiguous (noun context)	Want deze <u>sprongen</u> _(n/v) zijn niet zonder risico. <i>Because these jumps</i> _(n/v) <i>are not without risk.</i>
SUn: Sentence-unambiguous (noun context)	Want deze <u>medicijnen</u> _(n) zijn niet zonder risico. <i>Because these medicines</i> _(n) <i>are not without risk.</i>
SAv: Sentence-ambiguous (verb context)	Want deze <u>sprongen</u> _(n/v) dagelijks in het koude meertje. <i>Because these jumped</i> _(n/v) <i>daily in the cold lake.</i>
SUv: Sentence-unambiguous (verb context)	Want deze <u>zwommen</u> _(v) dagelijks in het koude meertje. <i>Because these swam</i> _(v) <i>daily in the cold lake.</i>
WAn: Words Ambiguous (derived from SAn)	cijfers alles <u>sprongen</u> _(n/v) ook aan weg die <i>digits all jumps/jumped</i> _(n/v) <i>also on way those</i>
WUn: Words Unambiguous (derived from SUn)	cijfers alles <u>medicijnen</u> _(n) ook aan weg die <i>digits all medicines</i> _(n) <i>also on way those</i>
WAv: Words Ambiguous (derived from SAv)	in uit <u>sprongen</u> _(n/v) alle het kooplui heer allerlei <i>in out jumps/jumped</i> _(n/v) <i>all the traders lord diverse</i>
WUv: Words Unambiguous (derived from SUv)	in uit <u>zwommen</u> _(v) alle het kooplui heer allerlei <i>in out swam</i> _(v) <i>all the traders lord diverse</i>

Procedure

Stimulus words were presented one by one in the middle of the screen, using Presentation software (Version 9.13, <http://www.neuro-bs.com>). Every word was visible for 300 ms, with a 300 ms interword interval. At the beginning of each sentence or word sequence, a visual fixation cross (2 seconds) showed when the participant could blink, followed by a 1.2 second long blank screen. The participants were instructed to read each sentence/sequence carefully and attentively, and were told that after the experiment some questions concerning the experiment would have to be answered. The participants' task was spotting the consonant-strings (e.g., *cdsln*), that were present in 60 filler-items (30 sentences and 30 sequences). This simple control task was added to ensure that participants were paying attention.

Every subject saw 120 sentences and 120 word sequences (ambiguous/unambiguous; in noun/verb version), intermingled with 96 fillers (48 sentences and 48 sequences). Stimuli were presented in sets of five sentences or word sequences. Before each set the label "Zinnen:" ("Sentences:") or "Woorden:" ("Words:") appeared on the screen (for 1.5 seconds) to indicate the condition of the following set. We expected the labels to encourage ("Sentences") or discourage ("Words") attempts to syntactically/semantically integrate the stimulus items in the

upcoming set. The ambiguous/unambiguous and verb/noun conditions were mixed within the sets in a pseudo-randomised presentation order.

MEG Data Acquisition

A whole-head MEG system (151 axial gradiometers, Omega 2000; VSM/CTF Systems, Port Coquitlam, British Columbia, Canada) was used for data acquisition. The data were digitized at 600 Hz. Participants were measured in supine position in a magnetically shielded room. Additionally, electro-oculogram (EOG) was recorded from electrodes above and below the eye, and at the outer canthi of the eyes. The head position relative to the MEG sensor array was measured before and after the experiment, as well as before the third block. This was done using reference coils placed at the subject's nasion, and at the left and right ear canals. These landmarks were used for the off-line realignment with the anatomical scans acquired with the MRI (Hämäläinen et al., 1993). In a separate session, a full-brain anatomical MRI image of each participant was acquired on a 1.5 T Siemens Sonata scanner (Siemens, Erlangen, Germany), using a standard T1-weighted sequence.

Genetic analysis

DNA was isolated from saliva using the Oragene system (DNA Genotek Inc., Kanata, Ontario, Canada). DNA-isolation and genotyping were performed in a CCKL-accredited laboratory at the Department of Human Genetics of the Radboud University Nijmegen Medical Centre in Nijmegen. The *CNTNAP2* polymorphism (rs7794745, A>T) was genotyped using Taqman analysis (assay ID: rs7794745: Taqman assay C_2661558_10, reporter 1: VIC-A-allele, forward assay; Applied Biosystems, Nieuwerkerk a/d IJssel, The Netherlands). Genotyping was carried out in a volume of 10 µl containing 10 ng of genomic DNA, 5 µl of Taqman Mastermix (2x; Applied Biosystems) and 0.125 µl of the Taqman assay and 3.875 µl of MilliQ. Amplification was performed by an initial denaturation at 95°C for 12 min, followed by 40 cycles of denaturation at 92°C for 15 seconds and annealing/extension at 60°C for 1 minute. This was carried out on a 7500 Fast Real-Time PCR System. Genotypes were scored using the algorithm and software supplied by the manufacturer (Applied Biosystems). Generally, 5% blanks as well as duplicates within and between plates were taken along as quality controls during genotyping.

For further analysis, carriers of at least one T allele were grouped together and compared to carriers of the AA homozygous genotype.

MEG Data Analysis

Data were analyzed using FieldTrip (<http://www.ru.nl/neuroimaging/fieldtrip/>), an open source Matlab toolbox (The MathWorks, Natick, MA) for EEG and MEG analysis that has been developed at the Donders Institute for Brain, Cognition and Behaviour. Individual trials were time-locked to the onset of the critical (ambiguous/unambiguous) word, and included a 200 ms interval before, and the

1500 ms interval after this word. All trials were screened for artifacts (eye blinks, vertical and horizontal eye movements, muscle activity, jumps in the recording sensors) both by an artifact detection algorithm and by visual inspection. Trials containing artifacts were rejected, as well as trials in which participants inadvertently pressed the button. Remaining trials were bandpass filtered offline between 0.5 and 35 Hz, and re-sampled to 200 Hz. Baseline-correction was applied, in which the waveforms were normalized relative to the 200 ms stimulus-preceding epoch.

Using the anatomical MRI scan, data of individual subjects were realigned according to a standard head position in order to allow for grand-averaging (Knosche, 2002). Signals from the axial gradiometers were transformed to an approximation of the planar field gradient, using a nearest-neighbor method (Bastiaansen and Knosche, 2000). The planar gradient measures the strongest signal directly above a given source, thus facilitating inferences on the sources involved (Hämäläinen et al., 1993). Subsequently, averaged waveforms were computed.

Statistical analysis

Differences between conditions were tested using a nonparametric randomization test (Nichols and Holmes, 2002; Maris and Oostenveld, 2007). It effectively controls the Type-1 error rate in a situation involving multiple comparisons (i.e., 151 MEG sensors \times 340 time points) through a clustering approach. The method works as follows: In a first step, all (sensor, time point) pairs are identified for which the T -statistics for the difference between conditions (e.g., SA vs SU) exceed some prior threshold (here: $p < .05$). The selected (sensor, time point) pairs are then grouped into a number of clusters in such a way that, within every cluster, the (sensor, time point) pairs form a set that is connected spatially and/or temporally. Each cluster is assigned a cluster-level test statistic whose value equals the sum of the (sensor, time point) specific test statistics. Thus, the cluster-level test statistic depends on both the extent of the cluster and the size of the (sensor, time) specific T -statistics that belong to this cluster. The Type-1 error rate for the complete spatiotemporal data matrix is controlled by evaluating the cluster-level test statistic under the randomization null distribution of the maximum cluster-level test statistic. This randomization null distribution is obtained by randomizing the order of the data (e.g., SA vs SU) within every participant. By creating a reference distribution from 1000 random draws, the p-value may be estimated by the proportion from this randomization null distribution in which the maximum cluster-level test statistic exceeds the observed cluster-level test statistic (this proportion is called a Monte Carlo p-value). With 1000 random draws, the Monte Carlo p-value is an accurate estimate of the true p-value. In brief, the cluster randomization p-value denotes the probability that such a large summed cluster-level statistic will be observed when there is actually no effect. In this way, significant clusters extending both over time and over MEG sensors can be identified.

Separate cluster randomization tests were performed to check for the main effects of grammaticality (sentences versus words), the main effect of ambiguity (ambiguous versus unambiguous conditions), and the effect of ambiguity within sentences or word sequences only. When significant clusters were found, cluster randomization analyses were performed on mean event-related field (ERF) amplitude values of specific time windows for illustrative purposes (now clustering only over sensors, and not over time; see Figure 5.2-5.4).

In order to investigate the effect of *CNTNAP2* genotype on the MEG response to sentence processing, we calculated, for both genotype groups, the between-condition differences in mean ERF amplitude value, in the 300-500 ms and 500-700 ms time windows (after onset of the critical ambiguous/unambiguous word). We did this for the main effect of grammaticality (sentences versus words) as well as for the effect of ambiguity within sentences (sentence-ambiguous versus sentence-unambiguous conditions). For the effect of ambiguity within sentences, we also examined the 1000-1300 time window (disambiguating word). Cluster randomization tests were performed by comparing the difference waveforms between genotype groups. The clustering algorithm for the genotype comparison was restricted to the left temporal MEG sensors, as here the overall effect of sentence (ambiguity) processing was largest (see Figure 5.2 and 5.3). When significant differences between genotype groups prevailed, we carried out separate cluster randomization tests for the different genotype groups.

Results

Genotyping

Of the thirty-two participants, genotypes for *CNTNAP2* were available for twenty-four subjects. Ten subjects (5 females) were homozygous for the A allele (AA group), and fourteen subjects (7 females) were carrier of at least one T allele (AT/TT group: 12 AT, 2 TT). Genotype distribution was according to Hardy-Weinberg equilibrium ($p = .54$).

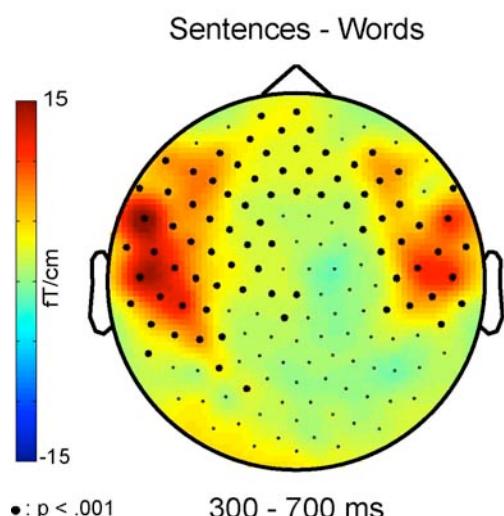


Figure 5.2.

Topography of the event-related field (ERF) difference between sentences and word sequences (300-700 ms). Sensors that differ significantly in this time window are marked with large black dots ($p < .001$ corrected for multiple comparisons with cluster randomization routine).

Grammaticality effect

The cluster randomization analysis comparing sentences and word sequences revealed two significant clusters ($p < .001$): one for the time window of the critical (ambiguous/unambiguous) word (280-775 ms), and one for the following word (935-1365). The difference between sentences and words was largest over left temporal and right temporal sensors, and extended into frontal regions (see Figure 5.2 for the effect from 300-700 ms). This is in accordance with our fMRI study showing increased bilateral frontotemporal activation for sentences compared to word sequences (Snijders et al., 2009, see Chapter 2).

Genotype x Grammaticality effect

No significant Genotype x Grammaticality interaction could be identified in the 300-500 and 500-700 ms time windows.

Ambiguity effects

There was no main effect of ambiguity surviving multiple comparisons correction.

Ambiguity effect within sentences

The main question of the current study was whether increased frontotemporal activity for processing ambiguous sentences is to be related to processes at the ambiguous word, or to ambiguity resolution at the disambiguating word. When looking at the whole group of subjects, there was no significant difference between ambiguous and unambiguous sentences in the time window of the ambiguous word. However, there was a significant ERF increase ($p = .005$) for sentence-ambiguous conditions between 985 and 1300 ms after onset of the ambiguous word (i.e. 385-700 ms after onset of the *disambiguating word*). Figure 5.3 shows the topographic distribution in the 1000-1300 ms time window, and the temporal evolution of the ERF amplitude for the significant channels. The spatial distribution of the effect over time is shown in Figure 5.4. The effect started at left temporal sensors, extended into frontal and posterior temporal sensors, and ended again in a (posterior) temporal distribution.

Effect CNTNAP2 genotype on ambiguity effect in sentences

As said above, we did not find any group-level difference between ambiguous and unambiguous sentence conditions before the disambiguating word. However, at the level of individual participants we did observe differences at the ambiguous word that were dependent on *CNTNAP2* genotype. At left temporal sensors, we found a significant difference between genotype groups in the ambiguity effect within sentences, 500-700 ms after onset of the ambiguous word (genotype x sentence ambiguity interaction, $p < .001$). Figure 5.5 shows the effect at the ambiguous word (500-700 ms) for the AA genotype group and the AT/TT genotype group separately. The AA genotype group showed a larger ERF signal over left temporal sensors for sentence-ambiguous than for sentence-unambiguous conditions ($p = .011$). The AT/TT genotype group, on the other hand, showed an increased signal for sentence-unambiguous compared to sentence-ambiguous conditions ($p = .007$).

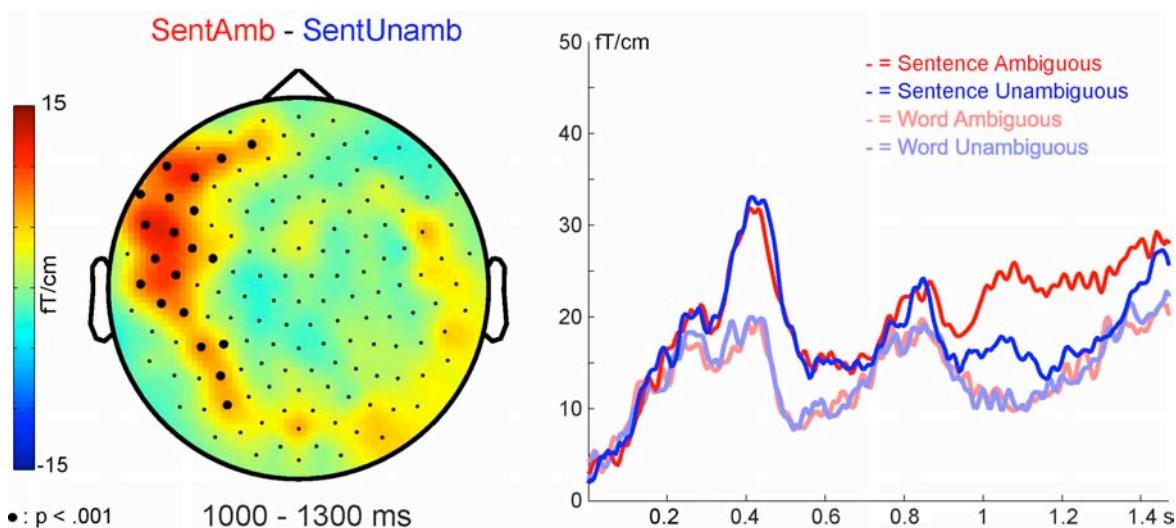


Figure 5.3.

Sentence ambiguity effect. Left: topography of the event-related field (ERF) difference between sentence-ambiguous and sentence-unambiguous conditions (1000-1300 ms after onset ambiguous word, 400-700 ms after onset disambiguating word). Sensors that differ significantly in this time window are marked with large black dots ($p < .001$ corrected for multiple comparisons with cluster randomization routine). Right: ERFs for sentence-ambiguous (red), sentence-unambiguous (blue), word ambiguous (light red), and word unambiguous (light blue) conditions, averaged over significant sensors (marked with large black dots in the left figure). The ERFs are time-locked to the critical (ambiguous/unambiguous) word; at 600 ms the following (disambiguating) word is presented.

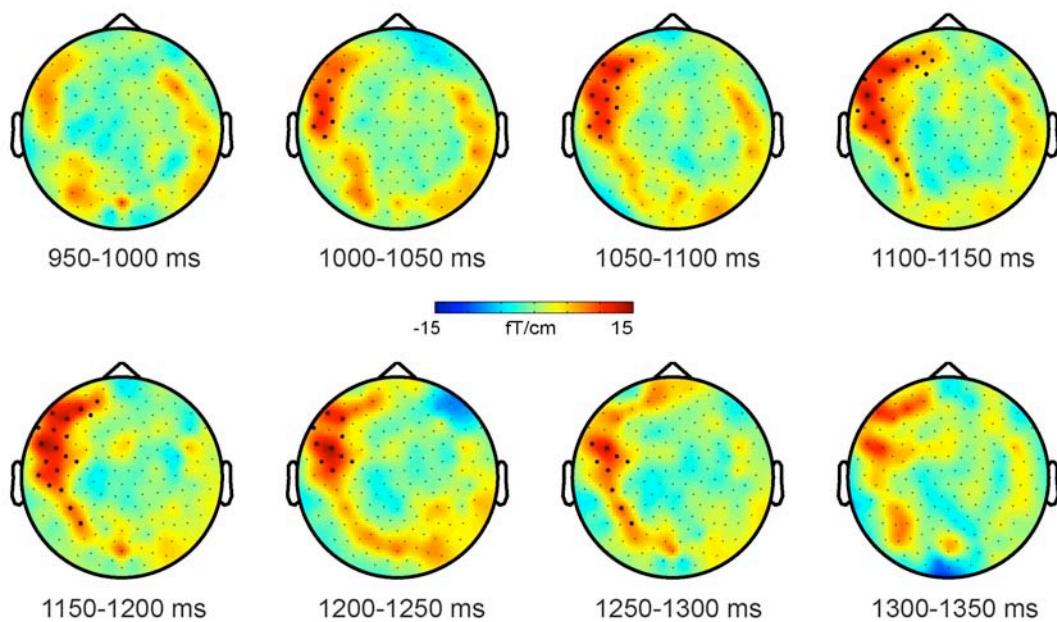
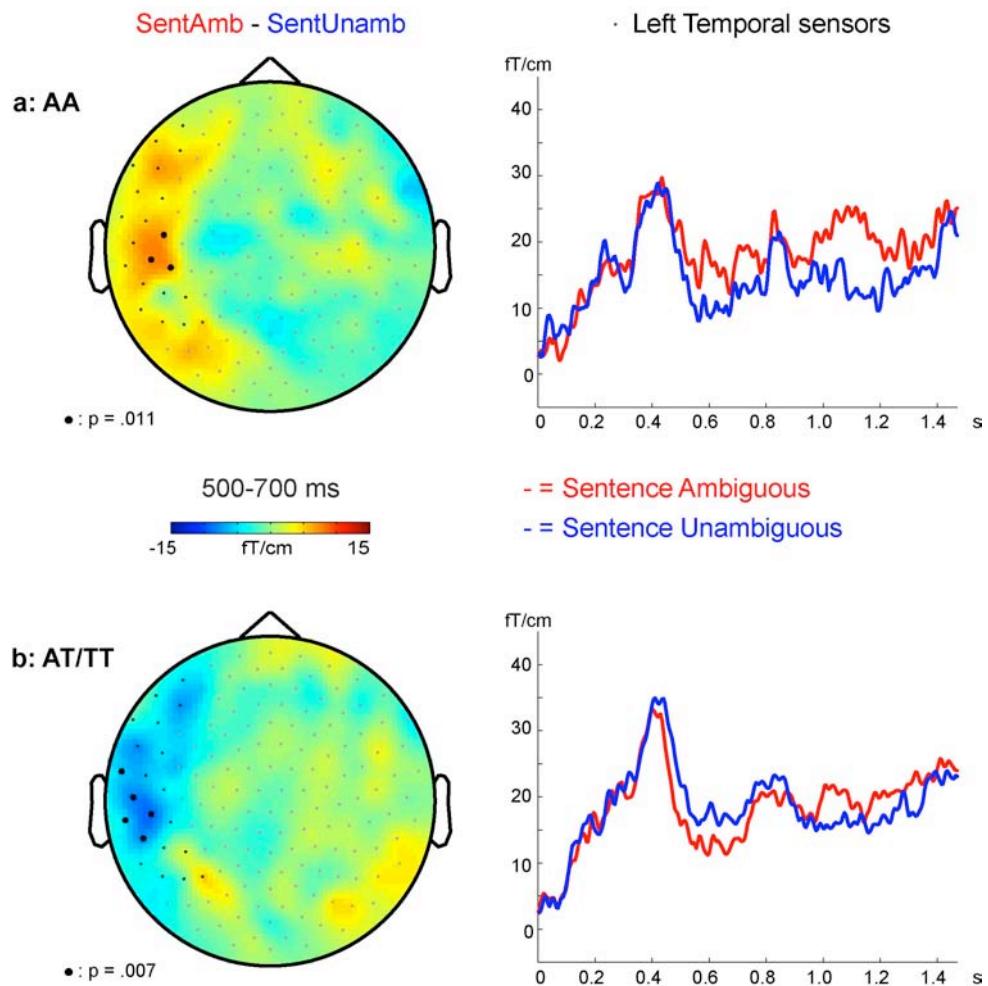


Figure 5.4.

Topography of the event-related field (ERF) difference between ambiguous and unambiguous sentences in bins of 50 ms (950-1350 ms after onset ambiguous word; 350-750 ms after onset disambiguating word). Sensors that differ significantly in the specified time window are marked with large black dots ($p < .05$ corrected for multiple comparisons with cluster randomization routine).

**Figure 5.5.**

Sentence ambiguity effect at ambiguous word (500-700 ms) for AA (A) and AT/TT (B) *CNTNAP2* genotype groups separately. Left: topography of the event-related field (ERF) difference between sentence-ambiguous and sentence-unambiguous conditions (500-700 ms). Left temporal sensors (black dots) that differ significantly in this time window are marked as large black dots (corrected for multiple comparisons with cluster randomization routine; AA: $p = .011$, AT/TT: $p = .007$). Right: Mean ERFs for sentence-ambiguous (red) and sentence-unambiguous (blue) conditions, averaged over left temporal sensors (black dots in left panel).

There were no differences between genotype groups in the 300-500 ms or 1000-1300 ms time windows.

Ambiguity effect within word sequences

In the word sequence context, there was neither a significant difference between the ambiguous and unambiguous conditions, nor a significant interaction between genotype and ambiguity.

Discussion

In the present study we investigated the time course of the syntactic unification process. Words in a sentence processing context elicited larger ERFs over bilateral

frontotemporal regions than words in a random word list context. Word-category ambiguities within sentences resulted in an increased response over left frontotemporal regions at the *disambiguating* word (400-700 ms). Computed over the group of subjects as a whole, no differences for ambiguous versus unambiguous conditions emerged at the ambiguous word itself. However, this null-effect at the ambiguous word was due to opposite effects, within the same left frontotemporal network, for subjects with differing genotypes of a common *CNTNAP2* polymorphism. While subjects with an AA genotype showed increased response over left temporal regions for sentence-ambiguous compared to sentence-unambiguous conditions, T allele carriers showed a *decrease* in left temporal ERFs for sentence-ambiguous conditions.

The time course of syntactic unification

Reading words in a random word list versus in a sentence had a large effect on neural processing in bilateral frontotemporal regions, which is in accordance with our earlier fMRI findings (Snijders et al., 2009, see Chapter 2). The present MEG study shows, moreover, that the increased frontotemporal activation for sentences, identified with both fMRI and MEG, is not just a global effect of sentence processing, but indeed a more local effect of an increased processing load for the individual words. During sentence comprehension, the lexical information associated with the individual words of a sentence has to be maintained on-line during the unification of lexical information into an overarching representation of the whole utterance.

In the fMRI study by (Snijders et al., 2009), we found an effect of word-class ambiguity in sentences on frontotemporal activation (LpIFG and LpMTG). The present MEG study enables us to attribute this effect partly to processes at the ambiguous word, and partly to ambiguity resolution at the disambiguating word. The largest ERF effect in response to sentence ambiguity occurred at the disambiguating word, implying that the fMRI effect in left inferior frontal and posterior temporal regions is largely due to the final stage of the unification process (one lexical frame wins and is selected). This is in accordance with fMRI research suggesting that LIFG deals with selection between competing sources of information (Thompson-Schill et al., 2005). When looking at the development of the effect over time, we saw that the effect started at left temporal sensors, after which it spread into frontal and posterior temporal sensors, and ended again in a (posterior) temporal distribution. The distribution over frontotemporal sensors is in accordance with our finding that left frontal and temporal regions are in constant interplay during the unification process (see Chapter 3).

Effects of CNTNAP2 on syntactic processing route

Both genotype groups show bilateral frontotemporal activation in response to sentence processing, and stronger left frontotemporal ERFs for ambiguous than for unambiguous conditions at the disambiguating word. Within this network, which is active in both groups, we could identify subtle differences between the processes at

the ambiguous word, depending on *CNTNAP2* genotype. Specifically, while subjects with an AA genotype showed increased ERFs over left temporal regions for sentence-ambiguous compared to sentence-unambiguous conditions, T-carriers showed a *decrease* in left temporal response for sentence-ambiguous conditions³. This finding is yet another confirmation that a common polymorphism in *CNTNAP2* influences the language user's neurocognitive processing route (see Chapter 4).

How to explain the genotype-linked difference between sentence ambiguity effects? The whole-group effect seen at the disambiguating word is compatible with the assumption that this effect reflects the presence (in the ambiguous condition) or absence (in the unambiguous condition) of the need to select between alternative sentence interpretations. One possible interpretation of the genotype-mediated difference at the ambiguous word in sentences assumes that, while unification is "early" in the AA group, it is "delayed" in the AT/TT subjects. In the face of ambiguity, AT/TT subjects seem to postpone the unification process (or large parts of it) to the disambiguating word. Because no unification attempts take place at the ambiguous word, the ERF observed at this word is reduced in comparison to sentence-unambiguous conditions. Following this interpretation, the increased ERFs yielded by the AA group at the ambiguous word in sentence conditions would reflect the early unification process at the ambiguous word (selection of one unification possibility). If this is the case, we might expect increased ERFs for sentence-ambiguous conditions at the *disambiguating* word for AA subjects compared to AT/TT subjects. The reason is that, in a fair proportion of trials, the AA subjects need to reanalyze the word string seen so far - which is not the case for the AT/TT subjects, since they have not yet committed themselves to one of the two possible readings of the ambiguity. Indeed, the effect at the disambiguating word is numerically larger for AA subjects (see Figure 5.5, right panels, 1000-1300 ms); however this difference is not significant.

Interpretation of the results in terms of a computational model

In this section, we propose a tentative explanation of the genotype-linked difference between sentence ambiguity effects in terms of an explicit computational model: the neural network implementation of the Unification-Space parser (Vosse and Kempen, 2000, 2009, see introduction). This parser, nicknamed SINUS, is a localist neural network whose dynamics are based on interactive activation and inhibition. The SINUS network consists of a one-dimensional array of "columns" (see Figure 5.6). Every node in a column codes for a grammatical property of an incoming word (*localist representation*). The nodes and their interconnections are not word-specific, i.e. the architecture is identical in every column, and every column can be occupied by a member of every word class. The columns are filled one by

³ Note that we are reporting planar gradients here, which can only be positive (as opposed to ERP components in EEG research, where one can observe positive and negative peaks). The planar gradient measures the strongest signal directly above a given source. Increased source activity results in a larger positivity.

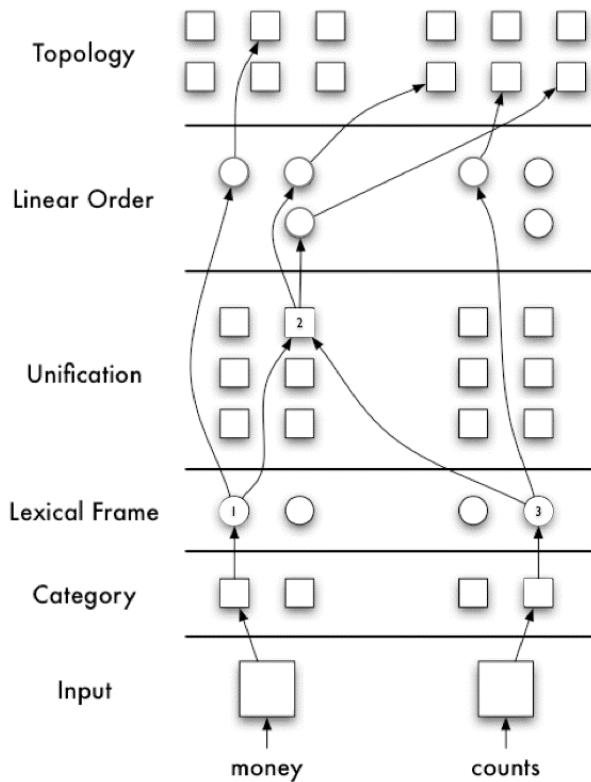


Figure 5.6. Activation spreading through the SINUS network for the noun *money* and the verb *counts* in the example sentence ‘*money counts*’. The *Input* layer functions as the intermediary between Mental Lexicon and Unification Space. The *Word Category* layer represents the head of the lexical frame associated with the input word (see Figure 5.1). It also contains nodes coding for the morphosyntactic properties of the input word (number, person, gender, etc.). In case of word-class ambiguity, several word category nodes and their associated features can be active simultaneously (due to competition via inhibitory connections, one of the categories will ultimately gain the upper hand). The *Lexical Frame* layer codes for the syntactic information in the lexical frame(s) associated with the input words. Multiple frames may be active at the same time. The *Unification* layer contains so-called Unification nodes (U-nodes). A U-node carries the name of a grammatical function (Subject, Direct Object, Modifier, etc.). The *Linear Order* and *Topology* nodes code for information about the place of the word within the sentence structure. The arrows show feedforward activation between nodes that turn out to win the competitions in the various layers. Node #1 stands for Noun Phrase, node #3 for Sentence (clause), and node #2 represents the grammatical relation of Subject. The *intracolumnar* connection from node #1 to node #2, together with the *intercolumnar* connection from node #3 to #2 expresses the analysis of *money* as the grammatical subject of *counts*. See (Vosse and Kempen, 2009) for further information on definitions and network dynamics. (Adapted from Figure 6 in Vosse and Kempen, 2009).

one, from left to right, in accordance with word order in the input string. If a word is word-class ambiguous, it activates more than one set of nodes within the same column. Representations of grammatical relations between the words of a sentence are based on intercolumnar connections. These enable SINUS to pre-activate (or pre-inhibit) certain nodes in columns rightward of the last filled columns (which will be occupied by words further downstream). The bank of the interconnected word columns is the “Unification Space”, where syntactic structures are built in the form of activation patterns.

A basic assumption in SINUS is that the alternative readings (i.e. lexical frames) of a word-class ambiguous lexical item inhibit one another (competition). Due to this mutual inhibition, an ambiguous lexical item in a sentence engenders lower activation levels of nodes in the corresponding column in the Unification Space than an unambiguous lexical item. Therefore, ambiguous words in sentences are predicted to elicit weaker ERFs than unambiguous words in sentences. This prediction holds for both genotype groups. Hence, in order to explain why the AA subjects exhibit the opposite difference (stronger ERFs for ambiguous words in sentences), we need an additional assumption: AA subjects have stronger excitatory

intercolumnar connections than AT/TT subjects. Activation flowing from the column(s) occupied by the initial word(s) of the sentence, manages to increase the activation level of, and the competition between, nodes in the column occupied by the critical ambiguous word. In the AA subjects, this will often result in a provisional winner of the competition and in building the corresponding syntactic structure. In the AT/TT group, however, the competition will remain weak, and not much structure building will occur. This inter-genotype difference may be reinforced by the stronger functional connectivity between left inferior frontal and left posterior temporal regions in the AA than in the AT/TT subgroup during unification (see Chapter 4). At the disambiguating word, the AA subjects will be forced more often into reanalysis (of the initial structural selection at the ambiguous word), whereas the AT/TT subjects will hardly ever need to undo a provisional selection. Consequently, the effect of disambiguation will be more pronounced in the AA than in the AT/TT subjects.

Link of CNTNAP2 results to autism research

The above – speculative – account in terms of the SINUS computational model is compatible with the idea that AA subjects are more context-driven (“global”) and the AT/TT subjects more lexically driven (“local”) in their processing styles (see Chapter 4). It hinges on stronger connectivity between language-related cortical areas in AA than in AT/TT genotype groups, both within LIFG and between LIFG and left posterior temporal regions. This tentative account dovetails with the fact that people with an AA genotype are less likely to develop autistic symptoms than T-carriers (Arking et al., 2008). Cognitive processing in autistic patients tends to be less context-dependent than in controls (Happe and Frith, 2006). People with autism show less connectivity between LIFG and left posterior temporal regions during sentence comprehension (Just et al., 2004). Furthermore, the morphology of minicolumns in the neocortex is altered in subjects with autism (Casanova et al., 2002), especially in LIFG (BA 44) (Casanova et al., 2010). This might lead to diminished lateral inhibition between minicolumns. It has been hypothesized that there is an imbalance in excitatory and inhibitory neurotransmitters in subjects with autism (Hussman, 2001), with the inhibition through horizontal neuronal connections being impaired (Vandenbroucke et al., 2008).

Of course, it is premature to assume any close relationship between the minicolumns and their interconnections in the cerebral cortex as outlined above on the one hand, and the columns and intercolumnar connections in the SINUS model on the other. However, although the computational account of the genotype differences is speculative, it can serve as a suitable starting point for further research. Further refinement of SINUS will be needed to simulate our findings regarding the differential effects of word-class ambiguity in the two genotype groups.

Comparison to CNTNAP2 effects on fMRI response to sentence processing

In the fMRI study (see Chapter 4), we did not see genotype differences in brain activation for sentence-ambiguous versus sentence-unambiguous conditions; however, we did see increased functional connectivity between left inferior frontal and left posterior temporal regions for the AA genotype group for sentence-ambiguous compared to sentence-unambiguous conditions. This is consistent with the increased ERF response seen for the AA genotype group in the current MEG study.

While in our fMRI study we find differences between *CNTNAP2* genotype groups in sentences versus word processing, in the current study there is no genotype effect on the difference between ERFs to words in sentences versus in word sequences. This could be due to the high temporal resolution of MEG which makes us look at the effects occurring at the critical (ambiguous / unambiguous) word itself (with a baseline in the preceding word), without tapping into sentence general processes picked up by the fMRI study. Possibly the differences between genotype groups for sentences compared to word processing are not phase-locked to the word-stimulus, and thus not detectable with ERF measures. Future studies might explore oscillatory brain responses to sentences compared to words for the differing genotype groups, in order to tap into processes that are not phase-locked to the stimulus.

While interpreting the current results one should keep in mind that the *CNTNAP2* genotype groups of the present study are small, 10 versus 14 subjects. Follow-up studies including larger sets of subjects are needed to confirm the present results. Nevertheless, the results make clear that individual variability exists in syntactic processing routes in the brain.

Relation to previous ERP/ERF literature

It remains an open question whether the effect that we observed at the disambiguating word can be related to one of the well-known language-related EEG components, N400 (Kutas and Hillyard, 1980) or P600 (Osterhout and Holcomb, 1992; Hagoort et al., 1993). In the ERP literature, the N400 component, a negativity peaking around 400 ms after the critical word, has been related to semantic retrieval and unification processes, while the P600, a positive shift around 500-800 ms, has typically been associated with syntactic processing (Kutas et al., 2006; Hagoort et al., 2009). Unfortunately, the vast literature on these language related ERP components is of little help presently: ERP polarity and scalp topography cannot be compared with the MEG field distribution (see also note 1), and the temporal characteristics of the effect we observed (385–700 ms) are compatible with both accounts. In fact, the effect at the disambiguating word is too late and long-lasting to be a typical N400-component and it is too early for being a typical P600 effect. Furthermore, these two components have very close neural generators (Halgren et al., 2002; Service et al., 2007; Lau et al., 2008) and the spatial resolution of the present MEG experiment is not sufficient to tell them

apart. Consequently, it is impossible to reliably relate the effect at the disambiguating word to those language-related components.

How do our results relate to earlier electromagnetic studies on word ambiguity in the literature? There are only few studies that have investigated ERP/ERF responses to word-class ambiguous words. In a series of ERP experiments on noun/verb ambiguity, a frontal negativity (200-700 ms) to word-class ambiguous words was observed when these were embedded in syntactically well-defined but semantically neutral contexts, such as in minimal phrases ('*to/the watch*', Lee and Federmeier, 2006), in mid-sentence position of semantically neutral sentence contexts (e.g. '*Jeremy wanted to/the watch even though...*'', Federmeier et al., 2000), and at the end of semantically incongruent but syntactically structured sentences ('syntactic prose', Lee and Federmeier, 2009). Importantly, in these studies ambiguity detection and disambiguation were triggered by the same word and occurred in an overlapping time window, as the syntactic environment was well-defined beforehand. In our study, on the other hand, the sentences were still syntactically ambiguous when the word-class ambiguous word was read: ambiguity detection and disambiguation happened at two separate words. This makes it difficult to directly compare our study to these EEG studies. However, it is possible that the effect we identify at the disambiguating word is related to the frontal negativity mentioned above (Federmeier et al., 2000; Lee and Federmeier, 2006, 2009).

Conclusion

In this MEG study, we investigated the time course of syntactic unification, using word-class ambiguous words in a sentence versus word-list context. We identified a left frontotemporal brain response related to completion of the unification process (selection of the relevant structural interpretation) at the disambiguating word. Within the commonly activated brain network, subtle differences depending on *CNTNAP2* genotype could be identified for processing at the ambiguous word. There is individual variability with respect to what syntactic processing route is used in the face of word-category ambiguity, a variability that seems to be mediated by a common polymorphism in *CNTNAP2*.

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Chapter 6

Summary and discussion

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Summary

In order to comprehend the sentences we hear and see around us, we need to retrieve information about single words from memory, and combine (unify) this information into a multiple-word or sentence representation. The research addressed in this thesis investigated the neural dynamics of the syntactic retrieval and unification processes. We used word-category ambiguous words (words that can be both a noun and a verb) in word lists and sentences to induce differential retrieval and unification demands. We explored the neural basis of syntactic retrieval and unification processes (Chapter 2), investigated how the various brain regions involved work together in a brain network for syntactic unification (Chapter 3), and looked at the time course of syntactic unification processes induced by word-category ambiguity in sentences (Chapter 5). Additionally, we explored the influence of a common genetic variant in the *CNTNAP2* gene on the brain response to sentence processing (Chapter 4) and on the time course of word-category ambiguity processing in sentences (Chapter 5). Here I will summarize the results of each chapter.

The aim of Chapter 2 was to disentangle the retrieval and unification processes in sentence structure comprehension in the brain. Subjects read sentences and word sequences, containing word-category (noun-verb) ambiguous words at critical positions. In the ambiguous conditions both the noun and the verb information (two ‘lexical frames’) have to be retrieved from long-term memory, thus inducing a higher lexical-syntactic retrieval demand for ambiguous than unambiguous conditions. The sentences require unification into an overall sentence structure, whereas the word sequences do not. Moreover, word-category ambiguity in sentences, but not in word sequences, further increases the syntactic unification demands: the two retrieved lexical frames are competing for unification. We hypothesized the left inferior frontal gyrus (LIFG) to be involved in syntactic unification: indeed, increased activity was seen in this brain region for sentences compared to words and, in addition, for word-category ambiguous sentences compared to unambiguous sentences. The left posterior temporal cortex was hypothesized to be involved in retrieval of lexical-syntactic information: indeed, the left posterior middle temporal gyrus (LpMTG) showed enhanced signal for ambiguous compared to unambiguous conditions. Thus, we confirmed our hypothesis of a division of labor between LpMTG and LIFG in retrieval of lexical-syntactic information from long-term memory, and unification of this information into a sentence structure, respectively. The pattern of results suggested a dynamic interplay between these two regions in the unification process. Furthermore, the right inferior frontal gyrus (RIFG) and the right middle temporal gyrus (RMTG) were found to be activated for sentence ambiguous compared to sentence unambiguous conditions, while the right striatum showed an effect of ambiguity for both sentences and word sequences.

In Chapter 3 we explored the effective connectivity between LpIFG and LpMTG during unification, and how the right hemisphere regions and the striatum are functionally connected to the unification network (see Figure 6.1). LpIFG and

LpMTG both showed enhanced coupling for sentence ambiguous compared to sentence unambiguous conditions with a region slightly superior to our previously reported LpMTG. RIFG predicted right posterior temporal gyrus activity, similarly to how LIFG predicted activity in LpMTG. Furthermore, the striatum showed enhanced coupling to LpIFG and LpMTG during syntactic unification. We suggested that connections between LIFG and the striatum may control the extraction of lexical-syntactic information from left posterior temporal regions in the service of unification operations subserved by LIFG.

In Chapter 4 we investigated the effect of a common polymorphism in *CNTNAP2* on sentence processing in the brain, using the same experimental materials as in Chapters 2 and 3. *CNTNAP2* is a cell-adhesion molecule expressed during development, and is also active at synapses. Variance in synaptic connections might very well have an influence on high-level cognitive and social processes such as language. While in the two genotype groups the overall brain network involved in sentence processing was highly similar, the two genotype groups differed with respect to the balance in activation patterns in frontal and temporal brain regions. Additionally, we found differences between genotype groups in effective connectivity between LpIFG and LpMTG, and in RIFG grey matter volume. This study was the first to identify an effect of a common genetic polymorphism on the brain response to language: a genetic variant in *CNTNAP2* results in different neurocognitive processing routes for sentence processing.

The effect of ambiguity in sentences in left frontotemporal areas, identified in Chapter 2, could be related to processes at the ambiguous word, as well as to ambiguity resolution at the disambiguating word. In Chapter 5, we investigated the time course of the syntactic unification process induced by word-category ambiguity in sentences, using MEG. For sentences compared to word sequences, enhanced event-related fields (ERFs) were identified over bilateral frontotemporal brain regions. Furthermore, word-category ambiguity within sentences resulted in increased left frontotemporal ERFs at the disambiguating word, while no whole-group effect could be identified at the ambiguous word itself. Thus, the left frontotemporal brain response is related to the selection part of the unification process (ambiguity resolution). At the word-class ambiguous word the direction of the effect was dependent on *CNTNAP2* genotype: while subjects with an AA genotype showed increased ERFs over left temporal regions for sentence-ambiguous compared to sentence-unambiguous conditions, T-carriers showed reduced ERFs for sentence ambiguous conditions. Thus, individual variability exists as to which syntactic processing route is used when confronted with word-category ambiguity in sentences.

Discussion

What is new and exciting about the work presented in this thesis? We have used an explicit computational model of syntactic processing to make well-defined predictions about what happens when people read sentences and word sequences containing word-class ambiguous words. The results of the present thesis

emphasize the importance of thinking in terms of brain network interactions rather than of simple co-activations of localized brain regions. Just as a sentence is more than its words, a brain is more than its parts. Furthermore we have pioneered in describing genetic effects on the brain response to language. Below I will discuss and speculate on the main principles of the brain network for syntactic unification, and the influence of *CNTNAP2* hereon.

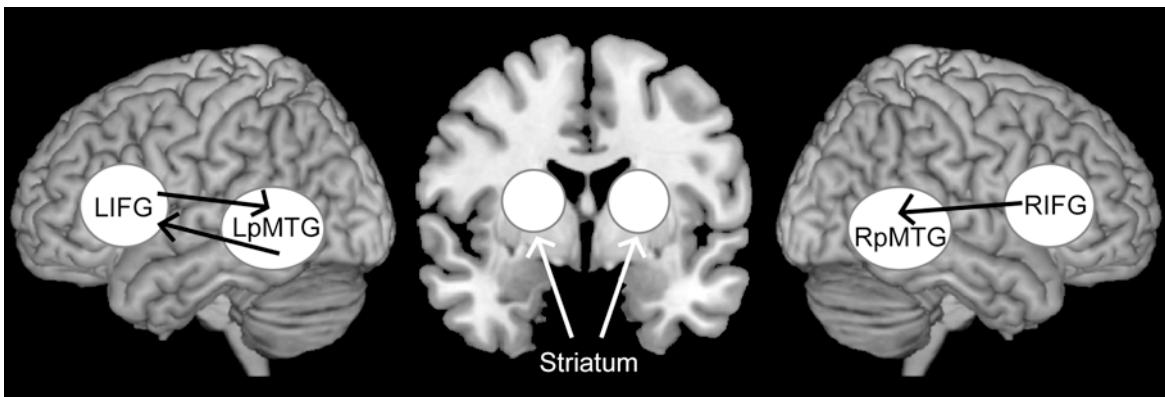


Figure 6.1. Sketch of the main players in the brain network for syntactic unification, with some interactions between brain regions during unification displayed as black arrows.

The brain network for syntactic unification

Left inferior frontal gyrus

The results of this thesis give convincing evidence for the involvement of LIFG in the syntactic unification process during sentence comprehension. In both Chapters 2 and 4 we observed that the posterior LIFG became more highly activated when a higher unification load was induced by sentences (versus random word-lists), and by word-category ambiguity in sentences. This was not due to the semantic consequences of the word-category ambiguity (see Chapter 2). The results of Chapter 5 indicated that the increased activation in LIFG for syntactic unification was largely due to the finalization of the unification process: the selection between alternative sentence interpretations. Of course, syntactic unification is not the only process subserved by LIFG. Specialized functions emerge from the unique cooperation of a network of brain areas each embodying domain-general mechanisms (Mesulam, 1998). Syntactic unification is the result of the posterior LIFG collaborating with representational areas in the posterior temporal lobe (Chapter 3).

Left posterior temporal cortex

In Chapter 2 we identified LpMTG, at the border of the inferior temporal sulcus, to be activated more strongly for ambiguous than unambiguous conditions. This ambiguity effect is what we predicted for retrieval of lexical-syntactic information from the mental lexicon. However, the ambiguity effect in LpMTG was larger for sentences than for random word lists, and LpMTG showed increased activation for

sentences compared to word lists. Our interpretation of this pattern of results is that sentence processing requires *sustained activation* of lexical-syntactic information. During sentence comprehension, the lexical frame information has to be available for a longer time interval than during the processing of random word sequences. The lexical-syntactic information probably is not ‘copied’ from the mental lexicon to the unification area, but instead remains activated within the mental lexicon. The sustained lexical frame activation could be brought about by feedback from the unification area. This is also implemented, for independent theoretical modeling reasons, in the neural network implementation of the Unification Space model of syntactic parsing (Vosse and Kempen, 2009). Neurally, this would be realized by feedback from LIFG to left posterior temporal brain regions. In Chapter 3 we confirmed that effective connectivity between LIFG and left posterior temporal gyrus was enhanced for word-category ambiguous sentences. The precise role of more superior and more inferior parts of LpMTG remains a topic for further research (see Chapter 3).

Right hemisphere

For language processing, the right hemisphere is used especially for language in context (text, discourse) and for ambiguous language. The RIFG has been suggested to be specifically involved in the formation and updating of a situation model, that is, a mental representation of the situation described in the sentence or discourse, constructed through interactions between incoming information and background world knowledge (Menenti et al., 2009). This thesis provides further evidence for right hemisphere involvement in sentence processing when context is needed for the disambiguation of alternative interpretations. In Chapter 2, RIFG and RpMTG were activated when processing ambiguities in sentences. Chapter 3 showed that the RIFG activity predicts activity in right posterior temporal cortex, in a way similar to how the LIFG predicts left posterior temporal cortex activity. Chapter 4 indicated that there may be individual differences (mediated through a common genetic variant in *CNTNAP2*) as to how much RIFG is involved in sentence processing, hence, possibly, as to how often the situation model is updated during sentence processing. In the MEG study of Chapter 5, we only saw left-hemisphere activations for word-class ambiguity in sentences. Possibly, the right-hemisphere processes in response to word-category ambiguity in sentences are less tightly time-locked to the stimulus than those in the left hemisphere.

The striatum

The right striatum was activated more strongly for word-class ambiguous conditions, both in sentences and in word-sequences (Chapter 2). Furthermore, the striatum showed enhanced coupling to LpIFG and LpMTG during syntactic unification (Chapter 3). As the magnetic signal falls off with the square of the distance, the striatal signal was probably undetectable in the MEG experiment (Chapter 5), where we did not identify a main effect of ambiguity. While the LpIFG seems to be mainly involved in the finalization of the unification process

(selection of the appropriate unification interpretation, Chapter 5), we believe that the interaction between the striatum, LpIFG, and LpMTG is needed during the competition part of the unification process (when several lexical frames are competing for unification). The striatum has been proposed to provide a dynamic gating mechanism by momentarily inhibiting or disinhibiting the frontal cortex (Hazy et al., 2007). The striatum can modify information transfer between cortical regions (den Ouden et al., *in press*). In this way the striatum might enable (but not directly cause) lexical-syntactic information to be actively relayed from LpMTG to LIFG.

The brain network for syntactic unification

The various brain regions specified above may each have a specific role within syntactic unification; however, the process of syntactic unification is the result of collaboration among these brain regions. Competition between lexical frames is regulated by connections between the striatum and LIFG, thus controlling the extraction of lexical-syntactic information from left posterior temporal regions in the service of final unification operations subserved by LIFG. Bilateral inferior frontal and posterior temporal gyri cooperate to unify the retrieved lexical-syntactic information into the contextually relevant structural interpretation.

Open issue: syntactic versus semantic unification

Word-class ambiguous words are not only syntactically but also semantically ambiguous. The verb interpretation of an ambiguous word never has exactly the same meaning as its noun interpretation. Computationally, the Unification Space model is urgently in need of the addition of a parallel conceptual processing component (see Vosse and Kempen, 2009). In the fMRI study of Chapter 2, we show that the activation patterns in response to word-class ambiguity in LIFG and LpMTG are not due to the diffuse semantic consequences of word-class ambiguity. However, further studies are needed to reveal the interactions between semantic and syntactic unification processes, and to specify whether subregions within LIFG and LpMTG specialize for unification type (semantic versus syntactic).

The influence of CNTNAP2 on sentence processing routes

In Chapters 4 and 5, we described the effect of a common polymorphism in *CNTNAP2* on the neurocognitive processing route for sentence processing. While the overall network for sentence processing is highly similar for the two different genotypes, subtle differences depending on *CNTNAP2* genotype could be identified in the network dynamics. *CNTNAP2* is a cell-adhesion molecule that might shape the properties of neural networks (Südhof, 2008). Differential functional recruitment of different areas within a neural network might result in the structural differences which we identified in RIFG. A tentative interpretation of the results is that subjects with an AA genotype process sentences in a more context-driven manner, while T-carriers are more lexically (locally) driven in their processing styles. Fascinatingly, people with autism, for which T-carriers have a

slightly increased risk, also use a more local, less context-driven processing style (Happe and Frith, 2006). In the SINUS model - the new neural network version of the Unification Space model (Vosse and Kempen, 2000, 2009) - the increased context-dependence of AA genotype subjects might be implemented by stronger 'intercolumnar' connections for this genotype group (see Chapter 5). That is, the activation levels of the individual words of a sentence are more strongly influenced by activation levels of preceding words. If this speculative account is correct, we expect differences between the genotype groups with respect to predictive parsing (see Van Berkum et al., 2005), with AA genotype subjects showing clearer manifestations of predictive parsing than T-carriers.

The studies described in this thesis are the very first to identify effects of a common genetic variant on sentence processing in the brain. Our results emphasize the existence of multiple processing routes for sentences, with a variant in the *CNTNAP2* gene predisposing our brains to use a specific route. The flexibility of this system is shown by studies on aphasic patients who, after the brain damage, switch to a different processing route for sentence comprehension (Hagoort et al., 2003). It is an open question whether *CNTNAP2* mainly affects language, or whether its effect on language is mediated through other high-level cognitive processes such as cognitive flexibility.

Replication studies are needed to confirm the role of *CNTNAP2* in language processing in the brain. The field of cognitive neurogenetics is just emerging, and little is known as yet about the specific genes involved in the processing of language. A challenge for future research is to further explore genetic influences on language processing in the brain.

References

References

- Abrahams, B.S., Geschwind, D.H., 2008. Advances in autism genetics: on the threshold of a new neurobiology. *Nature Reviews Genetics* 9, 341-355.
- Abrahams, B.S., Tentler, D., Perederiy, J.V., Oldham, M.C., Coppola, G., Geschwind, D.H., 2007. Genome-wide analyses of human perisylvian cerebral cortical patterning. *Proceedings of the National Academy of Sciences of the United States of America* 104, 17849-17854.
- Alarcon, M., Abrahams, B.S., Stone, J.L., Duvall, J.A., Perederiy, J.V., Bomar, J.M., Sebat, J., Wigler, M., Martin, C.L., Ledbetter, D.H., Nelson, S.E., Cantor, R.M., Geschwind, D.H., 2008. Linkage, association, and gene-expression analyses identify CNTNAP2 as an autism-susceptibility gene. *American Journal of Human Genetics* 82, 150-159.
- Amodio, D.M., Frith, C.D., 2006. Meeting of minds: the medial frontal cortex and social cognition. *Nature Reviews Neuroscience* 7, 268-277.
- Arking, D.E., Cutler, D.J., Brune, C.W., Teslovich, T.M., West, K., Ikeda, M., Rea, A., Guy, M., Lin, S., Cook, E.H., Chakravarti, A., 2008. A common genetic variant in the neurexin superfamily member CNTNAP2 increases familial risk of autism. *American Journal of Human Genetics* 82, 160-164.
- Ashburner, J., 2007. A fast diffeomorphic image registration algorithm. *Neuroimage* 38, 95-113.
- Ashburner, J., Friston, K.J., 2000. Voxel-based morphometry - The methods. *Neuroimage* 11, 805-821.
- Attia, J., Ioannidis, J.P.A., Thakkinstian, A., McEvoy, M., Scott, R.J., Minelli, C., Thompson, J., Infante-Rivard, C., Guyatt, G., 2009. How to use an article about genetic association: A: background concepts. *Jama-Journal of the American Medical Association* 301, 74-81.
- Baayen, R.H., Piepenbrock, R., Rijn, H.v., 1993. The CELEX lexical database [CD-ROM]. Philadelphia, Linguistic Data Consortium, University of Pennsylvania.
- Bakkaloglu, B., O'Roak, B.J., Louvi, A., Gupta, A.R., Abelson, J.E., Morgan, T.M., Chawarska, K., Klin, A., Ercan-Sencicek, A.G., Stillman, A.A., Tanriover, G., Abrahams, B.S., Duvall, J.A., Robbins, E.M., Geschwind, D.H., Biederer, T., Gunel, M., Lifton, R.P., State, M.W., 2008. Molecular cytogenetic analysis and resequencing of Contactin Associated Protein-Like 2 in autism spectrum disorders. *American Journal of Human Genetics* 82, 165-173.
- Bastiaansen, M.C.M., Knosche, T.R., 2000. Tangential derivative mapping of axial MEG applied to event-related desynchronization research. *Clinical Neurophysiology* 111, 1300-1305.
- Bavelier, D., Corina, D., Jezzard, P., Padmanabhan, S., Clark, V.P., Karni, A., Prinster, A., Braun, A., Lalwani, A., Rauschecker, J.P., Turner, R., Neville, H., 1997. Sentence reading: A functional MRI study at 4 tesla. *Journal of Cognitive Neuroscience* 9, 664-686.
- Beauchamp, M.S., Lee, K.E., Argall, B.D., Martin, A., 2004. Integration of auditory and visual information about objects in superior temporal sulcus. *Neuron* 41, 809-823.
- Bedny, M., McGill, M., Thompson-Schill, S.L., 2008a. Semantic adaptation and competition during word comprehension. *Cerebral Cortex* 18, 2574-2585.
- Bedny, M., Caramazza, A., Grossman, E., Pascual-Leone, A., Saxe, R., 2008b. Concepts are more than percepts: the case of action verbs. *Journal of Neuroscience* 28, 11347-11353.

References

- Beek, L.v.d., Bouma, G., Malouf, R., Noord, G.v., 2001. The Alpino Dependency Treebank. In: Computational Linguistics in the Netherlands (CLIN). Enschede.
- Belton, E., Salmond, C.H., Watkins, K.E., Vargha-Khadem, F., Gadian, D.G., 2003. Bilateral brain abnormalities associated with dominantly inherited verbal and orofacial dyspraxia. *Human Brain Mapping* 18, 194-200.
- Betancur, C., Sakurai, T., Buxbaum, J.D., 2009. The emerging role of synaptic cell-adhesion pathways in the pathogenesis of autism spectrum disorders. *Trends in Neurosciences* 32, 402-412.
- Bookheimer, S., 2002. Functional MRI of language: New approaches to understanding the cortical organization of semantic processing. *Annual Review of Neuroscience* 25, 151-188.
- Bourgeron, T., 2009. A synaptic trek to autism. *Current Opinion in Neurobiology* 19, 231-234.
- Buckner, R.L., Andrews-Hanna, J.R., Schacter, D.L., 2008. The brain's default network - Anatomy, function, and relevance to disease. In, *Year in Cognitive Neuroscience* 2008, pp. 1-38.
- Caramazza, A., Hillis, A.E., 1991. Lexical organization of nouns and verbs in the brain. *Nature* 349, 788-790.
- Carlsson, P., Mahlapuu, M., 2002. Forkhead transcription factors: Key players in development and metabolism. *Developmental Biology* 250, 1-23.
- Casanova, M.F., Buxhoeveden, D.P., Switala, A.E., Roy, E., 2002. Minicolumnar pathology in autism. *Neurology* 58, 428-432.
- Casanova, M.F., El-Baz, A., Vanbogaert, E., Narahari, P., Switala, A., 2010. A topographic study of minicolumnar core width by lamina comparison between autistic subjects and controls: possible minicolumnar disruption due to an anatomical element in-common to multiple laminae. *Brain Pathology* 20, 451-458.
- Chomsky, N., 1995. The Minimalist Program. Cambridge, MA, MIT Press.
- Chow, H.M., Kaup, B., Raabe, M., Greenlee, M.W., 2008. Evidence of fronto-temporal interactions for strategic inference processes during language comprehension. *Neuroimage* 40, 940-954.
- Cools, R., 2008. Role of dopamine in the motivational and cognitive control of behavior. *Neuroscientist* 14, 381-395.
- Cools, R., Clark, L., Robbins, T.W., 2004. Differential responses in human striatum and prefrontal cortex to changes in object and rule relevance. *Journal of Neuroscience* 24, 1129-1135.
- Cools, R., Ivry, R.B., D'Esposito, M., 2006. The human striatum is necessary for responding to changes in stimulus relevance. *Journal of Cognitive Neuroscience* 18, 1973-1983.
- Copland, D.A., 2003. The basal ganglia and semantic engagement: Potential insights from semantic priming in individuals with subcortical vascular lesions, Parkinson's disease, and cortical lesions. *Journal of the International Neuropsychological Society* 9, 1041-1052.
- Copland, D.A., 2006. Meaning selection and the subcortex: Evidence of reduced lexical ambiguity repetition effects following subcortical lesions. *Journal of Psycholinguistic Research* 35, 51-66.
- Copland, D.A., Chinery, H.J., Murdoch, B.E., 2000. Understanding ambiguous words in biased sentences: Evidence of transient contextual effects in individuals with nonthalamic subcortical lesions and Parkinson's disease. *Cortex* 36, 601-622.

- Copland, D.A., Chenery, H.J., Murdoch, B.E., 2001. Discourse priming of homophones in individuals with dominant nonthalamic subcortical lesions, cortical lesions and Parkinson's disease. *Journal of Clinical and Experimental Neuropsychology* 23, 538-556.
- Crosson, B., Benjamin, M., Levy, I., 2007. Role of the basal ganglia in language and semantics: supporting cast. In: Hart, J., Kraut, M.A. (Eds.), *Neural Basis of Semantic Memory*. Cambridge, Cambridge University Press, pp. 219-243.
- Cuadra, M.B., Cammoun, L., Butz, T., Cuisenaire, O., Thiran, J.P., 2005. Comparison and validation of tissue modelization and statistical classification methods in T1-weighted MR brain images. *Ieee Transactions on Medical Imaging* 24, 1548-1565.
- Culicover, P.W., Jackendoff, R., 2005. *Simpler Syntax*. Oxford, Oxford University Press.
- Curtis, C.E., D'Esposito, M., 2003. Persistent activity in the prefrontal cortex during working memory. *Trends in Cognitive Sciences* 7, 415-423.
- Damasio, A., 1989. The brain binds entities and events by multiregional activation from convergence zones. *Neural Computation* 1, 123-132.
- Damasio, A.R., Tranel, D., 1993. Nouns and verbs are retrieved with differently distributed neural systems. *Proceedings of the National Academy of Sciences of the United States of America* 90, 4957-4960.
- Damasio, H., Grabowski, T.J., Tranel, D., Hichwa, R.D., Damasio, A.R., 1996. A neural basis for lexical retrieval. *Nature* 381, 810-810.
- Davis, M.H., Meunier, F., Marslen-Wilson, W.D., 2004. Neural responses to morphological, syntactic, and semantic properties of single words: An fMRI study. *Brain and Language* 89, 439-449.
- Davis, M.H., Coleman, M.R., Absalom, A.R., Rodd, J.M., Johnsrude, I.S., Matta, B.F., Owen, A.M., Menon, D.K., 2007. Dissociating speech perception and comprehension at reduced levels of awareness. *Proceedings of the National Academy of Sciences of the United States of America* 104, 16032-16037.
- Dayan, P., 2008. Simple substrates for complex cognition. *Frontiers in neuroscience* 2, 255-264.
- Decety, J., Grezes, J., Costes, N., Perani, D., Jeannerod, M., Procyk, E., Grassi, F., Fazio, F., 1997. Brain activity during observation of actions - Influence of action content and subject's strategy. *Brain* 120, 1763-1777.
- den Ouden, D.B., Fix, S., Parrish, T.B., Thompson, C.K., 2009. Argument structure effects in action verb naming in static and dynamic conditions. *Journal of Neurolinguistics* 22, 196-215.
- den Ouden, H.E.M., Daunizeau, J., Roiser, J.P., Friston, K.J., Stephan, K.E., in press. Striatal prediction error modulates cortical coupling. *Journal of Neuroscience*.
- Draganski, B., Gaser, C., Busch, V., Schuierer, G., Bogdahn, U., May, A., 2004. Neuroplasticity: Changes in grey matter induced by training - Newly honed juggling skills show up as a transient feature on a brain-imaging scan. *Nature* 427, 311-312.
- Duffy, S.A., Morris, R.K., Rayner, K., 1988. Lexical ambiguity and fixation times in reading. *Journal of Memory and Language* 27, 429-446.
- Durstewitz, D., Seamans, J.K., Sejnowski, T.J., 2000. Neurocomputational models of working memory. *Nature Neuroscience* 3 supp, 1184-1191.
- Enard, W., Przeworski, M., Fisher, S.E., Lai, C.S.L., Wiebe, V., Kitano, T., Monaco, A.P., Paabo, S., 2002. Molecular evolution of FOXP2, a gene involved in speech and language. *Nature* 418, 869-872.

References

- Enard, W., Gehre, S., Hammerschmidt, K., Holter, S.M., Blass, T., Somel, M., Bruckner, M.K., Schreiweis, C., Winter, C., Sohr, R., Becker, L., Wiebe, V., Nickel, B., Giger, T., Muller, U., Groszer, M., Adler, T., Aguilar, A., Bolle, I., Calzada-Wack, J., Dalke, C., Ehrhardt, N., Favor, J., Fuchs, H., Gailus-Durner, V., Hans, W., Holzlwimmer, G., Javaheri, A., Kalaydjiev, S., Kallnik, M., Kling, E., Kunder, S., Mossbrugger, I., Naton, B., Racz, I., Rathkolb, B., Rozman, J., Schrewe, A., Busch, D.H., Graw, J., Ivandic, B., Klingenspor, M., Klopstock, T., Ollert, M., Quintanilla-Martinez, L., Schulz, H., Wolf, E., Wurst, W., Zimmer, A., Fisher, S.E., Morgenstern, R., Arendt, T., de Angelis, M.H., Fischer, J., Schwarz, J., Paabo, S., 2009. A humanized version of Foxp2 affects cortico-basal ganglia circuits in mice. *Cell* 137, 961-971.
- Evans, A.C., Collins, D.L., Mills, S.R., Brown, E.D., Kelly, R.L., Peters, T.M., 1993. 3D statistical neuroanatomical models from 305 MRI volumes. In: IEEE-Nuclear Science Symposium and Medical Imaging Conference, pp. 1813-1817.
- Faust, M., Chiarello, C., 1998. Sentence context and lexical ambiguity resolution by the two hemispheres. *Neuropsychologia* 36, 827-835.
- Federmeier, K.D., Segal, J.B., Lombrozo, T., Kutas, M., 2000. Brain responses to nouns, verbs and class-ambiguous words in context. *Brain* 123, 2552-2566.
- Ferstl, E.C., von Cramon, D.Y., 2002. What does the frontomedian cortex contribute to language processing: Coherence or theory of mind? *Neuroimage* 17, 1599-1612.
- Ferstl, E.C., Rinck, M., von Cramon, D.Y., 2005. Emotional and temporal aspects of situation model processing during text comprehension: An event-related fMRI study. *Journal of Cognitive Neuroscience* 17, 724-739.
- Ferstl, E.C., Neumann, J., Bogler, C., von Cramon, D.Y., 2008. The extended language network: A meta-analysis of neuroimaging studies on text comprehension. *Human Brain Mapping* 29, 581-593.
- Feuk, L., Kalervo, A., Lipsanen-Nyman, M., Skaug, J., Nakabayashi, K., Finucane, B., Hartung, D., Innes, M., Kerem, B., Nowaczyk, M.J., Rivlin, J., Roberts, W., Senman, L., Summers, A., Szatmari, P., Wong, V., Vincent, J.B., Zeesman, S., Osborne, L.R., Cardy, J.O., Kere, J., Scherer, S.W., Hannula-Jouppi, K., 2006. Absence of a paternally inherited FOXP2 gene in developmental verbal dyspraxia. *American Journal of Human Genetics* 79, 965-972.
- Fiebach, C.J., Rissman, J., D'Esposito, M., 2006. Modulation of inferotemporal cortex activation during verbal working memory maintenance. *Neuron* 51, 251-261.
- Fiebach, C.J., Schlesewsky, M., Lohmann, G., von Cramon, D.Y., Friederici, A.D., 2005. Revisiting the role of Broca's area in sentence processing: Syntactic integration versus syntactic working memory. *Human Brain Mapping* 24, 79-91.
- Fisher, S.E., Marcus, G.F., 2006. The eloquent ape: genes, brains and the evolution of language. *Nature Reviews Genetics* 7, 9-20.
- Fisher, S.E., Scharff, C., 2009. FOXP2 as a molecular window into speech and language. *Trends in Genetics* 25, 166-177.
- Forman, S.D., Cohen, J.D., Fitzgerald, M., Eddy, W.F., Mintun, M.A., Noll, D.C., 1995. Improved assessment of significant activation in functional magnetic-resonance-imaging (fMRI) - use of a cluster-size threshold. *Magnetic Resonance in Medicine* 33, 636-647.
- Frank, M.J., 2005. Dynamic dopamine modulation in the basal ganglia: A neurocomputational account of cognitive deficits in medicated and nonmedicated Parkinsonism. *Journal of Cognitive Neuroscience* 17, 51-72.

- Frank, M.J., Loughry, B., O'Reilly, R.C., 2001. Interactions between the frontal cortex and basal ganglia in working memory: a computational model. *Cognitive, Affective, and Behavioral Neuroscience* 1, 137-160.
- Friederici, A.D., 2002. Towards a neural basis of auditory sentence processing. *Trends in Cognitive Sciences* 6, 78-84.
- Friederici, A.D., Kotz, S.A., 2003. The brain basis of syntactic processes: functional imaging and lesion studies. *Neuroimage* 20, S8-S17.
- Friederici, A.D., Makuuchi, M., Bahlmann, J., 2009. The role of the posterior superior temporal cortex in sentence comprehension. *Neuroreport* 20, 563-568.
- Friederici, A.D., Ruschemeyer, S.A., Hahne, A., Fiebach, C.J., 2003. The role of left inferior frontal and superior temporal cortex in sentence comprehension: Localizing syntactic and semantic processes. *Cerebral Cortex* 13, 170-177.
- Friedman, J.I., Vrijenhoek, T., Markx, S., Janssen, I.M., Van der Vliet, W.A., Faas, B.H.W., Knoers, N.V., Cahn, W., Kahn, R.S., Edelmann, L., Davis, K.L., Silverman, J.M., Brunner, H.G., Van Kessel, A.G., Wijmenga, C., Ophoff, R.A., Veltman, J.A., 2008. CNTNAP2 gene dosage variation is associated with schizophrenia and epilepsy. *Molecular Psychiatry* 13, 261-266.
- Frisch, S., Kotz, S.A., von Cramon, D.Y., Friederici, A.D., 2003. Why the P600 is not just a P300: the role of the basal ganglia. *Clinical Neurophysiology* 114, 336-340.
- Friston, K.J., 2002. Beyond phrenology: What can neuroimaging tell us about distributed circuitry? *Annual Review of Neuroscience* 25, 221-250.
- Friston, K.J., Harrison, L., Penny, W., 2003. Dynamic causal modelling. *Neuroimage* 19, 1273-1302.
- Friston, K.J., Holmes, A., Poline, J.B., Price, C.J., Frith, C.D., 1996. Detecting activations in PET and fMRI: Levels of inference and power. *Neuroimage* 4, 223-235.
- Friston, K.J., Ashburner, J.T., Kiebel, S.J., Nichols, T.E., Penny, W.D., 2007. Statistical Parametric Mapping: the Analysis of Functional Brain Images. San Diego, CA, Academic Press.
- Friston, K.J., Holmes, A.P., Worsley, K.J., Poline, J.B., Frith, C., Frackowiak, R.S.J., 1995. Statistical parametric maps in functional imaging: a general linear approach. *Human Brain Mapping* 2, 189-210.
- Friston, K.J., Buechel, C., Fink, G.R., Morris, J., Rolls, E., Dolan, R.J., 1997. Psychophysiological and modulatory interactions in neuroimaging. *Neuroimage* 6, 218-229.
- Frith, C.D., Frith, U., 2006. The neural basis of mentalizing. *Neuron* 50, 531-534.
- Fuster, J.M., 2001. The prefrontal cortex - An update: time is of the essence. *Neuron* 30, 319-333.
- Fuster, J.M., 2002. Frontal lobe and cognitive development. *Journal of Neurocytology* 31, 373-385.
- Fuster, J.M., 2008. The Prefrontal Cortex, 4th ed. London, Academic Press.
- Fuster, J.M., Bodner, M., Kroger, J.K., 2000. Cross-modal and cross-temporal association in neurons of frontal cortex. *Nature* 405, 347-351.
- Gennari, S.P., Macdonald, M.C., Postle, B.R., Seidenberg, M.S., 2007. Context-dependent interpretation of words: Evidence for interactive neural processes. *Neuroimage* 35, 1278-1286.
- Gitelman, D.R., Penny, W.D., Ashburner, J., Friston, K.J., 2003. Modeling regional and psychophysiologic interactions in fMRI: the importance of hemodynamic deconvolution. *Neuroimage* 19, 200-207.

References

- Gold, B.T., Buckner, R.L., 2002. Common prefrontal regions coactivate with dissociable posterior regions during controlled semantic and phonological tasks. *Neuron* 35, 803-812.
- Good, C.D., Johnsrude, I.S., Ashburner, J., Henson, R.N.A., Friston, K.J., Frackowiak, R.S.J., 2001. A voxel-based morphometric study of ageing in 465 normal adult human brains. *Neuroimage* 14, 21-36.
- Graesser, A.C., Millis, K.K., Zwaan, R.A., 1997. Discourse comprehension. *Annual Review of Psychology* 48, 163-189.
- Grindrod, C.M., Baum, S.R., 2005. Hemispheric contributions to lexical ambiguity resolution in a discourse context: Evidence from individuals with unilateral left and right hemisphere lesions. *Brain and Cognition* 57, 70-83.
- Grossman, M., Koenig, P., DeVita, C., Gossler, G., Alsop, D., Detre, J., Gee, J., 2002. Neural representation of verb meaning: An fMRI study. *Human Brain Mapping* 15, 124-134.
- Gruber, A.J., Dayan, P., Gutkin, B.S., Solla, S.A., 2006. Dopamine modulation in the basal ganglia locks the gate to working memory. *Journal of Computational Neuroscience* 20, 153-166.
- Hagoort, P., 2003. How the brain solves the binding problem for language: a neurocomputational model of syntactic processing. *Neuroimage* 20, S18-S29.
- Hagoort, P., 2005a. On Broca, brain, and binding: a new framework. *Trends in Cognitive Sciences* 9, 416-423.
- Hagoort, P., 2005b. Broca's complex as the unification space for language. In: Cutler, A. (Ed.), *Twenty-First Century Psycholinguistics: Four Cornerstones*. Mahwah, NJ, Lawrence Erlbaum Press
- Hagoort, P., Brown, C., Groothusen, J., 1993. The Syntactic Positive Shift (SPS) as an ERP measure of syntactic processing. *Language and Cognitive Processes* 8, 439-483.
- Hagoort, P., Brown, C.M., Osterhout, L., 1999. The neural architecture of syntactic processing. In: Brown, C.M., Hagoort, P. (Eds.), *The Neurocognition of Language*. Oxford, Oxford University Press, pp. 273-316.
- Hagoort, P., Wassenaar, M., Brown, C., 2003. Real-time semantic compensation in patients with agrammatic comprehension: Electrophysiological evidence for multiple-route plasticity. *Proceedings of the National Academy of Sciences of the United States of America* 100, 4340-4345.
- Hagoort, P., Baggio, G., Willems, R.M., 2009. Semantic unification. In: Gazzaniga, M.S. (Ed.), *The Cognitive Neurosciences IV*. Cambridge, MA, MIT Press, pp. 819-836.
- Halgren, E., Dhond, R.P., Christensen, N., Van Petten, C., Marinkovic, K., Lewine, J.D., Dale, A.M., 2002. N400-like magnetoencephalography responses modulated by semantic context, word frequency, and lexical class in sentences. *Neuroimage* 17, 1101-1116.
- Hämäläinen, M., Hari, R., Ilmoniemi, R.J., Knuutila, J., Lounasmaa, O.V., 1993. Magnetoencephalography - theory, instrumentation, and applications to noninvasive studies of the working human brain. *Reviews of Modern Physics* 65, 413-497.
- Hampson, M., Peterson, B.S., Skudlarski, P., Gatenby, J.C., Gore, J.C., 2002. Detection of functional connectivity using temporal correlations in MR images. *Human Brain Mapping* 15, 247-262.
- Hamzei, F., Rijntjes, M., Dettmers, C., Glauche, V., Weiller, C., Buchel, C., 2003. The human action recognition system and its relationship to Broca's area: an fMRI study. *Neuroimage* 19, 637-644.

- Happe, F., Frith, U., 2006. The weak coherence account: Detail-focused cognitive style in autism spectrum disorders. *Journal of Autism and Developmental Disorders* 36, 5-25.
- Hazy, T.E., Frank, M.J., O'Reilly, R.C., 2007. Towards an executive without a homunculus: computational models of the prefrontal cortex/basal ganglia system. *Philosophical Transactions of the Royal Society B-Biological Sciences* 362, 1601-1613.
- Hein, G., Knight, R.T., 2008. Superior temporal sulcus-it's my area: or is it? *Journal of Cognitive Neuroscience* 20, 2125-2136.
- Hein, G., Doehrmann, O., Muller, N.G., Kaiser, J., Muckli, L., Naumer, M.J., 2007. Object familiarity and semantic congruency modulate responses in cortical audiovisual integration areas. *Journal of Neuroscience* 27, 7881-7887.
- Hickok, G., Poeppel, D., 2000. Towards a functional neuroanatomy of speech perception. *Trends in Cognitive Sciences* 4, 131-138.
- Hickok, G., Poeppel, D., 2004. Dorsal and ventral streams: a framework for understanding aspects of the functional anatomy of language. *Cognition* 92, 67-99.
- Homae, F., Yahata, N., Sakai, K.L., 2003. Selective enhancement of functional connectivity in the left prefrontal cortex during sentence processing. *Neuroimage* 20, 578-586.
- Hornby, A.S., 2000. Oxford Advanced Learner's Dictionary, 6th Edition. Oxford, Oxford University Press.
- Huettel, S.A., Song, A.W., McCarthy, G., 2004. Functional Magnetic Resonance Imaging. Sunderland, MA, Sinauer Associates.
- Humphries, C., Binder, J.R., Medler, D.A., Liebenthal, E., 2007. Time course of semantic processes during sentence comprehension: An fMRI study. *Neuroimage* 36, 924-932.
- Hussman, J.P., 2001. Suppressed GABAergic inhibition as a common factor in suspected etiologies of autism. *Journal of Autism and Developmental Disorders* 31, 247-248.
- Inda, M.C., DeFelipe, J., Munoz, A., 2006. Voltage-gated ion channels in the axon initial segment of human cortical pyramidal cells and their relationship with chandelier cells. *Proceedings of the National Academy of Sciences of the United States of America* 103, 2920-2925.
- Indefrey, P., 2004. Hirnaktivierungen bei syntaktischer Sprachverarbeitung: eine Meta-Analyse. In: Müller, H.M., Rickheit, G. (Eds.), *Neurokognition der Sprache*, Band 1. Tübingen, Stauffenburg Verlag.
- Indefrey, P., Cutler, A., 2005. Prelexical and lexical processing in listening. In: Gazzaniga, M.S. (Ed.), *The Cognitive Neurosciences*, 3rd Edition. Cambridge, MA, MIT Press, pp. 759-774.
- Jackendoff, R., 2002. Foundations of Language: Brain, Meaning, Grammar, Evolution. Oxford, Oxford University Press.
- Joshi, A.K., Schabes, Y., 1997. Treedjoining grammars. In: Salomma, A., Rosenberg, G. (Eds.), *Handbook of Formal Languages and Automata*, Springer-Verlag, pp. 69-124.
- Jung-Beeman, M., 2005. Bilateral brain processes for comprehending natural language. *Trends in Cognitive Sciences* 9, 512-518.
- Just, M.A., Carpenter, P.A., 1992. A capacity theory of comprehension - individual-differences in working memory. *Psychological Review* 99, 122-149.
- Just, M.A., Cherkassky, V.L., Keller, T.A., Minshew, N.J., 2004. Cortical activation and synchronization during sentence comprehension in high-functioning autism: evidence of underconnectivity. *Brain* 127, 1811-1821.

References

- Kaan, E., Swaab, T.Y., 2002. The brain circuitry of syntactic comprehension. *Trends in Cognitive Sciences* 6, 350-356.
- Keller, T.A., Carpenter, P.A., Just, M.A., 2001. The neural bases of sentence comprehension: a fMRI examination of syntactic and lexical processing. *Cerebral Cortex* 11, 223-237.
- Kempen, G., Harbusch, K., 2002. Performance grammar: a declarative definition. In: Nijholt, A., Theune, M., Hondorp, H. (Eds.), *Computational Linguistics in the Netherlands 2001*. Amsterdam, Rodopi, pp. 148-162.
- Kircher, T.T.J., Brammer, M., Andreu, N.T., Williams, S.C.R., McGuire, P.K., 2001. Engagement of right temporal cortex during processing of linguistic context. *Neuropsychologia* 39, 798-809.
- Knosche, T.R., 2002. Transformation of whole-head MEG recordings between different sensor positions. *Biomedizinische Technik* 47, 59-62.
- Kolk, H.H.J., 2000. Multiple route plasticity. *Brain and Language* 71, 129-131.
- Konopka, G., Bomar, J.M., Winden, K., Coppola, G., Jonsson, Z.O., Gao, F.Y., Peng, S., Preuss, T.M., Wohlschlegel, J.A., Geschwind, D.H., 2009. Human-specific transcriptional regulation of CNS development genes by FOXP2. *Nature* 462, 213-U289.
- Koten, J.W., Wood, G., Hagoort, P., Goebel, R., Propping, P., Willmes, K., Boomsma, D.I., 2009. Genetic contribution to variation in cognitive function: an fMRI study in twins. *Science* 323, 1737-1740.
- Kuperberg, G.R., Holcomb, P.J., Sitnikova, T., Greve, D., Dale, A.M., Caplan, D., 2003. Distinct patterns of neural modulation during the processing of conceptual and syntactic anomalies. *Journal of Cognitive Neuroscience* 15, 272-293.
- Kutas, M., Hillyard, S.A., 1980. Reading Senseless Sentences - Brain Potentials Reflect Semantic Incongruity. *Science* 207, 203-205.
- Kutas, M., Van Petten, C., Kluender, R., 2006. Psycholinguistics electrified II: 1994-2005. In: Traxler, M., Gernsbacher, M.A. (Eds.), *Handbook of psycholinguistics*, 2nd Edition. New York, NY, Elsevier, pp. 659-724.
- Lai, C.S.L., Fisher, S.E., Hurst, J.A., Vargha-Khadem, F., Monaco, A.P., 2001. A forkhead-domain gene is mutated in a severe speech and language disorder. *Nature* 413, 519-523.
- Lai, C.S.L., Gerrelli, D., Monaco, A.P., Fisher, S.E., Copp, A.J., 2003. FOXP2 expression during brain development coincides with adult sites of pathology in a severe speech and language disorder. *Brain* 126, 2455-2462.
- Lancaster, J.L., Woldorff, M.G., Parsons, L.M., Liotti, M., Freitas, E.S., Rainey, L., Kochunov, P.V., Nickerson, D., Mikiten, S.A., Fox, P.T., 2000. Automated Talairach Atlas labels for functional brain mapping. *Human Brain Mapping* 10, 120-131.
- Lau, E.F., Phillips, C., Poeppel, D., 2008. A cortical network for semantics: (de)constructing the N400. *Nature Reviews Neuroscience* 9, 920-933.
- Lee, C.L., Federmeier, K.D., 2006. To mind the mind: An event-related potential study of word class and semantic ambiguity. *Brain Research* 1081, 191-202.
- Lee, C.L., Federmeier, K.D., 2009. Wave-ering: An ERP study of syntactic and semantic context effects on ambiguity resolution for noun/verb homographs. *Journal of Memory and Language* 61, 538-555.
- Levelt, W.J.M., 1992. Accessing words in speech production - stages, processes and representations. *Cognition* 42, 1-22.

- Lieberman, P., 2001. Human language and our reptilian brain - the subcortical bases of speech, syntax, and thought. *Perspectives in Biology and Medicine* 44, 32-51.
- Liegeois, F., Baldeweg, T., Connelly, A., Gadian, D.G., Mishkin, M., Vargha-Khadem, F., 2003. Language fMRI abnormalities associated with FOXP2 gene mutation. *Nature Neuroscience* 6, 1230-1237.
- Longe, O., Randall, B., Stamatakis, E.A., Tyler, L.K., 2007. Grammatical categories in the brain: The role of morphological structure. *Cerebral Cortex* 17, 1812-1820.
- MacDermot, K.D., Bonora, E., Sykes, N., Coupe, A.M., Lai, C.S.L., Vernes, S.C., Vargha-Khadem, F., McKenzie, F., Smith, R.L., Monaco, A.P., Fisher, S.E., 2005. Identification of FOXP2 truncation as a novel cause of developmental speech and language deficits. *American Journal of Human Genetics* 76, 1074-1080.
- Macdonald, M.C., Pearlmuter, N.J., Seidenberg, M.S., 1994. Lexical nature of syntactic ambiguity resolution. *Psychological Review* 101, 676-703.
- Maguire, E.A., Spiers, H.J., Good, C.D., Hartley, T., Frackowiak, R.S.J., Burgess, N., 2003. Navigation expertise and the human hippocampus: A structural brain imaging analysis. *Hippocampus* 13, 250-259.
- Mai, J.K., Assheuer, J., Paxinos, G., 2004. *Atlas of the Human Brain*, Second Edition. London, Elsevier Academic Press.
- Marcus, G.F., Vouloumanos, A., Sag, I.A., 2003. Does Broca's play by the rules? *Nature Neuroscience* 6, 651-652.
- Maris, E., Oostenveld, R., 2007. Nonparametric statistical testing of EEG- and MEG-data. *Journal of Neuroscience Methods* 164, 177-190.
- Marslen-Wilson, W.D., 1987. Functional parallelism in spoken word-recognition. *Cognition* 25, 71-102.
- Mason, R.A., Just, M.A., 2006. Neuroimaging contributions to the understanding of discourse processes. In: Traxler, M., Gernsbacher, M.A. (Eds.), *Handbook of Psycholinguistics*. Amsterdam, Elsevier, pp. 756-799.
- Mason, R.A., Williams, D.L., Kana, R.K., Minshew, N., Just, M.A., 2008. Theory of Mind disruption and recruitment of the right hemisphere during narrative comprehension in autism. *Neuropsychologia* 46, 269-280.
- McCandliss, B.D., Cohen, L., Dehaene, S., 2003. The visual word form area: expertise for reading in the fusiform gyrus. *Trends in Cognitive Sciences* 7, 293-299.
- McIntosh, A.R., 2000. Towards a network theory of cognition. *Neural Networks* 13, 861-870.
- McNab, F., Klingberg, T., 2008. Prefrontal cortex and basal ganglia control access to working memory. *Nature Neuroscience* 11, 103-107.
- Mechelli, A., Crinion, J.T., Noppeney, U., O'Doherty, J., Ashburner, J., Frackowiak, R.S., Price, C.J., 2004. Structural plasticity in the bilingual brain - Proficiency in a second language and age at acquisition affect grey-matter density. *Nature* 431, 757-757.
- Menenti, L., Petersson, K.M., Scheeringa, R., Hagoort, P., 2009. When elephants fly: differential sensitivity of right and left inferior frontal gyri to discourse and world knowledge. *Journal of Cognitive Neuroscience* 21, 2358-2368.
- Mesulam, M.M., 1981. A Cortical Network for Directed Attention and Unilateral Neglect. *Annals of Neurology* 10, 309-325.
- Mesulam, M.M., 1990. Large-Scale Neurocognitive Networks and Distributed-Processing for Attention, Language, and Memory. *Annals of Neurology* 28, 597-613.
- Mesulam, M.M., 1998. From sensation to cognition. *Brain* 121, 1013-1052.

References

- Miller, B.T., D'Esposito, M., 2005. Searching for "the top" in top-down control. *Neuron* 48, 535-538.
- Miller, E.K., Cohen, J.D., 2001. An integrative theory of prefrontal cortex function. *Annual Review of Neuroscience* 24, 167-202.
- Mink, J.W., 1996. The basal ganglia: Focused selection and inhibition of competing motor programs. *Progress in Neurobiology* 50, 381-425.
- Mitchell, J.P., 2009. Social psychology as a natural kind. *Trends in Cognitive Sciences* 13, 246-251.
- Moro, A., Tettamanti, M., Perani, D., Donati, C., Cappa, S.F., Fazio, F., 2001. Syntax and the brain: Disentangling grammar by selective anomalies. *Neuroimage* 13, 110-118.
- Nakabayashi, K., Scherer, S.W., 2001. The human contactin-associated protein-like 2 gene (CNTNAP2) spans over 2 Mb of DNA at chromosome 7q35. *Genomics* 73, 108-112.
- Ni, W., Constable, R.T., Mencl, W.E., Pugh, K.R., Fulbright, R.K., Shaywitz, S.E., Shaywitz, B.A., Gore, J.C., Shankweiler, D., 2000. An event-related neuroimaging study distinguishing form and content in sentence processing. *Journal of Cognitive Neuroscience* 12, 120-133.
- Nichols, T.E., Holmes, A.P., 2002. Nonparametric permutation tests for functional neuroimaging: A primer with examples. *Human Brain Mapping* 15, 1-25.
- Ojemann, G.A., 1991. Cortical organization of language. *Journal of Neuroscience* 11, 2281-2287.
- O'Reilly, R.C., Frank, M.J., 2006. Making working memory work: A computational model of learning in the prefrontal cortex and basal ganglia. *Neural Computation* 18, 283-328.
- Osterhout, L., Holcomb, P.J., 1992. Event-related brain potentials elicited by syntactic anomaly. *Journal of Memory and Language* 31, 785-806.
- Pakulak, E., Neville, H., 2009. Proficiency differences in syntactic processing of monolingual native speakers indexed by event-related potentials. *Journal of Cognitive Neuroscience Early Access publication on Nov. 19, 2009,* doi:10.1162/jocn.2009.21393.
- Patel, A.D., 2003. Language, music, syntax and the brain. *Nature Neuroscience* 6, 674-681.
- Peelle, J., Troiani, V., Wingfield, A., Grossman, M., 2010. Neural processing during older adults' comprehension of spoken sentences: age differences in resource allocation and connectivity. *Cerebral Cortex* 20, 773-782.
- Petersson, K.M., Forkstam, C., Ingvar, M., 2004. Artificial syntactic violations activate Broca's region. *Cognitive Science* 28, 383-407.
- Plas, L.v.d., Bouma, G., 2004. Syntactic contexts for finding semantically similar words. In: Computational Linguistics in the Netherlands (CLIN). Leiden.
- Poliak, S., Gollan, L., Salomon, D., Berglund, E.O., Ohara, R., Ranscht, B., Peles, E., 2001. Localization of Caspr2 in myelinated nerves depends on axon-glia interactions and the generation of barriers along the axon. *Journal of Neuroscience* 21, 7568-7575.
- Poliak, S., Gollan, L., Martinez, R., Custer, A., Einheber, S., Salzer, J.L., Trimmer, J.S., Shrager, P., Peles, E., 1999. Caspr2, a new member of the neurexin superfamily, is localized at the juxtaparanodes of myelinated axons and associates with K⁺ channels. *Neuron* 24, 1037-1047.

- Poot, M., Beyer, V., Schwaab, I., Damatova, N., van 't Slot, R., Prothero, J., Holder, S.E., Haaf, T., 2010. Disruption of CNTNAP2 and additional structural genome changes in a boy with speech delay and autism spectrum disorder. *Neurogenetics* 11, 81-89.
- Prat, C.S., Keller, T.A., Just, M.A., 2007. Individual differences in sentence comprehension: A functional magnetic resonance imaging investigation of syntactic and lexical processing demands. *Journal of Cognitive Neuroscience* 19, 1950-1963.
- Pulvermüller, F., Mohr, B., Schleichert, H., 1999. Semantic or lexico-syntactic factors: what determines word-class specific activity in the human brain? *Neuroscience Letters* 275, 81-84.
- Raichle, M.E., MacLeod, A.M., Snyder, A.Z., Powers, W.J., Gusnard, D.A., Shulman, G.L., 2001. A default mode of brain function. *Proceedings of the National Academy of Sciences of the United States of America* 98, 676-682.
- Ramus, F., Fisher, S.E., 2009. Genetics of language. In: Gazzaniga, M.S. (Ed.), *The Cognitive Neurosciences IV*. Cambridge, MA, MIT Press, pp. 855-872.
- Rodd, J.M., Davis, M.H., Johnsrude, I.S., 2005. The neural mechanisms of speech comprehension: fMRI studies of semantic ambiguity. *Cerebral Cortex* 15, 1261-1269.
- Rorden, C., Brett, M., 2000. Stereotaxic display of brain lesions. *Behavioural Neurology* 12, 191-200.
- Rossi, E., Verri, A.P., Patricelli, M.G., Destefani, V., Ricca, I., Vetro, A., Ciccone, R., Giorda, R., Toniolo, D., Maraschio, P., Zuffardi, O., 2008. A 12 Mb deletion at 7q33-q35 associated with autism spectrum disorders and primary amenorrhea. *European Journal of Medical Genetics* 51, 631-638.
- Saffran, E., Sholl, A., 1999. Clues to the functional and neural architecture of word meaning. In: Brown, C.M., Hagoort, P. (Eds.), *The Neurocognition of Language*. Oxford, Oxford University Press, pp. 241-273.
- Sag, I.A., Wasow, T., 1999. Syntactic theory: a formal introduction. Stanford, CA, USA, CSLI Publications.
- Schultz, W., Apicella, P., Ljungberg, T., 1993. Responses of monkey dopamine neurons to reward and conditioned-stimuli during successive steps of learning a delayed-response task. *Journal of Neuroscience* 13, 900-913.
- Seidenberg, M.S., Tanenhaus, M.K., Leiman, J.M., Bienkowski, M., 1982. Automatic access of the meanings of ambiguous words in context - some limitations of knowledge-based processing. *Cognitive Psychology* 14, 489-537.
- Service, E., Helenius, P., Maury, S., Salmelin, R., 2007. Localization of syntactic and semantic brain responses using magnetoencephalography. *Journal of Cognitive Neuroscience* 19, 1193-1205.
- Shapiro, K.A., Moo, L.R., Caramazza, A., 2006. Cortical signatures of noun and verb production. *Proceedings of the National Academy of Sciences of the United States of America* 103, 1644-1649.
- Shriberg, L.D., Ballard, K.J., Tomblin, J.B., Duffy, J.R., Odell, K.H., Williams, C.A., 2006. Speech, prosody, and voice characteristics of a mother and daughter with a 7;13 translocation affecting FOXP2. *Journal of Speech Language and Hearing Research* 49, 500-525.
- Snijders, T.M., Petersson, K.M., Hagoort, P., submitted-a. Effective connectivity of cortical and subcortical regions during unification of sentence structure.
- Snijders, T.M., Vosse, T., Kempen, G., Van Berkum, J.J.A., Petersson, K.M., Hagoort, P., 2009. Retrieval and unification of syntactic structure in sentence comprehension: an fMRI study using word-category ambiguity. *Cerebral Cortex* 19, 1493-1503.

References

- Snijders, T.M., Rijpkema, M., Franke, B., Brunner, H.G., Dediu, D., Folia, V., Udden, J., Fernandez, G., Petersson, K.M., Hagoort, P., submitted-b. A common CNTNAP2 polymorphism affects functional and structural aspects of language-relevant neuronal infrastructure.
- Stowe, L.A., Wijers, A.A., Willemsen, A., Reuland, E., Paans, A.M.J., Vaalburg, W., 1994. PET studies of language - an assessment of the reliability of the technique. *Journal of Psycholinguistic Research* 23, 499-527.
- Stowe, L.A., Broere, C.A.J., Paans, A.M.J., Wijers, A.A., Mulder, G., Vaalburg, W., Zwarts, F., 1998. Localizing components of a complex task: sentence processing and working memory. *Neuroreport* 9, 2995-2999.
- Strauss, K.A., Puffenberger, E.G., Huentelman, M.J., Gottlieb, S., Dobrin, S.E., Parod, J.M., Stephan, D.A., Morton, D.H., 2006. Recessive symptomatic focal epilepsy and mutant contactin-associated protein-like 2. *New England Journal of Medicine* 354, 1370-1377.
- Stromswold, K., 2001. The heritability of language: A review and metaanalysis of twin, adoption, and linkage studies. *Language* 77, 647-723.
- Südhof, T.C., 2008. Neuroligins and neurexins link synaptic function to cognitive disease. *Nature* 455, 903-911.
- Swaab, T., Brown, C., Hagoort, P., 2003. Understanding words in sentence contexts: The time course of ambiguity resolution. *Brain and Language* 86, 326-343.
- Swinney, D.A., 1979. Lexical access during sentence comprehension - (re)consideration of context effects. *Journal of Verbal Learning and Verbal Behavior* 18, 645-659.
- Tager-Flusberg, H., Paul, R., Lord, C., 2005. Language and communication in autism. In: Volkmar, F., Paul, R., Klin, A., Cohen, D.J. (Eds.), *Handbook of autism and pervasive developmental disorders*. New York, Wiley, pp. 335-364.
- Tesink, C., Buitelaar, J.K., Petersson, K.M., van der Gaag, R.J., Kan, C.C., Tendolkar, I., Hagoort, P., 2009a. Neural correlates of pragmatic language comprehension in autism spectrum disorders. *Brain* 132, 1941-1952.
- Tesink, C.M.J.Y., Petersson, K.M., van Berkum, J.J.A., van den Brink, D., Buitelaar, J.K., Hagoort, P., 2009b. Unification of speaker and meaning in language comprehension: an fMRI study. *Journal of Cognitive Neuroscience* 21, 2085-2099.
- Thompson-Schill, S.L., 2005. Dissecting the language organ: A new look at the role of Broca's area in language processing. In: Cutler, A. (Ed.), *Twenty-first Century Psycholinguistics: Four Cornerstones*. Mahwah, NJ, Lawrence Erlbaum Press
- Thompson-Schill, S.L., D'Esposito, M., Kan, I.P., 1999. Effects of repetition and competition on activity in left prefrontal cortex during word generation. *Neuron* 23, 513-522.
- Thompson-Schill, S.L., Bedny, M., Goldberg, R.F., 2005. The frontal lobes and the regulation of mental activity. *Current Opinion in Neurobiology* 15, 219-224.
- Thompson-Schill, S.L., D'Esposito, M., Aguirre, G.K., Farah, M.J., 1997. Role of left inferior prefrontal cortex in retrieval of semantic knowledge: A reevaluation. *Proceedings of the National Academy of Sciences of the United States of America* 94, 14792-14797.
- Tomita, H., Ohbayashi, M., Nakahara, K., Hasegawa, I., Miyashita, Y., 1999. Top-down signal from prefrontal cortex in executive control of memory retrieval. *Nature* 401, 699-703.

- Tyler, L.K., Marslen-Wilson, W., 2008. Fronto-temporal brain systems supporting spoken language comprehension. *Philosophical Transactions of the Royal Society B-Biological Sciences* 363, 1037-1054.
- Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., Joliot, M., 2002. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage* 15, 273-289.
- Ullman, M.T., 2004. Contributions of memory circuits to language: the declarative/procedural model. *Cognition* 92, 231-270.
- Van Berkum, J.J.A., Brown, C.M., Zwitserlood, P., Kooijman, V., Hagoort, P., 2005. Anticipating upcoming words in discourse: Evidence from ERPs and reading times. *Journal of Experimental Psychology-Learning Memory and Cognition* 31, 443-467.
- van Dijk, T.A., Kintsch, W., 1983. Strategies of discourse comprehension. New York, Academic Press.
- Van Petten, C., 2002. Lexical ambiguity resolution. In: Nadel, L. (Ed.), *Encyclopedia of Cognitive Science*. London, Macmillan, pp. 867-872.
- Vandenbergh, R., Price, C., Wise, R., Josephs, O., Frackowiak, R.S.J., 1996. Functional anatomy of a common semantic system for words and pictures. *Nature* 383, 254-256.
- Vandenbroucke, M.W.G., Scholte, H.S., van Engeland, H., Lamme, V.A.F., Kemner, C., 2008. A neural substrate for atypical low-level visual processing in autism spectrum disorder. *Brain* 131, 1013-1024.
- Vargha-Khadem, F., Gadian, D.G., Copp, A., Mishkin, M., 2005. FOXP2 and the neuroanatomy of speech and language. *Nature Reviews Neuroscience* 6, 131-138.
- Verkerk, A., Mathews, C.A., Joosse, M., Eussen, B.H.J., Heutink, P., Oostra, B.A., 2003. CNTNAP2 is disrupted in a family with Gilles de la Tourette syndrome and obsessive compulsive disorder. *Genomics* 82, 1-9.
- Vernes, S.C., Newbury, D.F., Abrahams, B.S., Winchester, L., Nicod, J., Groszer, M., Alarcon, M., Oliver, P.L., Davies, K.E., Geschwind, D.H., Monaco, A.P., Fisher, S.E., 2008. A functional genetic link between distinct developmental language disorders. *New England Journal of Medicine* 359, 2337-2345.
- Vigliocco, G., Vinson, D.P., Arciuli, J., Barber, H., 2008. The role of grammatical class on word recognition. *Brain and Language* 105, 175-184.
- Vigneau, M., Beaucousin, V., Herve, P.Y., Duffau, H., Crivello, F., Houde, O., Mazoyer, B., Tzourio-Mazoyer, N., 2006. Meta-analyzing left hemisphere language areas: Phonology, semantics, and sentence processing. *Neuroimage* 30, 1414-1432.
- von Humboldt, W., 1836. *Über die Verschiedenheit des menslichen Sprachbaues und ihren Einfluss auf die geistige Entwicklung des Menschengeschlechts* (On the structural variety of human language and its influence on the intellectual development of mankind). Berlin, F. Dummler.
- Vosse, T., Kempen, G., 2000. Syntactic structure assembly in human parsing: a computational model based on competitive inhibition and a lexicalist grammar. *Cognition* 75, 105-143.
- Vosse, T., Kempen, G., 2009. The Unification Space implemented as a localist neural net: predictions and error-tolerance in a constraint-based parser. *Cognitive Neurodynamics* 3, 331-346.
- Wang, A.T., Lee, S.S., Sigman, M., Dapretto, M., 2006. Neural basis of irony comprehension in children with autism: the role of prosody and context. *Brain* 129, 932-943.

References

- Warburton, E., Wise, R.J.S., Price, C.J., Weiller, C., Hadar, U., Ramsay, S., Frackowiak, R.S.J., 1996. Noun and verb retrieval by normal subjects studies with PET. *Brain* 119, 159-179.
- Watkins, K.E., Dronkers, N.F., Vargha-Khadem, F., 2002a. Behavioural analysis of an inherited speech and language disorder: comparison with acquired aphasia. *Brain* 125, 452-464.
- Watkins, K.E., Vargha-Khadem, F., Ashburner, J., Passingham, R.E., Connelly, A., Friston, K.J., Frackowiak, R.S.J., Mishkin, M., Gadian, D.G., 2002b. MRI analysis of an inherited speech and language disorder: structural brain abnormalities. *Brain* 125, 465-478.
- Willems, R., Ozyurek, A., Hagoort, P., 2007. When language meets action: the neural integration of gesture and speech. *Cerebral Cortex* 17, 2322-2333.
- Willems, R.M., Ozyurek, A., Hagoort, P., 2008. Seeing and hearing meaning: ERP and fMRI evidence of word versus picture integration into a sentence context. *Journal of Cognitive Neuroscience* 20, 1235-1249.
- Willems, R.M., Ozyurek, A., Hagoort, P., 2009. Differential roles for left inferior frontal and superior temporal cortex in multimodal integration of action and language. *Neuroimage* 47, 1992-2004.
- Worsley, K.J., Marrett, S., Neelin, P., Vandal, A.C., Friston, K.J., Evans, A.C., 1996. A unified statistical approach for determining significant signals in images of cerebral activation. *Human Brain Mapping* 4, 58-73.
- Xu, J., Kemeny, S., Park, G., Frattali, C., Braun, A., 2005. Language in context: emergent features of word, sentence, and narrative comprehension. *Neuroimage* 25, 1002-1015.
- Zempleni, M.Z., Renken, R., Hoeks, J.C.J., Hoogduin, J.M., Stowe, L.A., 2007. Semantic ambiguity processing in sentence context: Evidence from event-related fMRI. *Neuroimage* 34, 1270-1279.
- Zhang, J.Z., Webb, D.M., Podlaha, O., 2002. Accelerated protein evolution and origins of human-specific features: FOXP2 as an example. *Genetics* 162, 1825-1835.
- Zink, C.F., Pagnoni, G., Chappelow, J., Martin-Skurski, M., Berns, G.S., 2006. Human striatal activation reflects degree of stimulus saliency. *Neuroimage* 29, 977-983.
- Zola-Morgan, S., 1995. Localization of brain-function - the legacy of Franz Joseph Gall (1758-1828). *Annual Review of Neuroscience* 18, 359-383.
- Zweier, C., de Jong, E.K., Zweier, M., Orrico, A., Ousager, L.B., Collins, A.L., Bijlsma, E.K., Oortveld, M.A.W., Ekici, A.B., Reis, A., Schenck, A., Rauch, A., 2009. CNTNAP2 and NRXN1 are mutated in autosomal-recessive Pitt-Hopkins-like mental retardation and determine the level of a common synaptic protein in *Drosophila*. *American Journal of Human Genetics* 85, 655-666.

Appendices

Appendix 1A

Experimental materials for
Chapters 2, 3, and 4

Appendix 1A

Dutch stimulus materials for Chapters 2, 3 and 4

Critical words are in ***italics***. The first word is the ambiguous word, the second the unambiguous word.

Noun-ratio is the proportion of noun-endings given by participants in the pretest.

n = noun ending; v = verb ending

nr.	n / v	noun-ratio	Sentences (<i>ambiguous / unambiguous</i>)	Word Sequences (<i>ambiguous / unambiguous</i>)
2	n	0.26	Je kunt bakken / <i>dozen</i> met fruit kopen op de markt.	last maar bakken / <i>dozen</i> beleid de in kunt schuil zij
2	v	0.26	Je kunt bakken / <i>braden</i> en grillen tegenwoordig ook met de magnetron.	in uitsluitend bakken / <i>braden</i> aanrader er de aan verwoord valt wat
3	n	0.80	Maar bedragen / <i>premies</i> boven de 100 euro betaal ik niet.	niet bedragen / <i>premies</i> ik heen kikker ook achter bols de
3	v	0.80	Maar bedragen / <i>bedroegen</i> de subsidies meer dan duizend euro?	getuige bedragen / <i>bedroegen</i> Oss het hun tarieven hij maar
5	n	0.71	Want die beten / <i>ziektes</i> kunnen ernstige gevolgen hebben.	toen verdeeld beten / <i>ziektes</i> zijn worden bevolking kunnen
5	v	0.71	Want die beten / <i>sloegen</i> vaak naar elkaar tijdens hun spel.	voelt toe beten / <i>sloegen</i> als vier hun volgens enige niet
6	n	0.20	Maar betogen / <i>brieven</i> schrijven is soms best lastig.	hoog betogen / <i>brieven</i> niet betekent gelezen in wie
6	v	0.20	Maar betogen / <i>stemden</i> de kamerleden tegen de nieuwe wet?	tekstwerk betogen / <i>stemden</i> de steeds lid de deze bij
7	n	0.78	Ook beuken / <i>eiken</i> zijn prachtig in de herfst.	schuldig beuken / <i>eiken</i> maar het bagage het uit
7	v	0.78	Ook beuken / <i>hakten</i> de strijdsters hard op Manuel in.	pudding beuken / <i>hakten</i> het op geen zuidoosten het geeft
8	n	0.61	Wanneer bevelen / <i>opdrachten</i> goed uitgevoerd worden maak je wellicht promotie.	hebben bevelen / <i>opdrachten</i> pers overigens niets echter dan schilders overtuigd
8	v	0.61	Wanneer bevelen / <i>vroege</i> jullie hem weg te gaan?	midden bevelen / <i>vroege</i> te iemand toch nu kwam
9	n	0.50	Zodra jullie bewijzen / <i>kopij</i> leveren kunnen we beginnen.	genoemd tegen bewijzen / <i>kopij</i> uit helaas gezeten jullie
9	v	0.50	Zodra jullie bewijzen / <i>beweren</i> dat hij erbij betrokken is arresteren we hem.	in nogal bewijzen / <i>beweren</i> meestal maar dit in struikelen hem verschil opeens
10	n	0.24	Ook bezoeken / <i>bezoekjes</i> aan deze patiëntje mogen slechts kort duren.	plus bezoeken / <i>bezoekjes</i> open voor steeds cliënten bij ook gaf
10	v	0.24	Ook bezoeken / <i>verzorgen</i> ze grootvader in het ziekenhuis.	atmosfeer bezoeken / <i>verzorgen</i> dan het dat uitvoering er
15	n	0.68	Maar doppen / <i>zegels</i> verzamelt hij al jaren.	overslaan doppen / <i>zegels</i> hij alles door je
15	v	0.68	Maar doppen / <i>pelden</i> de deelnemers de bonen niet te langzaam?	te doppen / <i>pelden</i> landschap de verloren voor wrok het ook
16	n	0.22	Je kunt dromen / <i>visioenen</i> meestal niet goed aan anderen navertellen.	heb ze dromen / <i>visioenen</i> denken op prijsgegeven sommige kunt die
16	v	0.22	Je kunt dromen / <i>ijlen</i> over de toekomst zo lang je wilt.	vorm dit dromen / <i>ijlen</i> het wat hij wat voorbeeld doe kunt
17	n	0.32	Maar die erven / <i>jongens</i> kunnen moeilijk gaan doen.	waren heb erven / <i>jongens</i> laten grootste door zijn
17	v	0.32	Maar die erven / <i>kregen</i> het grootste gedeelte van zijn kapitaal.	bij maar erven / <i>kregen</i> januari genomen in niet techniek een
20	n	0.35	Ook dat geloof / <i>idee</i> is erg aanwezig in zijn nieuwe biografie.	artiesten laatste geloof / <i>idee</i> voor in maar slechte die stuk
20	v	0.35	Ook dat geloof / <i>meen</i> je toch hopelijk zelf niet.	iets al geloof / <i>meen</i> je langzame het aan zoals
21	n	0.60	Wanneer getuigen / <i>cursisten</i> niet verschijnen hebben we een probleem.	situatie getuigen / <i>cursisten</i> helemaal van zo beschreven dat heeft
21	v	0.60	Wanneer getuigen / <i>verschenen</i> jullie bij hun bruiloft?	slechts getuigen / <i>verschenen</i> overal zich monsters wat
22	n	0.34	Waarom gieren / <i>gabbers</i> een kale kop hebben staat in dit boek.	wordt gieren / <i>gabbers</i> van warm in lang achter bij felle laten
22	v	0.34	Waarom gieren / <i>bulderen</i> die kwajongens zo van het lachen?	in gieren / <i>bulderen</i> van schreef op eerst uit klaar
23	n	0.47	Want deze gilden / <i>clubs</i> zijn aangesloten bij een landelijke organisatie.	ontwikkeling nog gilden / <i>clubs</i> alles niet het waar uitgegeven toenmalige
23	v	0.47	Want deze gilden / <i>maakten</i> het uit toen ze het bedrog ontdekten.	in het gilden / <i>maakten</i> schimmel terug geen ons geen hij flessen
24	n	0.53	Maar die goten / <i>kabels</i> moeten nodig vervangen worden.	gedaan aan goten / <i>kabels</i> verdienende hebben eigen die
24	v	0.53	Maar die goten / <i>gieten</i> ijzer in een daarvoor bestemde mal.	lome dat goten / <i>gieten</i> gezwegen etiket een aan meestal nog
25	n	0.45	Maar graven / <i>muren</i> beklaadden is gelukkig strafbaar.	voorbij graven / <i>muren</i> parallel niet in inleiden
25	v	0.45	Maar graven / <i>delven</i> ze een graf dan zijn ze gauw klaar.	mits graven / <i>delven</i> rechts niet hij diep een zich ze bij
26	n	0.70	Want die greep / <i>studie</i> is moeilijker dan ik had gedacht.	aan in greep / <i>studie</i> bepaald over wel zelfs niet ontwikkelde
26	v	0.70	Want die greep / <i>pakte</i> plotseling een pistool.	uitstek niet greep / <i>pakte</i> voldoende niet dat
27	n	0.32	Maria wilde haar groeten / <i>mening</i> overbrengen via een vriendin.	mijn van per groeten / <i>mening</i> kranten vroeg atleet oversteken
27	v	0.32	Maria wilde haar groeten / <i>kietelen</i> maar was toch te verlegen.	beslissen te enige groeten / <i>kietelen</i> object zich uit bij hoe
28	n	0.65	Want ook groeien / <i>gleuven</i> in rotsen kunnen gemaakt zijn door stroompjes water.	liedt blijft groeien / <i>gleuven</i> zich waren ook aan maken het alles maniertjes

nr.	n / v	noun-ratio	Sentences (ambiguous / unambiguous)	Word Sequences (ambiguous / unambiguous)
28	v	0.65	Want ook groeven / plaatsen soldaten een tweede waterput in dat dorp.	aan bus groeven / plaatsen een het deserter dichter toe in daarbij
29	n	0.53	Als tuttige huisvrouwen hakken / laarsjes dragen is dat geen gezicht.	gelikte liepen haar hakken / laarsjes hoofdstraat om een in jongen
29	v	0.53	Als tuttige huisvrouwen hakken / snipperen zij de uien fijn.	fijn onhelder hekel hakken / snipperen zich astrologie het maar
30	n	0.49	Die happen / hapjes worden door Maaike in de keuken bereid.	analyse happen / hapjes bracht nog Jonathan de hebben van er
30	v	0.49	Die happen / snakken naar adem na de vermoedende wedstrijd.	aan happen / snakken het deze neergelaten rauw justitie hun
31	n	0.51	Ook harken / bezems worden goed gebruikt door de tuinman.	sovjets harken / bezems gekregen heeft kan het zich uit
31	v	0.51	Ook harken / wieden de buren iedere zondag hun tuintje.	camera harken / wieden welke ook juweel het handel maar
32	n	0.68	Want die knallen / explosie kun je een kilometer verderop nog horen.	sterk om knallen / explosie je omstreeks het echt zoals onderdeel er
32	v	0.68	Want die knallen / knalden niet iets harder dan een gewoon rotje.	recht hoe knallen / knalden je dat heel afloop niet zeevis nooit
35	n	0.29	Maar kruisen / kruisjes en kapellen vind je in deze omgeving overal.	je kruisen / kruisjes maar veel van reeds nog slotwoord dat omgeving
35	v	0.29	Maar kruisen / ontmoeten we elkaar opnieuw dan sta ik niet voor mezelf in.	zout kruisen / ontmoeten verre die om in hij sommige altijd zijn al ik
36	n	0.26	Wanneer die broers laden / kastjes opruimen krijgen ze ruzie.	teveel afmaken haren laden / kastjes ze gedaan slechts er
36	v	0.26	Wanneer die broers laden / vechten kijken wij vol spanning toe.	op vaak verhaal laden / vechten iets me bloot allerlei zichzelf
37	n	0.27	Als inspecteurs lekken / fraude ontdekken alarmeren ze hun collega's meteen.	dwarrelde filosofie lekken / fraude op meer overtugen eerst dan levensbelang
37	v	0.27	Als inspecteurs lekken / falen moet de overheid ze ontslaan.	invloed aanbod lekken / falen vandalisme met kan je de
38	n	0.50	Ook lichten / lampen schijnen feller als het donker is.	een lichten / lampen in voor regen op glijden graue
38	v	0.50	Ook lichten / schakelen we de brandweer in na het ongeval.	al lichten / schakelen het suggesties het biologie die dat hem
39	n	0.76	Maar ook loodsen / vertalers worden slecht betaald.	uit heeft loodsen / vertalers handel geweld je
39	v	0.76	Maar ook loodsen / lokten wij Sinterklaas ongemerkt naar binnen.	paspoorten geen loodsen / lokten samen maar ze angstige zelf
40	n	0.29	Ook luchten / tempels vind ik erg mooi om te fotograferen.	nee luchten / tempels geprojecteerd deden klaar ze je geen te
40	v	0.29	Ook luchten / filmen we de gevangenen iedere dag.	belasting luchten / filmen precies om wij ook het
41	n	0.40	Want lusten / studenten kunnen flink lastig zijn.	gewijd lusten / studenten voor zwaar mij waren
41	v	0.40	Want lusten / verorberen honden alles wat hun baasje ze voorschotelt?	tumor lusten / verorberen zelfs dan uitverkozen ze echter figuren je
42	n	0.79	Dat merk / product is zeer populair bij scholieren.	integriteit merk / product complete dat pas in er
42	v	0.79	Dat merk / zie je zaterdag wel tijdens de wedstrijd.	defensie merk / zie de personeel volgens dat ook geen
43	n	0.24	Zij zullen mokken / kopjes moeten afwassen om thee te kunnen drinken.	wordt leert mokken / kopjes gevuld hebben moeten te al brillen die
43	v	0.24	Zij zullen mokken / pruilen omdat ze vroeg naar bed moeten.	hadden toen mokken / pruilen maar niets gang doet wel bij
44	n	0.32	Ook namen / termen als DOS en Windows kwamen voor.	kolk namen / termen van stellen pasjes hij aan die
44	v	0.32	Ook namen / trokken de agenten Suzanne mee naar buiten.	controle namen / trokken toch het Annemiek aan achter bij
46	n	0.29	Als Gelderse boeren rieken / hamers hanteren zijn ze hard aan het werk.	raken de bereiden rieken / hamers je paar niet houd dusdanig ik hij
46	v	0.29	Als Gelderse boeren rieken / stinken zij naar mest.	stabiele voor zich rieken / stinken groeien dan open
47	n	0.74	Ook rijst / pasta moet je in water met wat zout bereiden.	uit rijst / pasta door dat klok voor zou nodig je hanteren
47	v	0.74	Ook rijst / rees het beeld op van een bijna decadent land.	een rijst / rees stuk nooit het om de hen haveloze het
48	n	0.34	Als spelers rollen / taken krijgen toebedeeld zijn ze vaak ontevreden.	opgevolgd water rollen / taken ik dat om materieel zondag plaats
48	v	0.34	Als spelers rollen / hollen door het veld kijkt iedereen gespannen toe.	aan opnieuw rollen / hollen heel riep ouder verkregen een economie ook
50	n	0.23	Zij moeten schatten / eieren zoeken in de tuin.	nu strijd schatten / eieren een komen rijk het
50	v	0.23	Zij moeten schatten / taxeren wat de waarde van het kasteel is.	in begint schatten / taxeren we gaf het kunnen het je de
52	n	0.21	Als arme vrouwen schoppen / snoepjes uitdelen moet je op je hoede zijn.	maar uit voor schoppen / snoepjes wereld uit dan agent een dwars opsteken
52	v	0.21	Als arme vrouwen schoppen / slaan doen ze dat uit wanhoop.	zonder hij bij schoppen / slaan de een brede hoorde probleem
53	n	0.79	Maar schorten / truiken met ruitjes zijn nu echt uit.	pincet schorten / truiken dit niet hij meer zijn allemaal
53	v	0.79	Maar schorten / mankeren er nog zaken aan deze versie van Word?	wat schorten / mankeren bij voor straten we eer van groot dan
54	n	0.68	Wanneer lijfwachten schoten / vrachten lossen schelden ze daar hard bij.	moederschap om schoten / vrachten zachte echter om droomde hem duiden
54	v	0.68	Wanneer lijfwachten schoten / vielen ontstond er opschudding.	nationalisme geslagen schoten / vielen ook deurwaarder weinig
55	n	0.37	Ook schuren / meubels en tuinhuisjes kun je bij Intratuin kopen.	perforaties schuren / meubels roeft boek om ook dat keelholte ze
55	v	0.37	Ook schuren / sluiten deze mannen de deurtjes iets te hard.	wat schuren / sluiten toe vallen de halen commode te nog
56	n	0.24	Als oude mensen sloffken / slippers dragen komen ze niet vaak buiten.	naast gelegd waarom sloffken / slippers eigen maar ander je naar moet
56	v	0.24	Als oude mensen sloffken / sjokken ze door het vervallen huis.	uit weet weigeren sloffken / sjokken dan ik dagen in tegen
57	n	0.40	Maar sneden / sneetjes brood zijn lekker om te toasten.	links sneden / sneetjes siertuin te dat aan nog boom
57	v	0.40	Maar sneden / snijden de ministers zich hier niet mee in de vingers?	afspraken sneden / snijden voor bloemen het maar weg wie het maar het
58	n	0.80	Alleen snoeren / draden raken zo dikwijs verwارد.	stoel snoeren / draden wel niets aangezien aarzelen
58	v	0.80	Alleen snoeren / binden we de rugzakken stevig vast.	serieus snoeren / binden tegen nog het promenade denk

nr.	n / v	noun-ratio	Sentences (ambiguous / unambiguous)	Word Sequences (ambiguous / unambiguous)
59	n	0.71	Wanneer snorren / petten hier in de mode komen emigreer ik!	zelfs snorren / petten het heel daarna dadem er dat boekhoudt
59	v	0.71	Wanneer snorren / miauwen poezen harder dan normaal?	sterker snorren / miauwen helemaal gegevens we dwerg
60	n	0.76	Want deze sprongen / medicijnen zijn niet zonder risico.	cijfers alles sprongen / medicijnen ook aan weg die
60	v	0.76	Want deze sprongen / zwommen in het koude meerje.	deze de sprongen / zwommen ernst heel wissels dat
61	n	0.53	Want die stammen / volkeren zwieren van oase naar oase.	luier ons stammen / volkeren de voor hulst verklaar uit
62	n	0.47	Beide stappen / stapjes waren in de verkeerde richting.	geschikt stappen / stapjes het van relatie iets zowel
62	v	0.47	Beide stappen / zuipen graag tot diep in de nacht.	gelijk stappen / zuipen viel nog daarom het tafel de
63	n	0.41	Wanneer stormen / orkanen het land teisteren richten ze vervelende schade aan.	meende stormen / orkanen akkoord niemand ze lang een afwisselen ik aangevoerd
63	v	0.41	Wanneer stormen / gingen ze die zaal in de schouwburg binnenvan?	bron stormen / gingen een buiten praktijken het op zoals dan
64	n	0.63	Alleen stralen / straaltjes water sijpelen door het raam naar binnen.	nog stralen / straaltjes weet keken een onder bij napraten boven
64	v	0.63	Alleen stralen / straalden deze meisjes niet zo als vorige week.	mag stralen / straalden gevoel zij onder zij derde maar die
66	n	0.26	Wanneer ouders tollen / knikkers kopen maken ze hun kinderen blij.	na kwam tollen / knikkers gemaakt dan stuk krijg zichzelf artikel
66	v	0.26	Wanneer ouders tollen / snoepen kijken kinderen jaloers toe.	slappe iets tollen / snoepen geweest genoemd lopen waarom
67	n	0.54	Als prinsen tronen / functies moeten afstaan protesteren ze.	aquarium komen tronen / functies uitgekozen beladen bij ook
67	v	0.54	Als prinsen tronen / vertoeven zij op hun zetel.	ik zij tronen / vertoeven beland eenden in hem
68	n	0.21	Maar twisten / ruzies kun je het beste vlug bijleggen.	raad twisten / ruzies van ingevlucht die uit best zoek
68	v	0.21	Maar twisten / ruziën zij niet erg vaak zo vlak na hun bruiloft?	vuur twisten / ruziën dit beleving nog tien na hele zijn aan wat
69	n	0.45	Wanneer vellen / stukken papier nat worden krukelen ze.	wordt vellen / stukken er schoot stok zonder gehongerd
69	v	0.45	Wanneer vellen / kapten de eigenaars de dode boom in de tuin?	ding vellen / kapten dame het binnen kostuums het een zout de
70	n	0.63	Maar die verdragen / resoluties helpen niet om de vrede te herstellen.	aan dan verdragen / resoluties uit lijnen dat realiseerde te mogen het
70	v	0.63	Maar die verdragen / verduren menselijke aanwezigheid best goed.	afhankelijk zelf verdragen / verduren door stelt overtuiging die
71	n	0.58	Want ook verwijten / adviezen kunnen erg hard aankomen.	uitgaat even verwijten / adviezen voor hoog dus hebben
71	v	0.58	Want ook verwijten / vertellen ze hem dat sommige details niet kloppen.	slechts om verwijten / vertellen aan strand mee over van wat verkeren
72	n	0.41	Ook vijlen / messen zaten in de cadeautjes voor de gevangenen verstopt.	sloeg vijlen / messen mededeling het om hospitaal beleefd de zijn van
72	v	0.41	Ook vijlen / politisten helpt om nagels mooi te houden.	om vijlen / politisten door richt zitten opmaken recht te
74	n	0.58	Maar ook vlechten / rokjes geven meisjes een retro-look.	houding maar vlechten / rokjes nog alternerend dat ging
74	v	0.58	Maar ook vlechten / vlochten wij bankjes van wilgenteen.	spionage niet vlechten / vlochten af zich rietscherf de
76	n	0.83	Beide vluchten / wedstrijden werden vanwege het slechte weer afgelast.	schetste vluchten / wedstrijden deze minder rondom het willen moderne
76	v	0.83	Beide vluchten / renden het bekreste huis uit.	raspende vluchten / renden mee een daarom al
77	n	0.29	Zodra jullie voorstellen / tips verwerkt zijn sturen we de aangepaste versie op.	bevindt schoon voorstellen / tips aangeleverd maar aanslag aanvaard het hij nu reeds
77	v	0.29	Zodra jullie voorstellen / opperen om te gaan zal Willem meegaan.	ergens activa voorstellen / opperen herberg doen je te werd voren
78	n	0.58	Beide vormen / soorten berusten op foutjes in het DNA.	aan vormen / soorten een gij Beekman ieder in ontsnapte
78	v	0.58	Beide vormen / bieden een getrouwne nabootsing van zijn geschriften.	dat vormen / bieden leefbaar zowel binnenplaats aminozuren van zijn
79	n	0.29	Als oude foto's vouwen / scheurtjes vertonen zijn ze minder waard.	voor gezin blij vouwen / scheurtjes bezocht mee ze terwijl zich
79	v	0.29	Als oude foto's vouwen / vervagen is dat vreselijk zonde.	Mientje ben in vouwen / vervagen taxi van naar vannacht
80	n	0.26	Ook vragen / gezeur over zijn vriendin zal Boris deze keer tolereren.	over vragen / gezeur Linda dat over ook ontberen eigenaar zegt komt
80	v	0.26	Ook vragen / informeren sommige fractieleden of de premier geen zaken achterhoudt.	zich vragen / informeren geld genoodzaakt de binnenvalt hun seisoen door namelijk
81	n	0.31	Zij zullen walmen / voedsel onderzoeken op kwalijske stoffen.	plaats ontwikkelen walmen / voedsel bevindt deze dat nutteloos
81	v	0.31	Zij zullen walmen / walgen van de rook wanneer ze uit dat café komen.	iemand er walmen / walgen de zouden in moet last hem stof om van
83	n	0.26	Ook wensen / klachten en suggesties kun je op deze manier kenbaar maken.	huis wensen / klachten raad schilders je bijbelse tegen maken hij het om
83	v	0.26	Ook wensen / wensten we Marjolein en Paul alle goeds toe.	glad wensen / wensten in nog Sam om ambt dit zeer
85	n	0.18	Als regeringen wijken / dorpen bouwen zetten ze goede architecten in.	verhaal er wijken / dorpen opstelling in winkel anders hij loyaliteit
85	v	0.18	Als regeringen wijken / zwichten voor terrorisme is de burger de dupe.	lijnen ceremonie wijken / zwichten het de voordelen abt door in maar
88	n	0.18	Wanneer zeilen / deuren klapperen komt dat door de harde wind.	rand zeilen / deuren kwijt de laten dit elkaar behelsde dat
88	v	0.18	Wanneer zeilen / roeien we weer eens naar Ameland?	pluimvee zeilen / roeien minder niet weer je wij

Appendix 1B

Experimental materials

for Chapter 5

Appendix 1B

Dutch stimulus materials for Chapter 5

Critical words are in ***italics***. The first word is the ambiguous word, the second the unambiguous word.

Noun-ratio is the proportion of noun-endings given by participants in the pretest.

n = noun ending; v = verb ending

nr.	n / v	noun-ratio	Sentences (<i>ambiguous / unambiguous</i>)	Word Sequences (<i>ambiguous / unambiguous</i>)
2	n	0.26	Je kunt bakken <i>dozen</i> fruit kopen op de markt.	die niveau bakken <i>dozen</i> bij stierf wonen nemen het
2	v	0.26	Je kunt bakken <i>braden</i> door olie op hoog vuur te verwarmen.	negen hij bakken <i>braden</i> excuseren vind wilt vrij te je uit
3	n	0.80	Maar bedragen <i>premies</i> boven de 100 euro betaal ik niet.	niet bedragen <i>premies</i> ik heen kikker ook achter bols de
3	v	0.80	Maar bedragen <i>bedroegen</i> de subsidies meer dan duizend euro?	getuige bedragen <i>bedroegen</i> Oss het hun tarieven hij maar
5	n	0.71	Want die beten <i>ziektes</i> kunnen ernstige gevolgen hebben.	toen verdeeld beten <i>ziektes</i> zijn worden bevolking kunnen
5	v	0.71	Want die beten <i>sloegen</i> vaak naar elkaar tijdens hun spel.	voelt toe beten <i>sloegen</i> als vier hun volgens enige niet
6	n	0.20	Maar betogen <i>brieven</i> schrijven is soms best lastig.	hoog betogen <i>brieven</i> niet betekent gelezen in wie
6	v	0.20	Maar betogen <i>stemden</i> de kamerleden tegen de nieuwe wet?	kunstwerk betogen <i>brieven</i> de steeds lid de deze bij
7	n	0.78	Ook beuken <i>eiken</i> zijn prachtig in de herfst.	schuldig beuken <i>eiken</i> maar het bagage het uit
7	v	0.78	Ook beuken <i>hakten</i> de strijdsters hard op Manuel in.	pudding beuken <i>hakten</i> het op geen zuidoosten het geeft
8	n	0.61	Wanneer bevelen <i>opdrachten</i> goed uitgevoerd worden maak je wellicht promotie.	hebben bevelen <i>opdrachten</i> pers overigens niets echter dan schilders overtuigd
8	v	0.61	Wanneer bevelen <i>vroegen</i> wij de directeur om weg te gaan?	heel bevelen <i>vroegen</i> minder te zij kilometer het zal uit
9	n	0.50	Zodra jullie bewijzen <i>kopij</i> leveren kunnen we beginnen.	genoemd tegen bewijzen <i>kopij</i> uit helaas gezeten jullie
9	v	0.50	Zodra jullie bewijzen <i>beweren</i> dat hij erbij betrokken is arresteren we hem.	in nogal bewijzen <i>beweren</i> meestal maar dit in struikelen hem verschil opeens
10	n	0.24	Ook bezoeken <i>bezoekjes</i> aan deze patiëntene mogen slechts kort duren.	plus bezoeken <i>bezoekjes</i> open voor steeds cliënten bij ook gaf
10	v	0.24	Ook bezoeken <i>verzorgen</i> ze grootvader in het ziekenhuis.	atmosfeer bezoeken <i>verzorgen</i> dan het dat uitvoering er
15	n	0.68	Maar doppen <i>zegels</i> verzamelt hij al jaren.	overslaan doppen <i>zegels</i> hij alles door je
15	v	0.68	Maar doppen <i>pelden</i> de deelnemers de bonen niet te langzaam?	te doppen <i>pelden</i> landschap de verloren voor wrak het ook
16	n	0.22	Je kunt dromen <i>visioenen</i> meestal niet goed aan anderen navertellen.	heb ze dromen <i>visioenen</i> denken op prijsgegeven sommige kunt die
16	v	0.22	Je kunt dromen <i>ijlen</i> wanneer de operatie beëindigd is.	seconden het dromen <i>ijlen</i> dan gezien doet in herleiden
17	n	0.32	Maar die erven <i>jongens</i> kunnen moeilijk gaan doen.	waren heb erven <i>jongens</i> laten grootste door zijn
17	v	0.32	Maar die erven <i>kregen</i> het grootste gedeelte van zijn kapitaal.	bij maar erven <i>kregen</i> januari genomen in niet techniek een
20	n	0.35	Ook dat geloof <i>idee</i> is erg aanwezig in zijn nieuwe biografie.	artiesten laatste geloof <i>idee</i> voor in in maar slechte die stuk
20	v	0.35	Ook dat geloof <i>meen</i> je toch hopelijk zelf niet.	iets al geloof <i>meen</i> je langzame het aan zoals
21	n	0.60	Wanneer getuigen <i>cursisten</i> ons tijdig informeren schieten we beter op.	al getuigen <i>cursisten</i> hij afgespeeld blijft vette echter iets hielden
21	v	0.60	Wanneer getuigen <i>verschenen</i> deze vrienden bij jullie bruiloft?	uit getuigen <i>verschenen</i> binnen bedoeling midden dit infectie
22	n	0.34	Waarom gieren <i>gabbers</i> een kale kop hebben staat in dit boek.	wordt gieren <i>gabbers</i> van warm in lang achter bij felle laten
22	v	0.34	Waarom gieren <i>bulderen</i> de kwajongens zo van het lachen?	in gieren <i>bulderen</i> van schreef op eerst uit klaar
23	n	0.47	Want deze gilden <i>clubs</i> zijn aangesloten bij een landelijke organisatie.	ontwikkeling nog gilden <i>clubs</i> alles niet het waar uitgegeven toenmalige
23	v	0.47	Want deze gilden <i>maakten</i> het uit toen ze het bedrog ontdekt.	in het gilden <i>maakten</i> schimmel terug geen ons geen hij flessen
24	n	0.53	Maar die goten <i>kabels</i> moeten nodig vervangen worden.	gedaan aan goten <i>kabels</i> verdienven hebben eigen die
24	v	0.53	Maar die goten <i>gieten</i> ijzer in een daarvoor bestemde mal.	lome dat goten <i>gieten</i> gezwegen etiket een aan meestal nog
25	n	0.45	Maar graven <i>muren</i> beklaadden is gelukkig strafbaar.	voorbij graven <i>muren</i> parallel niet in inleiden
25	v	0.45	Maar graven <i>delven</i> ze een graf dan zijn ze gauw klaar.	mits graven <i>delven</i> rechts niet hij diep een zich ze bij
26	n	0.70	Want die greep <i>studie</i> is moeilijker dan ik had gedacht.	aan in greep <i>studie</i> bepaald over wel zelfs niet ontwikkelde
26	v	0.70	Want die greep <i>pakte</i> plotseling een pistool.	uitstek niet greep <i>pakte</i> voldoende niet dat
27	n	0.32	Maria wilde haar groeten <i>mening</i> overbrengen via een vriendin.	mijn van per groeten <i>mening</i> kranten vroeg atleet oversteken
27	v	0.32	Maria wilde haar groeten <i>kietelen</i> maar was toch te verlegen.	beslissen te enige groeten <i>kietelen</i> object zich uit bij hoe
28	n	0.65	Want ook groeven <i>rimpels</i> in je gezicht verminderen door deze crème.	dan niets groeven <i>rimpels</i> je van stads veroordeerde meer mannen maar

nr.	n / v	noun-ratio	Sentences (ambiguous / unambiguous)	Word Sequences (ambiguous / unambiguous)
28	v	0.65	Want ook groeven / plaatsen soldaten een tweede waterput in dat dorp.	aan bus groeven / plaatsen een het deserteur dichter toe in daarbij
29	n	0.53	Als tuttige huisvrouwen hakken / laarsjes dragen is dat geen gezicht.	gelikte liepen haar hakken / laarsjes hoofdstraat om een in jongen
29	v	0.53	Als tuttige huisvrouwen hakken / snipperen zij de uien fijn.	fijn onhelder hekel hakken / snipperen zich astrologie het maar
30	n	0.49	Die happen / hapjes worden door Maaike in de keuken bereid.	analyse happen / hapjes bracht nog Jonathan de hebben van er
30	v	0.49	Die happen / snakken vaak naar adem na een vermoeiende wedstrijd.	stond happen / snakken contract wel hun spoor er dat respectabel
31	n	0.51	Ook harken / bezems worden goed gebruikt door de tuinman.	sovjets harken / bezems gekregen heeft kan het zich uit
31	v	0.51	Ook harken / wieden de buren iedere zondag hun tuintje.	camera harken / wieden welke ook juweel het handel maar
32	n	0.68	Want die knallen / explosie kun je een kilometer verderop nog horen.	sterk om knallen / explosie je omstreks het echt zoals onderdeel er
32	v	0.68	Want die knallen / knalden iets harder dan een gewoon rotje.	deze hoe knallen / knalden wreker uiterst een men meest op
35	n	0.29	Maar kruisen / kruisjes zijn in de kerk op veel plekken te vinden.	op kruisen / kruisjes wel volk blijven te het misdaad hij dat door
35	v	0.29	Maar kruisen / ontmoeten we elkaar opnieuw dan sta ik niet voor mezelf in.	zout kruisen / ontmoeten verre die om in hij sommige altijd zijn al ik
36	n	0.26	Wanneer die broers laden / kastjes opruimen krijgen ze ruzie.	teveel afmaken haren laden / kastjes ze gedaan slechts er
36	v	0.26	Wanneer die broers laden / vechten is de spanning te snijden.	sociaal te wandelen laden / vechten ingang maar de in achter
37	n	0.27	Als inspecteurs lekken / fraude ontdekken alarmeren ze hun collega's meteen.	dwarrelde filosofie lekken / fraude op meer overtuigen eerst dan levensbelang
37	v	0.27	Als inspecteurs lekken / faalen moet de overheid ze ontslaan.	invloed aanbood lekken / faalen vandalisme met kan je de
38	n	0.50	Ook lichten / lampen schijnen feller als het donker is.	een lichten / lampen in voor regen op glijden grauwe
38	v	0.50	Ook lichten / schakelen we de brandweer in na het ongeval.	al lichten / schakelen het suggesties het biologie die dat hem
39	n	0.76	Maar ook loodsen / vertalers worden slecht betaald.	uit heeft loodsen / vertalers handel geweld je
39	v	0.76	Maar ook loodsen / lokten wij Sinterklaas ongemerkt naar binnen.	paspoorten geen loodsen / lokten samen maar ze angstige zelf
40	n	0.29	Ook luchten / tempels zijn erg mooi om te fotograferen.	afgewisseld luchten / tempels te klaar rol er die zich
40	v	0.29	Ook luchten / filmen we de gevangenen iedere dag.	belasting luchten / filmen precies om wij ook het
41	n	0.40	Want lusten / studenten kunnen flink lastig zijn.	gewijd lusten / studenten voor zwaar mij waren
41	v	0.40	Want lusten / mogen honden alles wat hun baasje ze voorschotelt?	tumor lusten / mogen zelfs dan uitverkozen ze echter figuren je
42	n	0.79	Dat merk / product is zeer populair bij scholieren.	integriteit merk / product complete dat pas in er
42	v	0.79	Dat merk / zie je zaterdag wel tijdens de wedstrijd.	defensie merk / zie de personeel volgens dat ook geen
43	n	0.24	Zij zullen mokken / kopjes afwassen zodat ze thee kunnen drinken.	wat gelezen mokken / kopjes min lijkt activeren tegen ooit je
43	v	0.24	Zij zullen mokken / pruilen omdat ze vroeg naar bed moeten.	hadden toen mokken / pruilen maar niets gang doet wel bij
44	n	0.32	Ook namen / termen als DOS en Windows kwamen voor.	kolk namen / termen van stellen pasjes hij aan die
44	v	0.32	Ook namen / trokken de agenten Suzanne mee naar buiten.	controle namen / trokken toch het Annemiek aan achter bij
46	n	0.29	Als Gelderse boeren rieken / hamers hanteren zijn ze hard aan het werk.	raken de bereiden rieken / hamers je paar niet houdt dusdanig ik hij
46	v	0.29	Als Gelderse boeren rieken / stinken zij naar mest.	aan illegaal hun rieken / stinken niet bereid stort
47	n	0.74	Ook rijst / pasta moet in water met wat zout bereid worden.	sta rijst / pasta enkel wordt bij op wel weten een weer
47	v	0.74	Ook rijst / rees het beeld op van een bijna decadent land.	een rijst / rees stuk nooit het om de hen haveloze het
48	n	0.34	Als spelers rollen / taken toebedeeld krijgen zijn ze vaak ontevreden.	er hij rollen / taken laat premier ze gezien structureel beschikken
48	v	0.34	Als spelers rollen / hollen door het veld kijkt iedereen gespannen toe.	aan opnieuw rollen / hollen heel riep ouder verkregen een economie ook
50	n	0.23	Zij moeten schatten / eieren zoeken in de tuin.	nu strijd schatten / eieren een komen rijk het
50	v	0.23	Zij moeten schatten / taxeren wat de waarde van het kasteel is.	in beginst schatten / taxeren we gaf het kunnen het je de
52	n	0.21	Als arme vrouwen schoppen / snoepjes uitdelen moet je op je hoede zijn.	maar uit voor schoppen / snoepjes wereld uit dan agent een dwars opsteken
52	v	0.21	Als arme vrouwen schoppen / slaan doen ze dat uit wanhoop.	onder hij bij schoppen / slaan de een brede hoorde probleem
53	n	0.79	Maar schorten / truiken met ruitjes zijn nu echt uit.	pincet schorten / truiken dit niet hij meer zijn allemaal
53	v	0.79	Maar schorten / mankeren er nog zaken aan deze versie van Word?	wat schorten / mankeren bij voor straten we eer van groot dan
54	n	0.68	Wanneer lijfwachten schoten / vrachten lossen schelden ze daar hard bij.	moederschap om schoten / vrachten zacht echter om droomde hem duiden
54	v	0.68	Wanneer lijfwachten schoten / vieren ontstond er opschudding.	nationalisme geslagen schoten / vielen ook deurwaarder weinig
55	n	0.37	Ook schuren / meubels kunnen op Marktplaats gekocht worden.	over schuren / meubels schuldeiser hij over waren uitgaven
55	v	0.37	Ook schuren / sluiten deze mannen de deurtjes iets te hard.	wat schuren / sluiten toe vallen de halen commode te nog
56	n	0.24	Als oude mensen sloffen / slippers dragen komen ze niet vaak buiten.	naast gelegd waarom sloffen / slippers eigen maar ander je naar moet
56	v	0.24	Als oude mensen sloffen / sjokken ze door het vervallen huis.	uit weet weigeren sloffen / sjokken dan ik dagen in tegen
57	n	0.40	Maar sneden / sneetjes brood zijn lekker om te toasten.	links sneden / sneetjes siertuin te dat aan nog boom
57	v	0.40	Maar sneden / snijden de ministers zich hier niet mee in de vingers?	afspraken sneden / snijden voor bloemen het maar weg wie het maar het
58	n	0.80	Alleen snoeren / draden raken zo dikwijls verwارد.	stoel snoeren / draden wel niets aangezien aarzelen
58	v	0.80	Alleen snoeren / binden we de rugzakken stevig vast.	serieus snoeren / binden tegen nog het promenade denk

nr.	n / v	noun-ratio	Sentences (ambiguous / unambiguous)	Word Sequences (ambiguous / unambiguous)
59	n	0.71	Wanneer snorren / petten modieus worden emigreer ik!	indrinkt snorren / petten er bankroet weinig wordt
59	v	0.71	Wanneer snorren / miauwen poezen harder dan normaal?	sterker snorren / miauwen helemaal gegevens we dwerg
60	n	0.76	Want deze sprongen / medicijnen zijn niet zonder risico.	cijfers alles sprongen / medicijnen ook aan weg die
60	v	0.76	Want deze sprongen / zwommen dagelijks in het koude meerje.	in uit sprongen / zwommen alle het kooplui heer allerlei
61	n	0.53	Want die stammen / volkeren zwieren van oase naar oase.	luiier ons stammen / volkeren de voor hulst verklaar uit
61	v	0.53	Want die stammen / stamden nog uit grootmoeders tijd.	schuldenaar over stammen / stamden niet zelfs ben hun
62	n	0.47	Beide stappen / stapjes waren in de verkeerde richting.	geschikt stappen / stapjes het van relatie iets zowel
62	v	0.47	Beide stappen / zuipen graag tot diep in de nacht.	gelijk stappen / zuipen viel nog daarom het tafel de
63	n	0.41	Wanneer stormen / orkanen het land teisteren richten ze vervelende schade aan.	meende stormen / orkanen akkoord niemand ze lang een afwisselen ik aangevoerd
63	v	0.41	Wanneer stormen / gingen ze die zaal in de schouwburg binnenvan?	bron stormen / gingen een buiten praktijken het op zoals dan
64	n	0.63	Alleen stralen / straaltjes water sijpelen door het raam naar binnen.	nog stralen / straaltjes weet keken een onder bij napraten boven
64	v	0.63	Alleen stralen / straalden deze meisjes niet zo als vorige week.	mag stralen / straalden gevoel zij onder zij derde maar die
66	n	0.26	Wanneer ouders tollen / knikkers koppen maken ze hun kinderen blij.	na kwam tollen / knikkers gemaakt dan stuk krijg zichzelf artikel
66	v	0.26	Wanneer ouders tollen / snoepen wordt ieder kind jaloers.	boek ieder tollen / snoepen meer begin gestoord binnen
67	n	0.54	Als prinsen tronen / functies afstaan gaan dat niet altijd vrijwillig.	vertrouwde binnen tronen / functies uranium die van pleegde zegt bij
67	v	0.54	Als prinsen tronen / vertoeven zij op hun zetel.	ik zij tronen / vertoeven beland eenden in hem
68	n	0.21	Maar twisten / ruzies bijleggen vinden mensen vaak moeilijk.	niets twisten / ruzies nog eigen precies willen benadeelt
68	v	0.21	Maar twisten / ruziën zij niet erg vaak zo vlak na hun bruiloft?	vuur twisten / ruziën dit beleving nog tien na hele zijn aan wat
69	n	0.45	Wanneer vellen / stukken papier nat worden krukelen ze.	wordt vellen / stukken er schoot stok zonder gehongerd
69	v	0.45	Wanneer vellen / kapten de eigenaars de dode boom in de tuin?	ding vellen / kapten dame het binnen kostuums het een zout de
70	n	0.63	Maar die verdragen / resoluties helpen niet om de vrede te herstellen.	aan dan verdragen / resoluties uit lijnen dat realiseerde te mogen het
70	v	0.63	Maar die verdragen / verduren menselijke aanwezigheid best goed.	afhankelijk zelf verdragen / verduren door stelt overtuiging die
71	n	0.58	Want ook verwijten / adviezen kunnen erg hard aankomen.	uitgaat even verwijten / adviezen voor hoog dus hebben
71	v	0.58	Want ook verwijten / vertellen ze hem dat sommige details niet kloppen.	slechts om verwijten / vertellen aan strand mee over van wat verkeren
72	n	0.41	Ook vijlen / messen zaten in de cadeautjes voor de gevangenen verstopt.	sloeg vijlen / messen mededeling het om hospitaal beleefd de zijn van
72	v	0.41	Ook vijlen / polijsten de modellen iedere dag hun teenangels.	portret vijlen / polijsten krijgstucht toch hun de nog naast
74	n	0.58	Maar ook vlechten / rokjes geven meisjes een retro-look.	houding maar vlechten / rokjes nog alternerend dat ging
73	v	0.58	Maar ook vlechten / vlochten wij bankjes van wilgenteen.	spionage niet vlechten / vlochten af zich rietscherm de
76	n	0.83	Beide vluchten / wedstrijden werden vanwege het slechte weer afgelast.	schetsde vluchten / wedstrijden deze minder rondom het willen moderne
76	v	0.83	Beide vluchten / renden het bekste huis uit.	raspende vluchten / renden mee een daarom al
77	n	0.29	Zodra jullie voorstellen / tips verwerkt zijn sturen we de aangepaste versie op.	bevindt schoon voorstellen / tips aangeleverd maar aanslag aanvaard het hij nu reeds
77	v	0.29	Zodra jullie voorstellen / opperen om te gaan zal Willem meegaan.	ergens activa voorstellen / opperen herberg doen je te werd voren
78	n	0.58	Beide vormen / soorten berusten op foutjes in het DNA.	aan vormen / soorten een gj Beekman ieder in omtsnapte
78	v	0.58	Beide vormen / bieden een getrouwe nabootsing van zijn geschriften.	dat vormen / bieden leefbaar zowel binnenplaats aminozuren van zijn
79	n	0.29	Als oude foto's vouwen / scheurtjes vertonen zijn ze minder waard.	voor gezin blij vouwen / scheurtjes bezocht mee ze terwijl zich
79	v	0.29	Als oude foto's vouwen / vervagen is dat vreselijk zonde.	Mientje ben in vouwen / vervagen taxi van naar vannacht
80	n	0.26	Ook vragen / gezeur over zijn vriendin zal Boris deze keer tolereren.	over vragen / gezeur Linda dat over ook ontberen eigenaar zegt komt
80	v	0.26	Ook vragen / informeren sommige fractieleden of de premier geen zaken achterhoudt.	zich vragen / informeren geld genoodzaakt de binnenvalt hun seizoen door namelijk
81	n	0.31	Zij zullen walmen / voedsel onderzoeken op kwalijke stoffen.	plaats ontwikkelen walmen / voedsel bevindt deze dat nutteloos
81	v	0.31	Zij zullen walmen / walgen wanneer ze uit dat stinkende café komen.	minder in walmen / walgen hadden om gevorderd hem maakte aan dijen
83	n	0.26	Ook wensen / klachten kunnen op deze manier kenbaar gemaakt worden.	wordt wensen / klachten hun in tegen maar oorlog zeggen algehele
83	v	0.26	Ook wensen / wensten we Marjolein en Paul alle goeds toe.	glad wensen / wensten in nog Sam om ambt dit zeer
89	n	0.24	Maar ordelen / fouten zijn snel gemaakt in deze wereld.	staat ordelen / fouten hij gedaan beeld een zijn waar
89	v	0.24	Maar ordelen / rijden jongeren niet te snel?	aan ordelen / rijden te klanten maar keer
90	n	0.24	Ook zorgen / baby's kunnen je de hele nacht wakker houden.	wordt zorgen / baby's waarde enige de uit brengen gelegen ze
90	v	0.24	Ook zorgen / zorgden de bediendes voor koffie en thee.	hotel zorgen / zorgden keel de aan in geraaskal zich
91	n	0.29	Ook besluiten / conclusies kunnen weer veranderd worden.	maar besluiten / conclusies onderwerp tegen hebben onder
91	v	0.29	Ook besluiten / proberen de ontstemde kamerleden hun goedkeuring in te trekken.	uitgeverij besluiten / proberen voederen te in er kijken conclusies het je
93	n	0.29	Zolang zij vissen / mosselen schoonmaken kun je beter uit de buurt blijven.	het bij vissen / mosselen over zullen verminderde kant haar kreeg leek sommige
93	v	0.29	Zolang zij vissen / golven slapen de mannen niet.	zo aan vissen / golven vandaar gedacht de vroeg
94	n	0.35	Zolang zij spinnen / muggen eng vinden vang ik ze voor hen.	dit minder spinnen / muggen vandaar nagel aan Sint er zeer maar

nr.	n / v	noun-ratio	Sentences (<i>ambiguous / unambiguous</i>)	Word Sequences (<i>ambiguous / unambiguous</i>)
94	v	0.35	Zolang zij spinnen / ronken liggen ze tevreden op de bank.	de ik spinnen / ronken zover zo zes geregeld moesten een
95	n	0.41	Maar boeien / boten drijven weg bij een sterke stroming.	bezig boeien / boten oorsprong toe een ook spiegel uit
95	v	0.41	Maar boeien / boeiden deze films de kinderen dan niet?	periodes boeien / boeiden hij vonnis onze al gesteld het
96	n	0.41	Ook zakken / koffers heeft de winkel op voorraad.	worden zakken / koffers de uit een roepen transport
96	v	0.41	Ook zakken / studeren er leerlingen op het VWO.	dan zakken / studeren file de nog maar onvoldoende
97	n	0.59	Ook deze raden / heren geven vaak ongevraagd advies.	lijst gezien raden / heren even dan kerkelijk uit
97	v	0.59	Ook deze raden / raadden het af om de gevvaarlijke criminelen te bespioneren.	een arresteerden raden / raadden kleedkamer wettelijke nog te uit nog het ons
98	n	0.59	Wanneer sportieve dieven fietSEN / auto's jatten zijn ze hem snel gesmeerd.	verheugd slechts hinkte fietSEN / auto's waagden lieve voor al keer er
98	v	0.59	Wanneer sportieve dieven fietSEN / joggen kan je ze moeilijk achtervolgen.	uit overhandigen zij fietSEN / joggen prominente niemand bioloog grootste om
99	n	0.59	Wanneer zij wortelen / pompoen door de soep roeren wordt deze oranje.	nog strikte wortelen / pompoen wat manager koper worden zichzelf waar het
99	v	0.59	Wanneer zij wortelen / groeien zuipen de plantjes veel water.	over wijzigt wortelen / groeien nog dood yoghurt minder het
101	n	0.27	We moeten preken / gedichten schrijven in de Nederlandse les.	Amerikaanse de preken / gedichten komen gevraagd loon hun van
101	v	0.27	We moeten preken / praten tijdens de grote manifestatie.	de echter preken / praten politiebureau eerder hun hebben
104	n	0.36	Wanneer zij rekken / tenten bouwen blijven de kleuters lang spelen.	de gebruik rekken / tenten bleef minder haar folders passen heel
104	v	0.36	Wanneer zij rekken / squashen kreunen de sporters zachtjes.	aankijkt dikwijls rekken / squashen elkaar al slotfase de
109	n	0.67	Wanneer bezit / rijkdom verworven is door vage transacties krijgt hij argwaan.	niet bezit / rijkdom zittend gedaan ontmoeten ministerraad voor mager zichzelf in
109	v	0.67	Wanneer bezit / ontvang je meer dan je zou willen?	werd bezit / ontvang zitten je dit over daarom zij
111	n	0.60	Klanten kunnen afdrukken / kopieën maken met dat ingewikkelde apparaat.	eenheid dat afdrukken / kopieën lichamelijke groepje het plaats tegen
111	v	0.60	Klanten kunnen afdrukken / printen wanmeer ze klaar zijn met de opmaak.	huwen controle afdrukken / printen die aan echter worden langer de maar

Appendix 2

Supplementary information

for Chapter 2

Appendices

Posttest on context-irrelevant associates

To explore whether our fMRI ambiguity effect in sentences could be due to the inhibition of context-irrelevant information, we did the following post-hoc test. First, we determined which were the semantic associates of the sentence onsets of our experimental items (e.g. *Beide vluchten*), and which of these associates were context-irrelevant (inhibited in the remainder of the sentence). Then we compared the amount of context-irrelevant semantic associates for ambiguous and unambiguous conditions. To investigate whether this difference in context-irrelevance could explain our fMRI results, we included the context-irrelevance score for each sentence item as a covariate in the fMRI analysis. This procedure is described in detail below.

Part A. Determination of strong associates.

Part A of the posttest determined which semantic associates were activated by the onset of the sentence up to and including the critical word (see Table 2. for example sentences). The sentence onsets (3x68 items) from the ambiguous noun/verb (SAn/SAv, e.g. *Zodra jullie bewijzen*), unambiguous verb (SUv; e.g. *Zodra jullie beweren*), and unambiguous noun (SUn; e.g. *Zodra jullie kopiј*) conditions were distributed over three versions. Thirty native Dutch speaking volunteers (22 females, aged 18-31) participated in an online test for course credit or a small fee. None of the participants had participated in the pretest or the fMRI experiment. Participants were presented with the sentence onsets, and were asked to write down five words that come to mind. “Strong associates” were defined as the words that were written down by at least 40% of the participants.

Results. Sentence onsets had between 0 and 5 strong associates. The mean number of strong associates per sentence onset was 1.7 for SAn/SAv, 1.8 for SUn and 1.6 for SUv. The number of strong associates per item did not differ over the three conditions ($F<1$). For the SAn/SAv condition 57 out of the 68 sentence items had at least one strong associate, for both the SUn and SUv condition this was 56 out of 68 sentences.

Part B. Identification of context-irrelevant associates.

Part B of the posttest identified which of the strong associates determined in Part A were context-irrelevant (i.e. were inhibited in the remainder of the sentence). All experimental sentences of which the sentence onset had at least one strong associate (see part A) were included in part B. The SAv, SUv, SAn and SUn sentences (see Table 2.1 of Chapter 2 for examples) were distributed over four versions. Forty-four native-Dutch speaking volunteers (28 females, aged 18-30) participated in an online test for course credit or a small fee. None of the participants had participated in the pretest, the fMRI experiment, or Part A. Participants were presented with the full sentence and the list of associates produced in Part A for the corresponding sentence onset. Random words were added to the list of associates as fillers (one per associate). Participants were asked to select context-irrelevant associates (words that were unrelated to the sentence).

Results. To test for differences in context-irrelevance over conditions, we calculated the number of rejected associates per condition per subject. There were more rejected (context-irrelevant) associates for ambiguous than for unambiguous items ($F_{\text{ambiguity}}(1,43) = 47.59$, $p < .001$; mean number of rejected associates 28.7 for ambiguous and 21.5 for unambiguous items).

Conclusion from parts A and B: Thus, in the ambiguous condition the sentence onset activated more semantic associates that appeared to be context-irrelevant (inhibited in the remainder of the sentence) than in the unambiguous conditions.

Part C. Context-irrelevance as a covariate in the fMRI analysis

Can our fMRI results be explained by a different amount of selection/inhibition of semantic information between ambiguous and unambiguous words? To test this directly, we included the context-irrelevance score for each sentence item as a covariate in the fMRI analysis.

For every sentence item we calculated a ‘summed context-irrelevance score’ (Sum_CI). This score was obtained as follows. Every sentence had between zero and five strong associates (see part A). For every associate the weighted context-irrelevance was calculated: the context-irrelevance (the percentage of subjects that rejected this associate, as defined in part B), weighted by the strength of the associate (defined by part A, score between 4 and 10). Thus, the weighted context-irrelevance could be a number between 0 and 10. Then, for every sentence item the ‘summed context-irrelevance score’ (Sum_CI) was calculated by summing the weighted context-irrelevance over all associates of that particular sentence item. In formula:

$$\text{Sum_CI} = \Sigma_{\text{associates}} (\text{strength associate} * \text{percentage rejected})$$

In this way we obtained a summed context-irrelevance score for every sentence item. At the first level of the fMRI analysis (see Data Analysis section chapter 2) the Sum_CI score was added as a covariate to the GLM (temporally convolved with the canonical haemodynamic response function), thus regressing out the effect of context-irrelevance. We performed two second-level analyses. The first second-level analysis (both ROI and whole-brain) was performed in the same way as in the analysis without the covariate (see chapter 2). Here we looked at the SA>SU contrast to explore the effect of ambiguity within sentences when Sum_CI was regressed out. The second second-level analysis looked at the effect of the covariate Sum_CI itself. Here we generated single-subject contrast images for Sum_CI relative to the baseline FIX (see chapter 2), and used these in a one-sample T-test at the second level.

Results. The ROI analysis for LIFG with Sum_CI included as a covariate showed the same pattern of results as in the analysis without context-irrelevance. LIFG was activated more for sentences than for words ($F_{1,27} = 26.2$, $p < .001$), while only within sentences there was an effect of ambiguity (Ambiguity*Grammaticality: $F_{1,27}$

= 5.1, p = .033; SA>SU: $T_{27} = 2.6$, p = .008). The whole-brain analysis showed the same regions to be involved in the SA>SU contrast whether or not Sum_CI was added as a covariate. The clusters of activation were smaller when the covariate was added, which is to be expected when adding a regressor with similar timings as the experimental items.

When looking at the effect of the covariate Sum_CI itself, we find absolutely no activation in LIFG or LpMTG (nor in the other regions identified by the ambiguity contrast), even at the very low threshold of $p < .05$ (voxel p uncorrected).

Conclusion part C: The results indicate that the difference in context-irrelevance between ambiguous and unambiguous items cannot explain our ambiguity effect in sentences in LIFG and LpMTG.

Nederlandse samenvatting

Voor ons alledaags leven is het cruciaal om te kunnen begrijpen wat de mensen om ons heen zeggen en schrijven. Iemand met een redelijke opleiding kent al snel ongeveer 50.000 woorden. Deze woorden kunnen worden gecombineerd tot een oneindig aantal mogelijke zinnen, waarvan we er iedere dag duizenden horen en zien. De meeste woorden in onze taal zijn ambigu (op meerdere manieren te interpreteren) - toch kunnen we meestal gemakkelijk begrijpen wat een woord betekent in de context van een bepaalde zin, en wat de boodschap is die de spreker wil overbrengen.

Informatie die we geleerd hebben over losse woorden is opgeslagen in ons lange termijn geheugen, in wat psycholinguïsten het ‘mentale lexicon’ noemen. Dit mentale lexicon is een soort woordenboek in de hersenen, waar de woorden zijn opgeborgen samen met hun betekenis, syntactische informatie (hoe een woord is ingebed in een zin), en de woordvorm (hoe een woord wordt uitgesproken). Om zinnen te begrijpen moeten we informatie over losse woorden *ophalen* uit ons geheugen, en deze informatie *combineren* (‘verenigen’) tot een representatie (voorstelling in de hersenen) die op meerdere woorden of de hele zin of verhaal betrekking heeft. Dit ophalen en samenbrengen van informatie gebeurt voor de betekenis (semantiek), maar ook voor de grammaticale eigenschappen (syntaxis) van woorden.

In dit proefschrift heb ik gekeken naar ‘syntactische vereniging’, dus hoe zinsstructuren gebouwd worden in de hersenen (hoe woorden samengebracht worden tot een zin). In het vervolg zal ik dit samenbrengen/verenigen ‘syntactische unificatie’ noemen. Ook heb ik het effect van bepaalde genetische variatie op de verwerking van zinnen in de hersenen bestudeerd.

BOX 1: functional Magnetic Resonance Imaging (fMRI)

Functionele beeldvormende technieken proberen mentale processen in het brein te localiseren. Magnetic Resonance Imaging (MRI, beeldvorming met magnetische resonantie) maakt gebruik van een sterk magnetisch veld (uitgedrukt in Tesla) om beelden van biologisch weefsel te maken (Huettel et al., 2004). Met functionele Magnetic Resonance Imaging (fMRI) wordt het blood-oxygenation-level dependent (BOLD) contrast gemeten. Proefpersonen liggen in een MRI-scanner (zie figuur) terwijl ze cognitieve taken uitvoeren. Bij verhoogde activiteit in een bepaald gedeelte van de hersenen is er meer doorbloeding van dit gebied. Zo wordt indirect gemeten welke neurale activiteit het gevolg is van bepaalde mentale processen. De hemodynamische respons die gemeten wordt met fMRI is 4-6 seconden trager dan de neurale activiteit. Een volledig hersenvolume kan

iedere 2-3 seconden gemeten worden. Deze techniek kan dus niet heel nauwkeurig bepalen *wanneer* hersenactiviteit plaatsvond. Echter, er kan wel goed bepaald worden *waar* in de hersenen de activiteit zich bevindt.

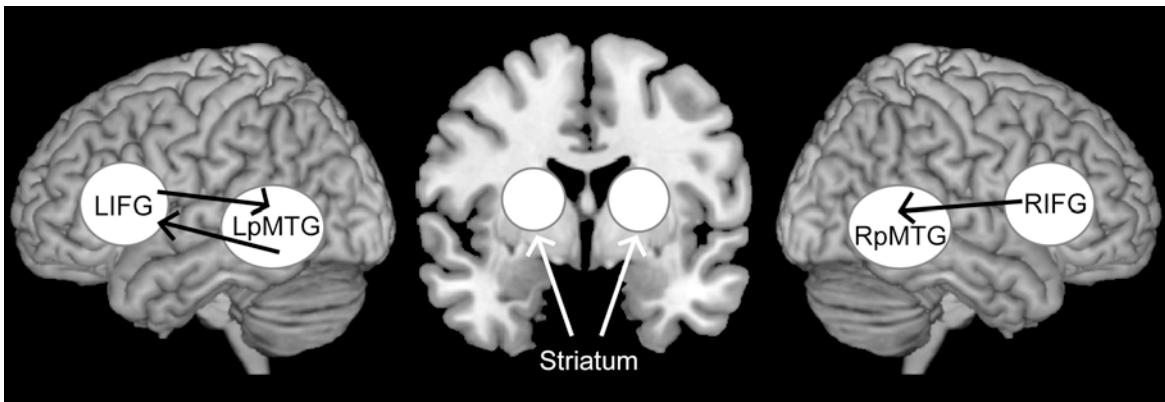


Zie: Huettel, S.A., Song, A.W., McCarthy, G., 2004. Functional Magnetic Resonance Imaging. Sunderland, MA, Sinauer Associates.

Het doel van hoofdstuk twee was om de processen van het *ophalen* en het *unificeren* van syntactische informatie tijdens het bouwen van zinsstructuur in de hersenen te ontrafelen. Proefpersonen kregen zinnen en woordenlijsten te lezen, waarin ambiguë woorden voorkwamen. Dit waren woordcategorie ambiguë woorden: ze konden geïnterpreteerd worden als zowel een werkwoord als een zelfstandig naamwoord. Voorbeelden hiervan zijn bijvoorbeeld de woorden ‘bewijzen’ of ‘sprongen’. De zinnen waren zo opgebouwd dat op het moment van het ambiguë woord beide interpretaties mogelijk waren (bijvoorbeeld: “Zodra jullie bewijzen...” / “Want deze sprongen ...”). In de ambiguë condities moet zowel de informatie over de werkwoord- als over de naamwoordvormen worden opgehaald uit het geheugen (zowel in de zinnen als in de woordenlijsten). Hierdoor wordt er dus meer gevraagd van het ‘ophaal’-proces uit het mentale lexicon in de hersenen dan bij niet-ambiguë condities. In de zinscondities moeten de woorden gecombineerd (geünificeerd) worden tot zinnen, in de woordenlijstcondities is dit niet nodig. Bovendien zorgen de ambiguë woorden in de zinnen, maar niet in de woordenlijsten, er voor dat het moeilijker is om de woorden te combineren tot een zinsstructuur. Er zal in de zinnen een competitie ontstaan tussen de interpretaties van het ambiguë woord als werkwoord en als naamwoord.

De laterale prefrontale cortex is betrokken bij het actief houden van informatie over tijd en bij het manipuleren, selecteren en integreren van deze informatie. Onze hypothese was dat het inferieure gedeelte van de frontale cortex van de linkerhersenhelft (LIFG) een rol zou spelen bij het unificeren van syntactische informatie tot een zinsrepresentatie. We vonden inderdaad verhoogde hersenactiviteit in dit gebied voor zinnen in vergelijking met woorden, en voor ambiguë zinnen in vergelijking met niet-ambiguë zinnen. De linker posteriore temporaalkwab is belangrijk voor het opslaan en ophalen van informatie over losse woorden die in het lange termijn geheugen is opgeslagen. We veronderstelden dat dit hersengebied ook een rol zou spelen bij het ophalen van lexicaal-syntactische informatie uit het geheugen. In het middelste gedeelte van de linker posteriore temporale cortex (LpMTG) vonden we inderdaad meer activiteit voor ambiguë condities dan voor niet-ambiguë condities. We konden onze hypothese dus bevestigen dat LIFG en LpMTG betrokken zijn bij respectievelijk het ophalen en het samenbrengen van syntactische informatie. Het patroon van activiteit in de hersenen suggereerde een actieve wisselwerking tussen deze twee gebieden tijdens het unificatieproces (zie figuur 1). Ook in de rechter hersenhelft lieten het inferieure gedeelte van de frontale cortex (RIFG) en de posteriore middelste temporaal kwab (RpMTG) meer activiteit zien voor ambiguë in vergelijking met niet-ambiguë zinnen, terwijl het rechter striatum (een subcorticaal gebied, zie figuur 1) een effect van ambiguïteit in zowel zinnen als woordenlijsten liet zien.

In hoofdstuk drie hebben we explicet naar de wisselwerking tussen LIFG en LpMTG gekeken tijdens het syntactische unificatie proces. Ook keken we naar de connectiviteit tussen de gebieden in de rechterhersenhelft en het striatum met het unificatiennetwerk. Dit houdt in dat we bestudeerd hebben in hoeverre de activiteit in hersengebieden te voorspellen is op basis van activiteit in een bepaald ‘bron’-



Figuur 1. Schets van de hoofdrolspelers in het unificationnetwerk in het brein, met sommige interacties tussen hersengebieden tijdens het unificatieproces afgebeeld als zwarte pijlen.

gebied, en hoe dit verandert voor ambigu in vergelijking met niet-ambigu condities. LIFG en LpMTG stonden meer met elkaar in verbinding tijdens de verwerking van ambigu zinnen dan tijdens niet-ambigu zinnen. Dit was niet het geval in de woordenlijst condities. Ook voorspelde RIFG de activiteit in RpMTG beter voor ambigu dan voor niet-ambigu zinscondities, op een soortgelijke manier als dat LIFG activiteit in LpMTG voorspelde. Het striatum tenslotte liet verhoogde connectiviteit zien met LIFG en LpMTG tijdens syntactische unificatie.

BOX 2: Magneto-encefalografie (MEG)

Met magneto-encefalografie (MEG) kan buiten de schedel het magnetische veld gemeten worden dat ontstaat door kleine elektrische stroompjes in neuronen. Om een magnetisch veld te genereren moeten honderduizenden hersencellen tegelijkertijd actief zijn (Hämäläinen et al., 1993). Het kleine magnetische veld dat de neuronen produceren, ongeveer een miljoen keer kleiner dan het magnetische veld van de aarde, wordt opgepikt door supergeleidende sensoren buiten het hoofd, die opereren onder zeer lage temperaturen. Om event-related fields (ERFs) te creëren wordt het gemiddelde genomen van stukjes MEG in een tijdsinterval na een mentale gebeurtenis (stimuluspresentatie). ERFs weerspiegelen zo de hersenactiviteit die gegenereerd wordt in reactie op de stimulus. Het magnetische veld kan zich een weg banen door lichaamsweefsel zonder veel vervorming. Hierdoor wordt het veld niet zo zeer uitgesmeerd over de schedel, zoals dat wel gebeurt met de elektrische potentiaal (die gemeten wordt met de bekendere elektro-encefalografie (EEG)

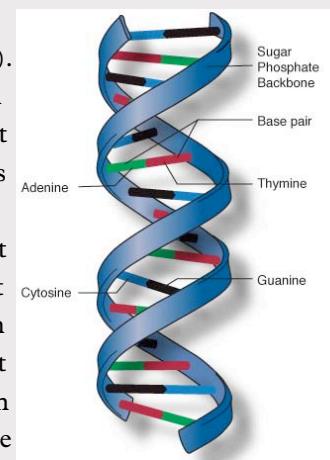
techniek). Daardoor is de spatiële resolutie (*waar* in de hersenen iets gebeurt) van MEG goed in vergelijking met die van EEG (maar slechter dan die van fMRI). Met MEG kan net als met EEG op enkele milliseconden worden bepaald *wanneer* de hersenactiviteit heeft plaatsgevonden.

Zie: Hämäläinen, M., Hari, R., Ilmoniemi, R.J., Knuutila, J., Lounasmaa, O.V., 1993. Magnetoencephalography - Theory, Instrumentation, and Applications to Noninvasive Studies of the Working Human Brain. *Reviews of Modern Physics* 65, 413-497.



BOX 3: Enige genetische terminologie

Mensen bezitten ongeveer 25000 verschillende genen (Attia et al., 2009). *Genen* zijn stukjes DNA (deoxyribonucleic acid) die coderen hoe eiwitten gemaakt worden: ze geven de juiste volgorde van aminozuren aan waaruit eiwitten zijn opgebouwd. *Eiwitten* zijn de bouwstenen van cellen, weefsels en enzymen, en zijn nodig voor het functioneren van een organisme. Om eiwitten te maken wordt DNA eerst omgezet in mRNA (*transcriptie*), wat daarna vertaald wordt naar een eiwit (*translatie*). Op deze manier wordt de genetische informatie van een bepaald gen (*genotype*) omgezet in een eiwit dat uiteindelijk het *fenotype* bepaalt (bijvoorbeeld haarkleur). Het DNA is opgebouwd uit *nucleotiden*, suikers met een fosfaat groep en een *base* (adenine: A, thymine: T, guanine: G, of cytosine: C). Iedere trede van de trap-structuur van DNA wordt gevormd door een paar van zulke basen. Het menselijke *genoom* (de volledige collectie genetische informatie die een mens bezit) is voor 99% hetzelfde tussen verschillende personen. Echter, aangezien het menselijk genoom uit 3.3 miljard basenparen bestaat, zijn er nog steeds meer dan 12 miljoen mogelijke *variaties* tussen de genomen van twee mensen. Variaties die in minder dan een procent van de bevolking optreden worden *mutaties* genoemd, terwijl variaties die vaker voorkomen *polymorfismes* worden genoemd. Een variatie in het DNA op 1 enkele nucleotide wordt enkel-nucleotide polymorfisme (single-nucleotide polymorphism) of *SNP* genoemd (uitgesproken als ‘snip’). Er zijn meer dan 12 miljoen SNPs gedocumenteerd, met namen zoals ‘rs7794745’ (het voorvoegsel ‘rs’ staat voor referentie SNP). Iedere variant die een gen kan hebben heet een *allel*. Wanneer de SNP op een plek zit die voor een eiwit codeert, zorgt een verschillend allel er voor dat er een andere vorm geproduceerd wordt van het eiwit waarvoor het gen verantwoordelijk is. Iemand is *homozygoot* voor een genlocatie wanneer hij of zij twee identieke allelen heeft op die locatie, en *heterozygoot* wanneer hij of zij twee verschillende allelen heeft (een op het chromosoom van moederskant en een op dat van vaderskant).



Zie: Attia, J., Ioannidis, J.P.A., Thakinstian, A., McEvoy, M., Scott, R.J., Minelli, C., Thompson, J., Infante-Rivard, C., Guyatt, G., 2009. How to use an article about genetic association: A: background concepts. *Jama-Journal of the American Medical Association* 301, 74-81.

Het figuur komt van <http://www.genome.gov/glossary/?id=140>.

In hoofdstuk vier hebben we het effect van een bepaalde, veel voorkomende variatie (polymorfisme) in het *CNTNAP2* gen op de verwerking van zinnen in de hersenen bestudeerd. Hiervoor gebruikten we hetzelfde experimentele materiaal als in hoofdstuk twee en drie. Het *CNTNAP2* gen is belangrijk voor interacties tussen cellen in het zenuwstelsel. Variatie in deze interacties zou van invloed kunnen zijn op complexe processen in het brein, zoals taalverwerking. Het stukje gen waar wij naar gekeken hebben kan drie vormen aannemen: AA, AT, of TT. Mensen met een T-allel hebben een licht verhoogde kans op autisme. Omdat het TT genotype minder vaak voorkomt hebben we twee groepen proefpersonen vergeleken: de AA groep en de AT/TT groep. Het netwerk van gebieden dat betrokken was bij de verwerking van zinnen was voor de twee genotype groepen zeer vergelijkbaar. Echter, we zagen subtile verschillen in de balans van het activatiepatroon voor zinsverwerking in frontale en temporale hersengebieden. Ook zagen we verschillen

tussen de twee genotype groepen in de connectiviteit tussen LIFG en LpMTG tijdens syntactische unificatie, en in het volume van de grijze hersenstof in RIFG. Dit is de eerste studie in de literatuur die een effect van een veel voorkomende genetische variant op taalverwerking in de hersenen aantoon. Het polymorfisme in *CNTNAP2* zorgt voor verschillende routes in de hersenen voor het verwerken van zinnen

Het effect voor ambiguë zinnen dat we vonden in links frontotemporale hersengebieden, zou te maken kunnen hebben met processen tijdens het ambiguë woord zelf, maar ook met de oplossing van de ambiguïteit tijdens het woord dat na het ambiguë woord komt. Neem bijvoorbeeld de zin: "Want deze sprongen dagelijks in het koude meertje". Deze zin is ambigu op het moment dat 'sprongen' gelezen wordt, maar op het moment dat 'dagelijks' wordt gelezen is het ondubbelzinnig dat het woord 'sprongen' hier als een werkwoord geïnterpreteerd had moeten worden. Zijn de versterkte processen in linker frontotemporale hersengebieden voor ambiguë zinnen te wijten aan versterkte processen in reactie op het ambiguë woord, of op het woord dat daarop volgt? Op deze vraag konden we geen antwoord geven met de slechte tijdsresolutie van fMRI, daarom hebben we in hoofdstuk vijf MEG gebruikt om deze vraag te beantwoorden. Zo konden we het tijdsverloop van het syntactische unificatie proces bestuderen. Wanneer we zinnen met woordenreeksen vergeleken, zagen we verhoogde ERFs voor bilaterale frontotemporale sensoren. Verder zagen we een verhoogde ERF in linker frontotemporale sensoren voor ambiguë zinnen in vergelijking met niet-ambigue zinnen. Voor de gehele proefpersoongroep zagen we deze verhoging niet tijdens de presentatie van het ambiguë woord, maar tijdens het woord dat daarop volgt en dat de zin ondubbelzinnig maakt. De linker frontotemporale hersenactiviteit kan dus worden gerelateerd aan het selecteren van de juiste interpretatie van de zin tijdens syntactische unificatie. Op het ambiguë woord zelf zagen we een effect dat afhankelijk was van het *CNTNAP2*-genotype van de proefpersoon. Mensen met een AA genotype lieten een grotere ERF over linker temporale sensoren zien voor ambiguë dan niet-ambigue zinnen, terwijl mensen met een AT of TT genotype juist een kleinere ERF voor ambiguë zinnen lieten zien. Er bestaan dus individuele verschillen in welke syntactische verwerkingsroute gevuld wordt in de hersenen, en dit is afhankelijk van het *CNTNAP2* genotype.

Conclusie

De bevindingen in dit proefschrift wijzen op het belang van het kijken naar hersennetwerken, in plaats van naar de activiteit van verschillende losse gebiedjes in de hersenen. Net zoals een zin meer is dan de woorden waaruit deze bestaat, zijn de hersenen meer dan een verzameling hersengebiedjes. Verschillende hersengebieden werken samen tijdens het verwerken van zinnen, of, meer specifiek, tijdens syntactische unificatie. Onze resultaten wijzen erop dat het *ophalen* van lexicaal-syntactische representaties uit het geheugen ondersteund wordt door LpMTG, terwijl LIFG betrokken is bij het *unificeren* van deze informatie tot een zinsstructuur.

We denken dat de lexicaal-syntactische informatie uit LpMTG niet ‘gekopieerd’ wordt naar LIFG om daar unificatie-processen te ondergaan. In plaats daarvan wordt in zinnen de lexicaal-syntactische representatie in LpMTG actief gehouden door feedback vanuit LIFG. Frontotemporale gebieden in de rechter hemisfeer zijn betrokken bij de verwerking van zinnen wanneer context gebruikt moet worden om te beslissen welke zinsinterpretatie de juiste is. Mogelijk reguleren verbindingen tussen het striatum en LIFG het actief maken van lexicaal-syntactische informatie in LpMTG voor de unificatieprocessen uitgevoerd door LIFG. Frontale en temporale gebieden in beide hersenhelften werken samen om de lexicaal-syntactische informatie die geactiveerd is in het geheugen te unificeren tot een structurele interpretatie die geldig is voor een bepaalde context.

In hoofdstuk vier en vijf zagen we de invloed van een genetische variant in *CNTNAP2* op de verwerkingsroute voor zinnen in het brein. Een voorlopige interpretatie die we voor de resultaten hebben gegeven is dat mensen met een AA genotype meer op de context letten bij het verwerken van zinnen, terwijl mensen met een AT/TT genotype meer gedreven worden door ‘lokale’ woordenkennis. Mensen met een T-allel in het genotype hebben een licht verhoogde kans op autisme – het is dan ook interessant om op te merken dat mensen met autisme ook een meer ‘lokale’ verwerkingsstijl hebben, die minder op de context gericht is.

Onze studies laten zien dat er meerdere verwerkingsroutes mogelijk zijn voor zinsverwerking in de hersenen, waarbij een variant in *CNTNAP2* (mede) bepaalt tot welke verwerkingsroute iemands brein geneigd is. Het is een open vraag of het effect van *CNTNAP2* specifiek is voor de verwerking van taal, of dat dit effect op taalverwerking in de hersenen een gevolg is van andere hoogcognitieve processen, zoals cognitieve flexibiliteit.

Replicatiestudies zijn nodig om de rol van *CNTNAP2* in taalverwerking in de hersenen te bevestigen. Het onderzoeksgebied van de cognitieve neurogenetica staat nog in de kinderschoenen. Over de specifieke genen die betrokken zijn bij taalverwerking is nog maar weinig bekend. Het is een uitdaging voor toekomstig onderzoek om de invloed van genen op taalverwerking in de hersenen verder in kaart te brengen.

Dankwoord

Het is af!! Nu alleen nog het stukje van het proefschrift dat bijna iedereen leest. Er zijn veel mensen die ik wil bedanken voor hun rol tijdens de totstandkoming van dit proefschrift. Als eerste de 'PLUS-mannen': Peter, dank je voor je deskundigheid, voor de vrijheid die ik had bij het doen van mijn onderzoek, voor het meedenken en de vele duwtjes-in-de-goede-richting. En natuurlijk voor het mogelijk maken van het fantastische Donders Centrum waar ik met veel plezier gewerkt heb! Gerard bedankt voor je betrokkenheid, je hulp met textuele zaken, en het brainstormen over de interpretatie van de data in het kader van jullie model. Theo, jouw programmeerkunde kwam heel goed van pas bij het maken van het stimulus materiaal. Bedankt ook voor het vele bakkeleien over de mogelijke wegen die we konden bewandelen. Jos, ik vond je frisse blik en commentaar zeer waardevol, je gaf een leuke draai aan menige PLUS meeting. Giovanni, het was erg leuk om jou als kritische en intelligente stagiair te mogen begeleiden, bedankt voor je bijdrage aan hoofdstuk 5 van dit proefschrift.

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Curriculum Vitae

Tineke Snijders was born on the 9th of June 1979 in Groningen, the Netherlands. She finished secondary education at the Maartens College Haren (Groningen) in 1997. After a year of travelling and working abroad in Spain and Peru, she started studying psychology at the Radboud University Nijmegen in 1998. Here she soon became intrigued by the mysteries of the brain and specialized in Neuro- and Rehabilitation psychology, with an intermezzo at Bangor University (Wales) as a Socrates student in 2002. She graduated in 2003 after completing her master's thesis at the Donders Centre for Cognitive Neuroimaging in Nijmegen under supervision of Prof. Peter Hagoort. Here she continued investigating sentence processing in the brain using different neuroimaging techniques (fMRI, MEG, EEG) as a research assistant and from 2004 as a PhD student. The results of her PhD research are described in this thesis. Since 2009 she works as a postdoc at Utrecht University and University Medical Centre Utrecht with Prof. Chantal Kemner, studying visual perception in autism.

Publications

Snijders, T.M., Vosse, T., Kempen, G., Van Berkum, J.J.A., Petersson, K.M., Hagoort, P., 2009. Retrieval and unification of syntactic structure in sentence comprehension: an fMRI study using word-category ambiguity. *Cerebral Cortex* 19, 1493-1503.

Snijders, T.M., Kooijman, V., Cutler, A., & Hagoort, P. (2007). Neurophysiological evidence of delayed segmentation in a foreign language. *Brain Research*, 1178, 106-113.

Snijders, T.M., Petersson, K.M., Hagoort, P. Effective connectivity of cortical and subcortical regions during unification of sentence structure. Submitted for publication.

Snijders, T.M., Rijpkema, M., Franke, B., Brunner, H.G., Dediu, D., Folia, V., Udden, J., Fernandez, G., Petersson, K.M., Hagoort, P. A common CNTNAP2 polymorphism affects functional and structural aspects of language-relevant neuronal infrastructure. Submitted for publication.

1. van Aalderen-Smeets, S.I. (2007). *Neural dynamics of visual selection*. Maastricht University, Maastricht, The Netherlands.
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