Complex Grammar Processing in the Brain: Development and Evaluation of a Child-Friendly fMRI Paradigm

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Ich widme diese Arbeit meiner Familie.

Contents

Abbreviations

BA	Brodmann Area
BOLD	blood oxygenation level dependent
CT	computed tomography
EEG	electroencephalography
EPI	echo planar imaging
fMRI	functional magnetic resonance imaging
FWHM	full-width-at-half-maximum
IFG	inferior frontal gyrus
ISI	inter stimulus interval
MD	median
MEG	magnetoencephalography
mn	mean
MRI	magnetic resonance imaging
NIRS	near infrared spectroscopy
OVS	object-verb-subject
PET	positron emission tomography
PPVT	Peabody Picture Vocabulary Test
ROI	region of interest
SFB	Sonderforschungsbereich
SNR	signal-to-noise ratio
SR	sentence repetition
SVO	subject-verb-object
TE	time to echo
TMS	transcranial magnetic stimulation
TR	time to repetition
TVJ	truth value judgement

1 Introduction

1.1 Motivation for this study

Language is one of the most important prerequisites for the development and preservation of our society. It enables a sophisticated exchange of knowledge, opinions, and emotions, and therefore lays the foundations for social structures as well as for education and the advancement of sciences.

In the second half of the 19th century, the first hypotheses on the anatomy of language were based on experiences with individual aphasic patients. Two physicians and anatomists, Paul Broca and Karl Wernicke, related two different aphasic disorders to their respective anatomical correlate (Roth, 2002). These findings were a first big step in language research, and the gateway to new insights and ideas about the anatomical representation of higher cognitive functions in general (Roth, 2002). Even though our view on the organization of language has greatly changed since then, some of the earliest discoveries are still valid today (Poeppel and Hickok, 2004). While the long-since observed lateralization of numerous specific language functions to the left hemisphere today is considered confirmed, the contribution of right-hemispheric regions to language processing has become an important area of research during the last two decades (Demonet et al., 1994; Vigneau et al., 2011; Passeri et al., 2014).

If an adult suffers an acute injury to the left hemisphere, aphasic symptoms will commonly result (Benson and Ardila, 1996). Children, on the other hand, have much better chances to recover from left-hemispheric lesions without persistent language problems (Vargha-Khadem et al., 1985). In particular, if a lesion occurs in the pre- or perinatal time period, children have shown a delay of language development, but no obvious impairment of linguistic abilities after the completion of language acquisition (Eisele and Aram, 1995). Enabled by the greater capacity for plasticity of the young brain, a reorganization of language into the right hemisphere takes place (Muller et al., 1998; Liegeois et al., 2004). In these patients, language representation can be found in homotopic regions within the right hemisphere (Staudt et al., 2002). The strong left-lateralization of language processing observable in adults only develops during childhood and adolescence (Szaflarski et al., 2006). Further, lesion studies indicate an important role for the right hemisphere during early stages of language development (Marchman 1991). This adaptive process might be the neuronal foundation to the capability of reorganization of language to the right hemisphere in case of left-hemispheric damage. Yet, it is not clear whether right-hemispheric language abilities are really as good as when supported by a left-hemispheric network in the healthy brain. A study of Reilly et al., 2004 describes the language development of patients with left-hemispheric brain lesions as delayed, while at the age of 10 years, they are referred to as “within the normal range of performance for all narrative measures”. Eisele and Aram, 1995 find only “subtle deficits in the linguistic abilities of older children with unilateral brain lesions". However, there have been very few studies looking into specific linguistic abilities, or into the relation with lesion, language representation, and language abilities, in children and young adults with pre- or perinatal left-hemispheric lesions.

In the context of a collaborative research centre concerned with language dynamics and adaptivity (SFB 833: Bedeutungskonstitution - Dynamik und Adaptivität sprachlicher Strukturen), the "Experimental Paediatric Neuroimaging" group at University Children's Hospital Tübingen, in cooperation with the linguistic department, developed research questions pertaining to specific linguistic abilities and their neuronal representation in patients with early left-hemispheric lesions and reorganized language. In a behavioural pilot study by Schwilling et al., 2012, specific linguistic tasks revealed significant differences between patients with a reorganized language and healthy controls in both language comprehension and production. In order to investigate the anatomical correlate of these observable differences, we here set out to develop an fMRI paradigm suitable for children, adolescents and young adults with early left-hemispheric brain lesions. Our language experiment was developed on the bases of the language tasks used in the study by Schwilling et al., 2012. It was evaluated in young, healthy adults, investigating their processing of a complex grammatical sentence structure when compared to a simple structure.

In the following paragraphs, a brief overview over the relevant general aspects in this field is provided. Thereafter, the specific aspects pertaining to the conduction of this study are laid out.

1.2 Language organization

When in 1861 Paul Broca realized that a lesion in the left inferior frontal region had been responsible for his patient's speech problems, it was the first time a cognitive function was related to a specific anatomical brain region (Keller et al., 2009; Roth, 2002). This area, named after Broca (Bähr et al., 2009), was considered to be essential for language production (Keller et al., 2009). Broca discovered his patient's difficulties to form words even though he well understood communicated speech (Broca, 1861a). In 1874, Karl Wernicke described another type of aphasia which he related to a second brain region located in the left posterior superior temporal region (Bähr et al., 2009). This aphasia was characterized by fluent productive speech, but with word confusions and transpositions (Eggert, 1977). His patients showed less awareness of their speech problems than patients suffering from Broca's aphasia (Roth, 2002). Wernicke developed the concept that language functions are divided into a sensory component within Wernicke's area, containing a memory of acoustic images for words, and a motor component within Broca's area, containing a memory for motor images of speech (Roth, 2002; Poeppel and Hickok, 2004). Wernicke also termed a third type of aphasia, the "conduction aphasia", for lesions concerning the connecting pathway between Broca's and Wernicke's area, later identified as the arcuate fasciculus by the Neurologist and Neuropathologist Constantin von Monakow (Roth, 2002).

In 1885, Ludwig Lichtheim extended Wernicke's concept, describing two more types of aphasia with Broca's and Wernicke's aphasia-like problems, but retained function of repetition. He explained this phenomenon by a component he called "conceptual field". His idea was that, distributed in the brain, there was a storage of meanings of words (Lichtheim, 1885; Roth, 2002).

Many years later in 1965, Norman Geschwind, an American Neurologist and Neuroscientist, seized Wernicke's and Lichtheim's ideas and enlarged their model of language processing. He viewed the inferior parietal lobe as a tertiary association area that provides a conjunction between visual and auditory word forms (Geschwind, 1965). The “Wernicke-Lichtheim-Geschwind theory” provides a framework of language processing that has been of great influence for language research since (Weems and Reggia, 2006). Today it is widely accepted that the anatomy of language is composed of a distributed network of cortex areas and fibre tracts, including Broca’s and Wernicke’s areas as well as parts of the middle and inferior temporal gyrus, the premotor cortex, the cerebellum, the inferior parietal lobe and the angular as well as the supramarginal gyrus (Friederici, 2002; Hickok and Poeppel, 2007; Vigneau et al., 2006; Price, 2012).

Progress in research on the neurological underpinnings of language has been promoted by linguistics and cognitive neuroscience on the one hand, and technical advancement on the other hand, leading to a progression of ideas and evidence of more precise, but also more complex concepts (Poeppel and Hickok, 2004). Structural images from computed tomography (CT) and magnetic resonance imaging (MRI) provided the possibility of a lesion mapping in living patients, while positron emission tomography (PET) for the first time allowed glances into the normal functioning brain (Poeppel and Hickok, 2004; Petersen et al., 1988; Raichle, 2009). Functional MRI, applied in human research since 1992 (Raichle, 2009), contributed the possibility to examine healthy subjects even multiple times and gained importance through its wide availability (Poeppel and Hickok, 2004). In addition to a subsequent relating of language disorders and the corresponding brain lesion, a functional observation of the brain while a subject is working on a task was possible. It is important to note that functional MRI enables detection of areas that are indeed involved in, but not necessarily essential for a specific cognitive function (Bookheimer, 2002), and in case of damage thus might not lead to an obvious deficit. Electromagnetic recording (multichannel electro- and magnetoencephalography [EEG/MEG]), transcranial magnetic stimulation (TMS) and near infrared spectroscopy (NIRS) must be mentioned as further techniques to have contributed to research in this domain (Poeppel and Hickok, 2004).

When exploring the language network, linguistics distinguishes between three main language-processing component classes: "phonology", "semantics" and "(morpho)syntax" (Bußmann, 1983). The definitions are presented in the respective paragraphs below. *Figure* ***1*** shall serve as visual reference.

Using this classification, fMRI and PET studies have been trying to reveal brain regions related to these aspects of language processing. It should be remembered that all regions involved in different functions of language are part of larger networks (Price, 2012). Even though we try to correlate areas to their functions and functions to areas, it is important to consider that these areas never work alone but are integrated into specific networks, which may be recruited also according to demand (Sporns, 2013).

1.2.1 Phonology

Phonology is the linguistic discipline that deals with the different qualities, relations, and organization of speech sounds (phonemes) (Bußmann, 1983). A phoneme is the smallest linguistic unit which may bring about a change in meaning (Bußmann, 1983).

Areas involved in phonological processing were found in the left temporal lobe along the superior temporal gyrus in anterior (Leaver and Rauschecker, 2010; Agnew et al., 2011; Specht et al., 2009; Leff et al., 2009a) and posterior regions (Specht et al., 2009; Leech et al., 2009; Liebenthal et al., 2010; Dick et al., 2011). Furthermore, the left inferior frontal gyrus (Burton et al., 2005; Binder et al., 2004; Husain et al., 2006) and premotor areas (Burton et al., 2005; Wilson et al., 2004), as well as the supramarginal gyrus in the parietal lobe (Demonet et al., 1994; Elmer et al., 2011; Davis and Johnsrude, 2007; Zevin et al., 2010) were consistently shown to be involved in phonological processing. It was suggested that there is a separation into a fronto-temporal auditory-motor network and a fronto-parietal loop for phonological working memory functions (Vigneau et al., 2006).

1.2.2 Semantics

Semantics is the discipline of linguistics that deals with the analysis and description of literality ("wörtliche Bedeutung") of linguistical expressions (Bußmann, 1983).

Semantic processes during language tasks have been linked to the following regions: the left lateral temporal cortex, including the middle and inferior temporal gyrus (Demonet et al., 1992; Whitney et al., 2011) and superior temporal sulcus (Vandenberghe et al., 1996), as well as the hippocampal/parahippocampal area in the medial temporal lobe (Whitney et al., 2009; Binder et al., 2009). In the frontal lobe, the medial (Obleser et al., 2007) and left inferior prefontal regions (Thompson-Schill et al., 1997; Wagner et al., 2001), including the pars orbitalis (Demb et al., 1995; Whitney et al., 2011) and pars opercularis (Obleser and Kotz, 2010), have been identified to be involved in semantic processes. Likewise, right inferior frontal activation has also been reported in the context of conflicting semantic information, for example in pars opercularis and pars triangularis (Snijders et al., 2009; Peelle et al., 2009). Finally, the posterior inferior parietal region, especially the left and right angular gyrus (Obleser et al., 2007; Obleser and Kotz, 2010; Demonet et al., 1994) are involved in semantic decisions, also on written words and pictures (Vandenberghe et al., 1996).

1.2.3 Syntax

Syntax is a part of semiotics (general science of linguistic and non-linguistic symbol systems) that deals with the array and relationship of symbols and their semantic meanings (Bußmann, 1983). Secondly, syntax is a part of grammar in natural languages, implying a system of rules that describe how any correct sentence in a language can be derived from an inventory of basic linguistic elements (e.g. words, clauses) (Bußmann, 1983). According to this definition, it becomes obvious that as soon as sentence level is reached, the correct processing of syntax is required for both speech production and speech comprehension. Slight changes in syntax, for example the exchange of a noun marker, can change the meaning of a sentence to a completely new content. This explains why areas involved in syntax processing appear to be largely overlapping with semantic areas (Price, 2010; Vigneau et al., 2006; Röder et al.,

2002). However, it is not clear to what degree this is an implication of the difficulty to separate semantic processing from syntax processing related activation during complex sentence comprehension tasks (Price, 2010; Vigneau et al., 2006).
In the temporal lobe, the following regions have been associated with syntactic errors or complexity: the lateral part of the left and right posterior middle and superior temporal gyrus and sulcus (Baumgaertner et al., 2002; Stowe et al., 1998; Ben-Shachar et al., 2004; Friederici et al., 2010; Cooke et al., 2002) and the border between the left posterior planum temporale and the ventral supramarginal gyrus (Raettig et al., 2010; Friederici et al., 2009). In the inferior frontal gyrus, pars opercularis and pars triangularis showed semantic and syntax processing clusters in close proximity (Ben-Shachar et al., 2004; Caplan, 2001; Stromswold et al., 1996; Vigneau et al., 2006; Price, 2010). Frontal activation during syntax processing tasks without close proximity to semantic areas was found in the posterior middle frontal gyrus (Baumgaertner et al., 2002; Constable et al., 2004; Luke et al., 2002).

To conclude, the most frequently-confirmed language areas are organized along the left inferior frontal gyrus and along the left middle and superior temporal gyrus. Broca’s area in left inferior frontal gyrus has been identified to host phonological, syntactic, as well as semantic functions (Ben-Shachar et al., 2004; Obleser and Kotz, 2010; Burton et al., 2005), involved in both language production and language comprehension (Price, 2010). Ventral to Broca’s area, pars orbitalis is also involved in semantic processing (Demb et al., 1995; Whitney et al., 2011). The premotor cortex, on the other hand, seems to be important for phonological functions (Burton et al., 2005; Wilson et al., 2004). In the temporal lobe, superior to middle temporal gyri are involved in phonological and syntactic processing (Leaver and Rauschecker, 2010; Baumgaertner et al., 2002; Stowe et al., 1998; Friederici et al., 2010), while semantic processing functions are primarily located in the middle to inferior temporal gyri (Whitney et al., 2011). In the parietal lobe, supramarginal gyrus represents phonological functions (Demonet et al., 1994; Elmer et al., 2011), while the angular gyrus has been related to semantic processing functions (Obleser and Kotz, 2010; Obleser et al., 2007). This is illustrated in Figure 1.

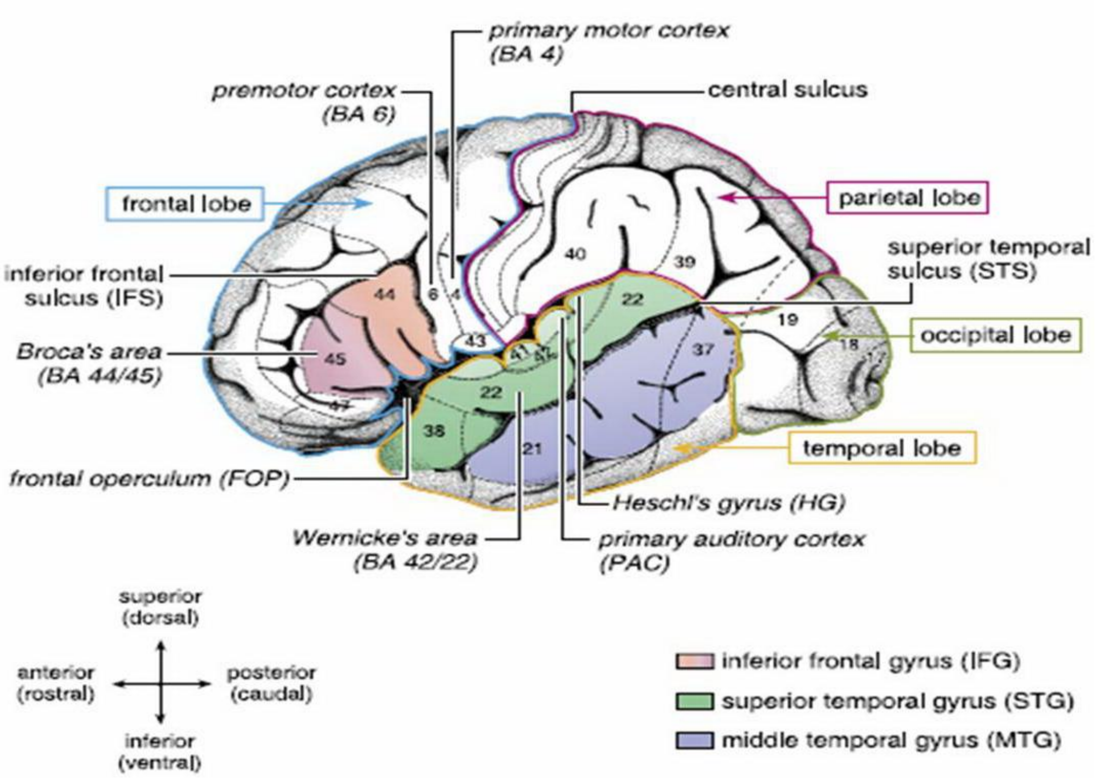

Figure 1: Cortical anatomy of the left hemisphere. The different lobes (frontal, temporal, parietal, occipital) are marked by colored borders. Major language-relevant gyri are color coded. Broca's area consists of the pars opercularis and the pars triangularis. Located anterior to Broca's area is the pars orbitalis. The primary auditory cortex and Heschl's gyrus are located in a lateral-to-medial orientation. Numbers indicate Brodmann Areas (BA) which Brodmann defined on the basis of cytoarchitectonic characteristics (Brodmann, 1925). Figure taken from Friederici, 2011, used with kind permission from the American Physiological Society.

The different functions are often difficult to separate and some areas seem to be involved especially when functions are combined within a task (Vigneau et al., 2006). As any given task will usually contain aspects of different language functions, it must be acknowledged that the separation of these functions is difficult at best (Vigneau et al., 2006; Price, 2012). In fact, it may ultimately be futile, given the complexity of interactions between brain regions (Bullmore and Sporns, 2009; Sporns, 2013), reflecting a shift towards a more integrated view of language as being distributed in complex, and partly overlapping networks.

1.3 Study framework

As shown in the previous paragraphs, the processing of language involves a distributed network of regions in the left and the right hemisphere, but with a clear lateralization to the left side (Price, 2010). Yet, in case of early damage of critical regions, a reorganization of language areas to the right hemisphere is possible (Staudt et al., 2002). In a pilot study, Schwilling et al., 2012 investigated language abilities of children affected by early left-hemispheric brain lesions and a reorganized language. The applied linguistic tasks revealed significant differences between the patients and healthy controls in both language comprehension and production (Schwilling et al., 2012). In particular, non-canonical sentences (see paragraph 1.3.1) in different constructions were used to explore the participants' syntactic understanding. The children, adolescents, and young adults with early left-hemispheric lesions and a reorganized language had more difficulties to understand and reproduce the non-canonical sentences than healthy controls (Schwilling et al., 2012). Based on these results, it was our interest to investigate the functional anatomy of the processing of non-canonical sentence structure in the setting of healthy and reorganized language representations.

For single sentences, non-canonical word order is sparsely used in everyday language (Gorrell, 2000) and is perceived as being more complex (Obleser et al., 2011; Knoll et al., 2012). The following paragraph shall explain the non-canonical sentence structure used in our experiment. Furthermore, an overview on previous research about the processing of complex sentence structures, and especially non-canonical sentences, is provided.

1.3.1 Sentence processing in German language

One of the core aspects when trying to understand a sentence consists of reconstructing the relationships between participants and events (Bußmann, 1983), or phrased simpler: "Who does what to whom?". A lexical recognition of the words of a sentence is not sufficient for the determination of their interrelation; rather, we need further cues in order to understand this correctly (Bates and MacWhinney, 1987). One important cue here is word order. In the English language, subject and object can be identified by their position within the

sentence, as word order is subject – verb – object (SVO: canonical word order) by default (see also the Competition Model by Bates and MacWhinney, 1987).
In German, however, nouns are case-marked locally, which allows for a relatively free word order (Kunkel-Razum and Münzberg, 2006). For example, object topicalization is a phenomenon of German and other case-marked languages, in which the grammatical object of the main clause appears in the sentence initial position preceding the finite verb, and thus receives more emphasis (OVS: non-canonical word order). In these cases, word order and case marking convey conflicting information (Bates and MacWhinney, 1987). For proper comprehension, the case marking cue has to be weighed over the word order cue. This is one of the aspects of German language that make it so hard to learn for foreigners (Mark Twain, 1880).

Example 1a) Canonical word order (SVO)

Der Hund	jagt	den Fuchs.
The_$_{\text{NOM}}$ dog	chases	the_$_{\text{ACC}}$ fox.
subject	verb	object

Example 1b) Non-canonical word order: object topicalization (OVS)

Den Fuchs	jagt	der Hund.
The_$_{\text{ACC}}$ fox	chases	the_$_{\text{NOM}}$ dog.
object	verb	subject

Table 1: Canonical and Non-canonical word order. In example 1b, the meaning of the sentence ("the fox is chased by the dog") is skewed by the translation; only the initial change in the German preposition signifies the passive role of the fox and the active role of the dog.

While most of language development usually is completed in pre-school age (Dittmar et al., 2008), object topicalization, as one of the most complicated grammatical structures in German language, often is not yet mastered until school age, dependent on the child's grammatical knowledge (Dittmar et al., 2008; Schipke et al., 2012). In a study by Lidzba et al., 2013, children aged 8 to

12 years still made more mistakes in this task than adolescents and adults. This argues for a longer developmental trajectory for this particular aspect of language in young school-aged children. However, longitudinal studies that could corroborate this assumption are as yet missing. A previous study by Knoll et al., 2012 suggests, that the activation pattern they observed during an object topicalization task in preschool children reflects the degree to which adult-like sentence processing strategies (necessary to process case-marking information) are already applied.

1.3.2 Complex sentence structures

Regarding syntax processing, studies try to reveal not only the location of areas that are generally involved in syntax processing, but try to make more precise distinctions of regions that activate for complex sentence structures. Complex sentence structures have been derived by manipulating, for example, the number of words, prepositions, or embeddings in a sentence, or by changing the common word order from canonical to non-canonical sentences. Canonical and non-canonical sentence structures are explained in Table 1. Researchers contrasting linguistically complex versus simple sentences consistently found activation in the pars opercularis (left inferior frontal gyrus) (Just et al., 1996; Caplan et al., 1998, 1999; Röder et al., 2002; Ben-Shachar et al., 2003; Ben-Shachar et al., 2004). There are two parts of the left inferior frontal gyrus that seem to play an important role: for one, the left ventral/inferior pars opercularis (Friederici et al., 2010; Raettig et al., 2010), which is also associated with verbal working memory and predicting the sequence of semantic or articulatory events (Price, 2010). Secondly, syntactic complexity increases activation in the left dorsal pars opercularis for auditory sentences (Makuuchi et al., 2009) and in written language (Newman et al., 2009). Makuuchi et al., 2009 attributes the activation in the left dorsal pars opercularis to the hierarchal organization of sequentially-occurring events. In her review, Price, 2010 suggested that left dorsal pars opercularis is involved in sequencing events, irrespective if they are linguistic or non-linguistic. In the left temporal lobe, the mid- to posterior portion of the superior temporal gyrus and sulcus has frequently been reported to be involved in complex grammar processing (Friederici et al., 2009; Friederici et al., 2010; Richardson et al., 2010; Cooke et al., 2002; Grodzinsky and Friederici, 2006). Grodzinsky and Friederici, 2006 as well as Friederici et al., 2009 suggested that this region subserves the integration of lexical-semantic and syntactic information, while Leff et al., 2009b argue for its involvement in auditory short-term memory functions in addition to speech comprehension abilities.

Friederici et al., 2006; Bahlmann et al., 2007; Ben-Shachar et al., 2004; Obleser and Kotz, 2010; Obleser et al., 2011 and Knoll et al., 2012 contrasted non-canonical to canonical sentence structure. The following regions were reported to show stronger activation for non-canonical compared to canonical word order. In the frontal lobe, non-canonical sentence structure was associated with activation in the left inferior frontal gyrus in all studies mentioned. Friederici et al., 2006 was able to further pinpoint left pars opercularis, interpreted as an area that reconstructs the underlying hierarchal dependencies between arguments in a complex grammatical sentence. Another area that repeatedly showed activation was the left and right superior temporal gyrus and sulcus (STG/STS) (Ben-Shachar et al., 2004; Knoll et al., 2012; Obleser and Kotz, 2010; Obleser et al., 2011), which could have been involved in the maintenance of the moved element in memory (Ben-Shachar et al., 2004; Leff et al., 2009b), or in abstracting the syntactic information (Obleser et al., 2011; Knoll et al., 2012). Bahlmann et al., 2007 examined the processing of sentences, which in their first half offered case-ambiguous initial noun-phrases. Only in their second half of unambiguous noun-phrases, the sentence structure could be matched to canonical or non-canonical word order. In this study, supramarginal gyrus was interpreted to reflect the reanalysis-requirements induced by this condition (Bahlmann et al., 2007). Additional areas are the left ventral precentral sulcus, which may be involved in searching for a semantically-appropriate element to be linked during syntactical movement (Ben-Shachar et al., 2004), and bilateral Heschl's complex, which was discussed in the same study to be explained by stress changes in object-first sentences, reflecting focus changes (Ben-Shachar et al., 2004). Knoll et al., 2012 also found increased activation in the anterior cingulate cortex for non-canonical compared to canonical sentences. However, it has to be taken to account that

Knoll et al., 2012 examined preschool children, while all other studies mentioned examined adults only. The anterior cingulate cortex has been implicated in several studies of working memory, response conflict, error detection and executive control functions (Carter et al., 1999; Duncan and Owen, 2000; Barch et al., 2001; van Veen and Carter, 2002; Owen et al., 2005).

In order to address the question of the neuronal representation of complex syntax processing in patients with reorganized language, this study was conducted to develop and evaluate an fMRI paradigm, suitable for children and young adults. Examining reorganized language networks with fMRI and comparing them to the common left-hemispheric network can provide valuable information. Indications not only on how the language network is interrelated, but also on plasticity aspects of the brain - what structures are recruited for language functions in case the originally designated language areas are damaged – can be gained (Yogarajah et al., 2010).

1.4 Task development

When investigating the different functions of language processing and production, the development of an appropriate task depends on the question to answer. In analogy to the behavioural studies by Schwilling et al., 2012, we aimed at investigating both production and comprehension of object-first sentences. Thus, two different types of tasks were used, a sentence repetition (SR) task and a truth-value judgement (TVJ) task. During the SR task, participants had to overtly repeat acoustically-presented sentences. While the sentences were presented, playmobil® stop motion movies supported the understanding of the information transported. When solving this task, the subject has to understand and memorize the sentence, and then reproduce it by planning and performing the articulation of the words; the longer the sentence, the harder it is to memorize the particular words and their order (Tewes and Rossmann, 2000). If the length of a sentence exceeds the capacity of the short-term memory, additional information has to be used, for example the meaning of the sentence (Grimm, 2001). Subject, verb, and object have to be identified in order to understand the relationships between participants and events within a sentence. This enables the storage of information not only as a set of words, but as a dynamic action (Lombardi and Potter, 1992). In this case, the repetition of a sentence is not only a retrieval from memory, but an active reproduction (Vinther, 2002). However, the problem of speaking tasks during fMRI scanning is a distinct increase of movement-related imaging artefacts, especially when scanning children (Birn et al., 2004; Yuan et al., 2009). In order to avoid this for a future employment in children, and since we wanted to investigate and compare both language production and comprehension, we additionally established a TVJ task. In this task, participants had to decide whether an acoustically-presented sentence correctly described the action performed in a simultaneously-presented playmobil® stop motion movie. The participants were instructed to press a button if they decided for a correct match. Importantly, only the actual processing of the sentence allowed them to understand the relations between actors and action. The syntax has to be decoded using cues such as word order and case marking to allocate the roles correctly (Bates and MacWhinney, 1987). These have to be held in memory and compared to the actions provided in the movie, before deciding whether to press the button or not. The particular advantage of the TVJ task is that the demands are confined to comprehension processes. This could be helpful to specify theories about language comprehension compared to language production strategies.

Another cue the human brain instinctively uses when trying to understand a sentence is phonological information (Butterworth, 1993). The intonation of a sentence, as one aspect of phonology, can provide important indications on content, emotion, and grammatical structure (Penner, 2000). It is therefore important to control for this confound. A trained speaker spoke the sentences equal in pitch and with neutral sentence intonation, so that subject and object could not be distinguished by a difference in accentuation. The length of the sentences was adjusted to always be four seconds.

1.5 MRI as a neuroscientific method

Magnetic resonance imaging, introduced by Paul C. Lauterbur and Sir Peter Mansfield in 1973, is a non-invasive imaging technique based on the principle of magnetic resonance (Lauterbur, 1973). It exploits the effect that atomic nuclei with uneven numbers of protons align along magnetic field lines (Amaro and Barker, 2006; Lange, 1996). In the human body, the largest contribution to the observable MRI signal comes from hydrogen (^1H), bound to water; a much smaller part is produced by hydrogen bound to fatty acid molecules. Magnetic field strengths employed in clinical practice lie between 0.5 and 3 Tesla (T). The protons are aligned by a static magnetic field and then deflected by a high frequency radiopulse. This pulse is centred on the resonance frequency of hydrogen and is characterized by the specific degree of deflection it induces ("flip angle") (Amaro and Barker, 2006). The deflection process causes a change of the magnetic field in either longitudinal (T1) or transversal (T2) direction (Horowitz, 1989). The signal change is dependent on the extent of deflection and number of deflected protons. Three additional, smaller magnetic fields (gradients) are used to spatially encode the signal in three dimensions. Thus, MRI allows to obtain three-dimensional images of the body with signal contrasts according to the tissue's density of water and fat molecules.

1.5.1 Functional MRI

Two main effects are exploited in fMRI: one, active brain regions have an increased demand of glucose, and two, this is followed by an increase in local blood flow. Different methods enable to visualize these effects. The most commonly used method to investigate brain function, also employed here, is the so called BOLD (blood oxygen level dependent) contrast imaging (Chen and Ogawa, 2000; Di Salle et al., 1999). This method is based on MR sequences sensitive to changes in the state of hemoglobin oxygenation (Magistretti and Pellerin, 1999; Villringer, 2000). The increased blood flow in active brain areas leads to a higher concentration of oxygen-saturated hemoglobin (oxyhemoglobin) and thus a relatively lower concentration of deoxygenated hemoglobin (deoxyhemoglobin) in the venous system. Due to different properties of oxygenated and deoxygenated hemoglobin within a magnetic field, this concentration shift can be detected (Di Salle et al., 1999). The resulting differences in signal strength, however, are very small. Their evaluation requires a statistical comparison of many images in different states. Images acquired during task performance are typically compared to images acquired while the subject rests, or performs a different task not involving the brain region of interest. Following statistical analyses, the thus-detected differences can then be attributed to the functional activation of a given region as induced by, or at least related to, the task (Di Salle et al., 1999).

1.5.2 Challenges in fMRI

Image quality (and thus, sensitivity and specificity) of fMRI is very vulnerable to subject movement, which leads to artefacts that can only partially be compensated by preprocessing steps aimed to minimize the differences between consecutive images (Friston et al., 1996). If the effects of motion are too strong, the images should be discarded (Hoffmann et al., 2015; Wilke, 2014). Especially paradigms requiring the participants to speak are susceptible to movement artefacts (Birn et al., 2004). Since children have more difficulties to keep still, any study aimed at including children is faced with important limitations regarding the possible task design (Thomas and Casey, 2000).

Another limitation of MRI is the presence of a powerful magnetic field. Any ferromagnetic metal brought into the MRI room can lead to injury (Savoy, 2001). Metal inside the body can lead to burns, or be loosened and damage the local tissue (Kwan Hoong Ng, 2003). Implanted cardiac pace-makers can be interrupted and damaged (Kwan Hoong Ng, 2003). Even though the magnetic field itself is considered not harmful to the human body (Kwan Hoong Ng, 2003; Holland et al., 2014), MRI can consequently become harmful when disregarding the necessary safety regulations.

The unfamiliar MRI scanner environment presents a further challenge when obtaining MR images. The narrow bore with loud background noise can appear frightening, especially to children (Byars et al., 2002; Wilke et al., 2003; Amaro and Barker, 2006). With the aim of a future application in children, we created playmobil® stop-motion movies to implement the language task. This familiar sight was intended to make children feel more comfortable and be able to concentrate on the task.

Figure 2: Siemens Avanto 1,5 Tesla Magnetom MRI scanner, similar to the one used for this study; photo by Siemens AG, used with kind permission

1.5.3 Other non-invasive brain imaging tools

Further approaches to functional neuroimaging providing both high temporal and spatial resolution mainly utilize two different approaches: electrophysiological and hemodynamic changes.

1.5.3.1 Electroencephalography and Magnetoencephalography

There are two technologies for non-invasively recording the electric activity of the human brain: electroencephalography (EEG) and magnetoencephalography (MEG) (Savoy, 2001). Both technologies are able to quantify continuous electrical activity ("brain-waves") (Savoy, 2001), as well as repeated responses to a fixed type of stimulus ("event-related potentials" or "event-related fields") (Michel and

Murray, 2012; Salmelin and Baillet, 2009). As the excitation of nerve cells is based on electric potential changes along the cell membranes, electromagnetic changes are the first parameters that can be measured during the activation of a brain region (Savoy, 2001). Hemodynamic changes occur only subsequently; as the vascular response requires more time and is sluggish, this effectively limits the obtainable temporal resolution of methods exploiting such effects (such as fMRI). The direct detection of electrical/magnetic signals allows for a higher temporal resolution (milliseconds or better) of EEG and MEG that cannot be achieved by techniques measuring changes in blood flow and/or oxygenation level. EEG and MEG are very safe technologies and not harmful for the human body, both requirements for experimental research involving healthy participants (Savoy, 2001). For anxious children and even adults, it might also feel less scary to “have electrodes attached to the head” than “to lie within a tube”, exposed to loud, unfamiliar noises. However, brain activity of point sources, as well as distributed activity, can only be measured by electrodes on the head’s surface, leading to an ill-posed inverse solution problem. Interpreting the surface data is one of the challenges of EEG and MEG. The primary way to deal with this problem is to combine them with anatomical information, usually MR imaging data (Dale et al., 2000; Dale and Sereno, 1993).

1.5.3.2 Positron Emission Tomography

Based on the decay of radioactive substances, Positron Emission Tomography (PET) can measure the concentration of a given substance in the brain. For example, radioactive oxygen (^{15}O) allows assessing the oxygenation levels within the brain and therefore provides indirect information on the blood flow (Otte and Halsband, 2006). It can be inhaled, or included in substances that can then be injected. Its half-life is about 2 minutes (Otte and Halsband, 2006; Shibasaki, 2008). Upon the decay of ^{15}O, a pair of oppositely directed high-energy γ-rays is generated, defining a line along which their source can be assumed (Otte and Halsband, 2006). The technology allows not only the observation of blood flow associated with neural activation. The range of opportunities to investigate the physiology of brain functions includes glucose metabolism, protein synthesis, DNA replications, specific neurotransmitters and more (Savoy, 2001). The most obvious disadvantage is the application of radioactive substances, which entails not only governmental restrictions, but also ethical problems (Savoy, 2001). Ionizing radiation is dangerous and healthy participants should not be exposed to it. Another problem lies in the technique itself: Radiation counts for one image last around 30-90 seconds, in which the subject should constantly be engaged in the same task (Savoy, 2001). This prerequisite limits the temporal resolution and thus precludes using faster types of study design. Although the spatial resolution may be comparable to fMRI (on the mm level), due to the limits in temporal resolution PET cannot compete with any other of the technologies mentioned (Saha, 2010).

1.5.3.3 Near-Infrared Spectroscopy

Near-infrared spectroscopy (NIRS) is based on the transparency of biological tissue or substances to light in a spectral range of 700-1000 nm. The basis for this approach is that oxyhemoglobin and deoxyhemoglobin have not only different magnetic, but also different optical properties (Rovati et al., 2007). Using optical fibers, near-infrared light is emitted into the brain. Re-emerging signals are collected by optical detectors and transmitted to a photodiode (Shibasaki, 2008). However, due to a high scattering effect of the scull and the white matter, near-infrared photons are able to penetrate the head only for a few centimeters and therefore are only useful for the investigation of superficial, i.e., cortical functions (Rovati et al., 2007). As in fMRI and PET, the level of blood oxygenation is considered to be indicative of the activation level of a certain brain area (Villringer and Chance, 1997), but again, hemodynamic changes are only observable in response to brain activation with a delay of several seconds. Yet, in contrast to PET and fMRI, NIRS has the capability to also detect and measure neural activity itself within milliseconds after stimulation (Rovati et al., 2007). The physiologic correlate of this first, fast signal is still under debate. It has been suggested that a localized increase of deoxyhemoglobin due to an increased oxygen-dependent metabolism might cause alterations in optical transparency (Cannestra et al., 2001). Other advantages of the technology are that oxygenated hemoglobin concentration as an index of brain function can be measured continuously (similar to PET), and the subject’s head does not have to remain stationary, which offers additional options for study design and facilitates research with children (Shibasaki, 2008). However, compared to fMRI and PET, NIRS still lacks spatial resolution and depth penetration, limiting researches to near-surface cortex areas (Cui et al., 2011).

Considering our specific research questions regarding the processing of complex grammatical structures compared to simple structures, we decided to use fMRI for this study. It does not use ionizing radiation and is locally well-established. Its high spatial resolution combined with an acceptable temporal resolution allows for flexible study designs, making fMRI by far the most used imaging technology in language research (Di Salle et al., 1999; Norris, 2006; Savoy, 2001).

1.6 Study design

The subtle signal changes evoked by functional MRI can only be detected using statistical analyses of a large number of images (Amaro and Barker, 2006). Results strongly depend on the implementation of the study, such as the various ways to present stimuli to a subject. The classic design in PET and fMRI is the so-called block design (Amaro and Barker, 2006). Stimuli are repeatedly presented as sequences of one condition, alternating with sequences of another condition, typically lasting about 30 seconds each. Analyses then contrast the two conditions (Amaro and Barker, 2006). Although subject to much criticism related to neuropsychological drawbacks, block design has frequently been demonstrated to yield high statistical power (Friston et al., 1999; Amaro and Barker, 2006). This is an important advantage, especially for the examination of children. As anatomical structures are smaller in young children, smaller voxel volumes are desirable, which comes at the cost of a lower signal-to-noise ratio (SNR) (Olsen, 2013). The SNR qualifies the proportion of “true” signal versus noise: while noise is a function of non-task-dependent brain activity and of different factors which affect the signal (heartbeat, movement, fluctuations of the magnetic field etc.), the “true” signal is considered to be related to the neural activation evoked by a specific task. The higher the SNR, the easier it is to separate task-induced signal from noise (Triantafyllou et al., 2011).

Due to the superior temporal resolution of fMRI compared to PET, new study designs were developed in addition to the common block design. In event-related designs, single stimuli are presented repeatedly (Friston et al., 1998). The hemodynamic response to each stimulus can be detected and analysed individually. Individual responses to trials can be explored, offering the possibility to analyse neural correlates of behavioural responses, such as errors in challenging conditions, or subjective judgement of emotional content (Braver, 2001; Kiehl et al., 2000). Stimuli can be randomized in order, and time between stimulus presentation (inter stimulus interval - ISI) can be varied. This prevents the participants from developing strategies for solving the task, and therefore helps to maintain the subject’s concentration (D'Esposito et al., 1999). The main disadvantage of such an approach is that it will usually have lower statistical power when compared to a block design (Amaro and Barker, 2006).

In order to mix these two types of designs, blocks of different tasks can be created, which are then filled with events of diverse conditions (Amaro and Barker, 2006). When analysing the data, the two different designs can be combined, and ‘maintained’ versus ‘transient’ neural activity can be separated (Donaldson et al., 2001). Exploring the hemodynamic response to the events within the blocks offers information on individual performance. Randomizing the event-conditions within the blocks maintains the attention level across the experiment (D'Esposito et al., 1999).

1.7 Objectives

This study was motivated by two aims. As a pilot study, we tried to develop a child-friendly paradigm, feasible for adults, children, and patients with left-hemispheric brain lesions. Secondly, we wanted to use this newly-developed paradigm to investigate the language network in young, healthy adults, investigating the neural correlates of processing complex compared to simple grammatical structures.

Functional MRI was employed and a language task was implemented using auditorily-presented sentences and short playmobil® stop-motion movies as stimuli. In a mixed block and event-related design, language production and perception were separated between blocks. Within the blocks, non–canonical object-first and canonical subject-first sentence structures were contrasted.

Our hypotheses were as follows: we expected activation in the left inferior frontal gyrus as the most-verified region to be involved in the processing of complex grammatical structure (Ben-Shachar et al., 2004; Friederici et al., 2006; Bahlmann et al., 2007; Obleser and Kotz, 2010). It is probably also involved in supporting the perception of hierarchal dependencies, which is an important step in the processing of object-first sentences (Price, 2010). We also expected activation in the left superior and middle temporal gyrus, further regions shown to activate in the context of object topicalization (Ben-Shachar et al., 2004; Obleser and Kotz, 2010; Knoll et al., 2012; Obleser et al., 2011).

2 Materials and Methods

2.1 Participants

Twenty-three young, healthy, right-handed adults (12 females) took part in this experiment. Exclusion criteria were neurological or psychiatric disorders, any kind of implanted or non-removable metal device, or tattoos. Data of 2 males had to be excluded due to technical failure or anatomical abnormalities, leaving data from 9 males and 12 females for further analysis. Age was m = 24.39 ± 3.39 years (mean ± standard deviation). All participants were native German speakers. Receptive vocabulary was average or above average as assessed by the German version of the PPVT-III (Peabody Picture Vocabulary Test, Bulheller and Häcker, 2003; median percentile: 93, range=59-99). Demographic data of all participants is summarized in Table 2. Experimental procedures were approved by the local ethics Committee according to the 1964 Declaration of Helsinki in the implementation of 2008 (World Medical Association, 2008). After providing detailed instructions on procedures and risks of the study, written informed consent was obtained from all participants.

Subjects	*Gender*	*Age*	*Highest degree*	*PPVT Percentile*
S1*	m	29	A-level[1]	94
S2*	m	26	A-level[1]	97
S3	f	29	A-level[1]	95
S4	f	28	A-level[1]	76
S5	m	23	A-level[1]	95
S6	f	19	A-level[1]	72
S7	f	24	A-level[1]	80
S8	f	28	A-level[1]	94
S9	m	28	A-level[1]	66
S10	m	27	A-level[1]	66
S11	f	25	GCSE[2]	72
S12	f	23	A-level[1]	99
S13	m	25	A-level[1]	81
S14	m	26	A-level[1]	95
S15	m	27	A-level[1]	80
S16	f	28	A-level[1]	94
S17	f	21	A-level[1]	90
S18	m	21	A-level[1]	93
S19	m	24	A-level[1]	97
S20	f	20	A-level[1]	99
S21	f	19	A-level[1]	59
S22	f	19	A-level[1]	70
S23	m	22	O-level[3]	99
Total	m=11;f=12	mn=24.39		MD=93

Table 2: Demographic data of participants

PPVT: Peabody Picture Vocabulary Test; m: male; f: female; mn: mean; MD: median

**Data was excluded due to technical failure or anatomical abnormalities; [1]Gymnasium/Fachhochschulreife; [2]Mittlere Reife; [3]Hauptschule*

2.2 Task Design

Two tasks were embedded in a mixed block and event-related design with a total of 24 blocks, 12 blocks of a sentence repetition (SR) task and 12 blocks of a truth-value judgement (TVJ) task alternating with each other. Each block contained four events consisting of the four grammatical conditions explained below (2.2.1). The sequence of grammatical conditions was randomized within the blocks, in order to prevent a solving by remembering the sequence of conditions, instead of concentrating on the content of each sentence. Task change was indicated by the short appearance of a green background on the screen.

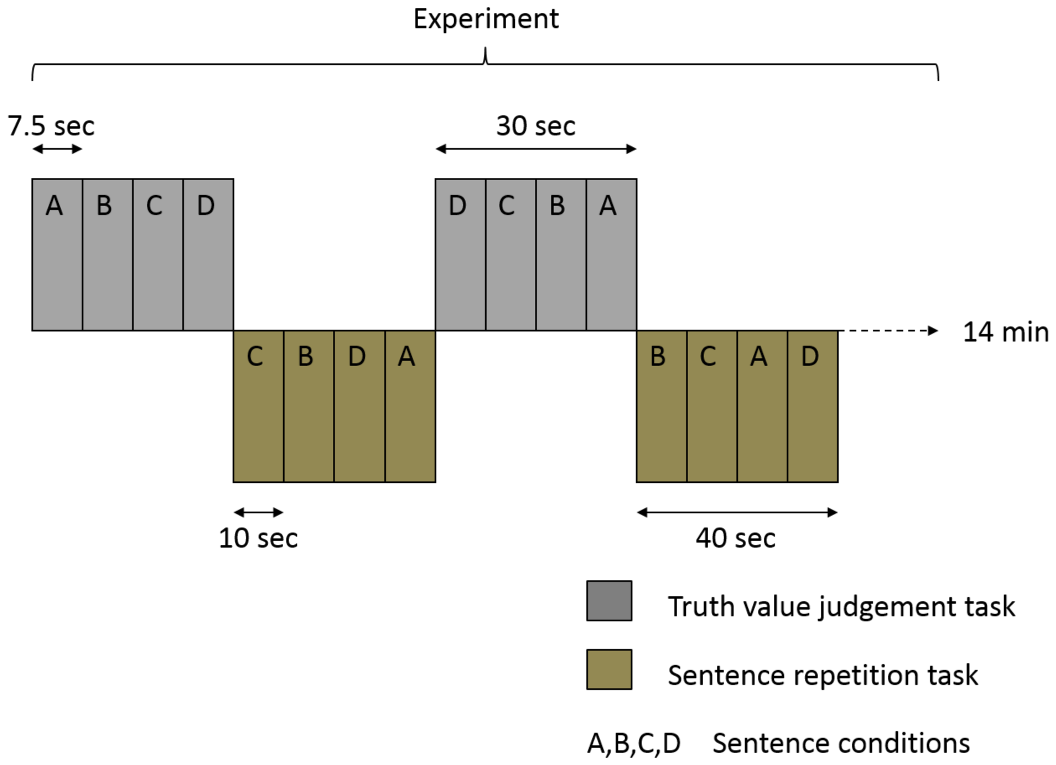

Figure 3: Task design

Generation of stimuli: A set of 48 short sentences describing simple actions was generated. Sentences were 4 seconds long and spoken consistent in pace, accentuation and pitch by a trained female speaker. Stop-motion movies were generated where playmobil ® figures were used to enact the actions described in the sentences. Overall, 12 background sceneries were generated. Serial pictures were taken using a Canon EOS 500 D camera, and short movies were then generated from these pictures using the Adobe Premiere Pro CS 5.5 software. Stop-motion movies were 5 seconds long. The spoken sentences started 1 second after the start of the stop-motion movies.

1. *Sentence repetition task* (Figure 4): concordance of movie and sentence was set to 100% of events and participants were asked to articulate the perceived sentence in a clear manner. Participants were given 5 seconds to repeat the sentences, initiated by a picture containing the instruction: “Bitte nachsprechen.”*(“Please repeat aloud.”)*. Participant’s responses were recorded during the scan, and the repetition of sentences was considered incorrect if a grammatical error was present in the recording.

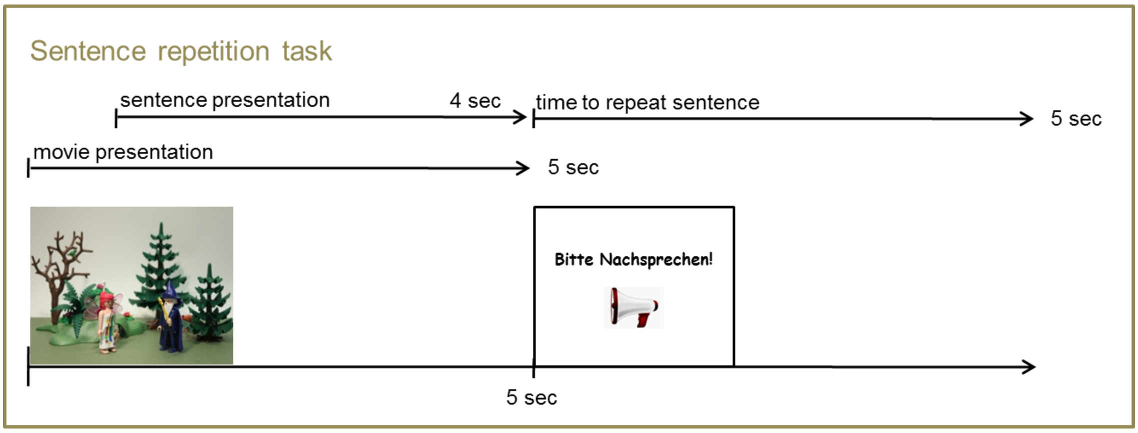

Figure 4: Sentence repetition task. Sentence presentation starts 1 second after movie presentation. Following the presentation of a visual cue, participants have 5 seconds to repeat the sentence.

2. *Truth-value judgement task* (Figure 5): All sentences were matched with a movie which was either content-congruent (50% of events) or content-incongruent (50% of events). Participants were instructed to indicate whether sentence and movie were congruent in content by pressing an MR-compatible pushbutton in their left hand. Not pressing the button consequently indicated discrepancy of content in movie and sentence. Participants were instructed to answer after each presentation of movie and sentence within a 2.5 seconds time window. This was indicated by a visually presented question of

“Stimmts?”*(“Correct?”)*. The truth-value judgment was considered incorrect if the button press was missing or incorrect.

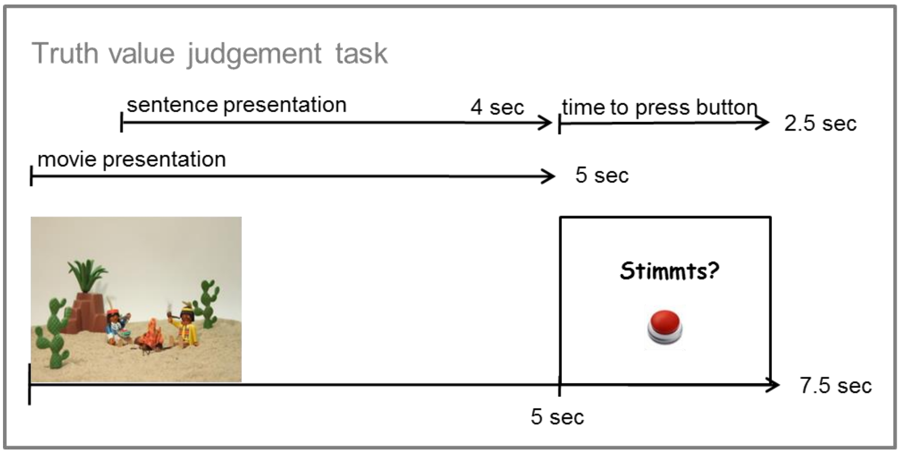

Figure 5: Truth-value judgement task. Sentence presentation starts 1 second after movie presentation. Following the presentation of a visual cue, participants have 2.5 seconds to answer (pressing the button or not).

2.2.1 Sentence conditions

Sentences were divided into four grammatical conditions. Two types of non-canonical sentences were developed (Table 3), one with case-marking as the only cue to separate subject and object (condition A) and one with a plural number of actors (subject) as an additional cue (condition B).

Two canonical sentence structures were added as control conditions (Table 4): condition C as a simple canonical structure, and condition D as a coordinated sentence structure with two different subjects and two different verbs/actions. In order to equalize the length of each sentence condition to four seconds, we dismissed the objects in sentence type B.

Non-canonical word order (object topicalization)			
A)Topicalization (case)	*object*	*verb*	*subject*
	Den bärtigen Kapitän	fesselt	die Piratin
	The_$_{ACC}$ bearded capitain	chains	the_$_{NOM}$ pirate.
B)Topicalization (case and number)	*object*	*verb*	*subject*
	Den bärtigen Kapitän	fesseln	die Piratinnen.
	The_$_{ACC}$ bearded capitain	chain	the_$_{NOM}$ pirates.

Table 3: Sentence conditions – non-canonical word order

Canonical word order					
C) Simple canonical sentences	*subject*	*verb*	*object*		
	Der bärtige Kapitän	fesselt	die Piratin.		
	The_$_{NOM}$ bearded capitain	chains	the_$_{ACC}$ pirate.		
D) Coordinated canonical sentences	*subject*	*verb*		*subject*	*verb*
	Der Kapitän	steuert	und	die Piratin	rudert.
	The_$_{NOM}$ capitain	steers	and	the_$_{NOM}$ pirate	oars.

Table 4: Sentence conditions – canonical word order

2.3 MRI data acquisition

2.3.1 Preparation of Participants

All participants were instructed regarding the standard safety precautions concerning the strong magnetic field inside the scanner room. Thereafter, the tasks were explained to them before entering the scanner, making sure that all remaining questions were answered. During the acquisition of anatomical images, participants were additionally presented an introduction movie explaining the task again.

2.3.2 Technical setup

During fMRI data acquisition, visual stimuli were displayed on an MRI-compatible screen using a digital LCD projector, while auditory stimuli were presented by air-conducting, sound-insulating headphones. An MRI-compatible microphone (Optoacoustics, FOMRI3) was positioned in front of the participants' mouth in order to record the spoken sentences during the task. A single MRI-compatible pushbutton (Current Design Inc. Philadelphia, PA, USA) was used to report the participants' decisions. For stimulus presentation, instructions, and recording of responses, Presentation® software (Neurobehavioral Systems, inc.) was used.

2.3.3 Data acquisition

Image data was acquired using a 1.5 Tesla Avanto Scanner with a 12-channel head-coil (Siemens Medizintechnik, Erlangen, Germany). Blood oxygenation level dependent (BOLD) contrast sensitive images were acquired using a whole-brain multislice echo-planar imaging (EPI) sequence (time to repetition TR = 3 sec, time to echo TE = 40 ms, matrix = 64 x 64, 40 slices covering the whole brain, yielding a voxel size of 3 x 3 x 3 mm^3). Overall, 287 volumes were acquired in 14 Minutes. Additionally, a gradient-echo B0 fieldmap was acquired with TR = 546 ms, TE = 5.19/9.95 ms, and with the same slice prescription as the functional series. An anatomical T1-weighted 3D-data set with TR = 1300 ms, TE = 2.92 ms was also acquired, 176 contiguous slices with an in-plane matrix of 256 x 256, yielding a voxel size of 1 x 1 x 1 mm^3.

2.4 Preprocessing

Before the image data can be statistically analyzed, several data pre-processing steps are necessary. Preprocessing corrects for artifacts on the one hand, and prepares the data for statistical analyses on both single subject and group level on the other hand.

Data was processed using SPM8 software (Wellcome Trust Centre for Neuroimaging, London, UK), running in Matlab (Mathworks, Natick, MA, USA). The first three scans of each functional series were rejected to allow for a stabilization of longitudinal magnetization.

2.4.1 Wavelet-based denoising

In order to improve the signal-to-noise ratio, we applied a wavelet based denoising as the first step in our processing stream, facilitating the detection of true signal in ensuing statistical analyses (Wink and Roerdink, 2004).

2.4.2 Realignment and unwarping

Even if the subject's head is positioned tightly within the acquisition coil, there will always be minimal subject movement. This is "corrected" for using a rigid-body realignment procedure (Friston et al., 1996). Here, subject movement is described by six parameters, three for rotation (pitch, roll, yaw) and three for translation (x, y, and z). The overall sum of subject motion is only described by combining these parameters, resulting in a net "total displacement" indicator (Wilke, 2014). All EPI images were then realigned according to these movement parameters and thus are registered to a reference image (Friston et al., 1996; Jenkinson et al., 2002). In our study, we chose the mean image of each series as the reference, as this is more representative than the first image. Depending on the voxel size, the tolerable amount of subject motion should be defined a priori (Wilke, 2014; Hoffmann et al., 2015). In our study, none of the participants showed a total displacement exceeding this limit (3 mm = 1 voxel size) so that no subject had to be excluded from the analyses because of excessive movement.

Any biological object inside a magnetic field will affect the field in its homogeneity (Andersson et al., 2001; Wohlschläger et al., 2007). Interfaces between tissues in general, and air-tissue interfaces in particular, disturb the homogeneity of the magnetic field and the images produced by it. As a result of this effect, the magnetic field homogeneity changes in the course of a scanning session, as a function of the subject's movement (Andersson et al., 2001). After realigning the images to correct for movement, the resulting contortions of the field have to be considered. To this effect, B0 fieldmaps were acquired for each subject, effectively capturing the individually-distorted magnetic field. This allows estimating the distortion present in the EPI data. The field inhomogeneities over subsequent scans are then estimated with respect to the changing subject position, using the EPI data and estimated realignment parameters (Andersson et al., 2001), upon which these additional inhomogeneities can be removed from the images. This step allows to remove EPI-inherent image distortions as well as to reduce motion-induced signal changes in the functional images.

2.4.3 Coregistration

The spatial resolution of EPI images is low. In order to improve precision of anatomical assignment of activation clusters in later processing steps, anatomical T1-weighed high-resolution images were acquired (for details see 2.3.3). For each subject, the anatomical image was coregistered to a reference image, in our case the mean image of the time series, by means of a rigid-body transformation (Ashburner and Friston, 1997). This step allows to use the anatomical image for ensuing data processing steps.

2.4.4 Slice timing

Echo planar imaging is the acquisition of initially two-dimensional images. In our study, 40 slices were acquired over the course of 3 seconds; this data then has to be assembled into one volume covering the whole brain. This implies that the signals recorded within one volume come from multiple measurement processes during different points of time, over the course of one TR (Wohlschläger et al., 2007; Sladky et al., 2011). With our TR being 3 seconds, slices of one volume, including their signals, differ in their point of recording time up to a maximum of 3 seconds. Since the event-related design depends on a temporal resolution of split seconds, we chose to correct for the different times of acquisition. This process is called “slice time correction” (Wohlschläger et al., 2007). During this process, all slices of one volume are interpolated to correspond to the acquisition time of a specific slice, in our case the middle one (Wohlschläger et al., 2007; Sladky et al., 2011). This step allows to correct for time differences arising during the acquisition of the imaging data.

2.4.5 Spatial Normalization

The step of spatial normalizing allows for the comparison of corresponding anatomical structures between subjects (Ashburner et al., 1999). In order to enable a group analysis, the anatomical structures of each subject have to be transformed into a standard space. To this effect, a template based on the imaging data from a large number of subjects is used (Ashburner et al., 1999). For our study, transformation was achieved using functionality available within the vbm8-toolbox by Gaser (Gaser, 2010), constituting an extension to the unified segmentation approach (Ashburner, 2000; Ashburner and Friston, 2005). During this procedure, each subject's high-resolution anatomical dataset is partitioned into the three main tissue classes (grey matter, white matter, and cerebrospinal fluid) dependent on the signal intensity. This is then followed by an iterative registration using the diffeomorphic DARTEL registration approach developed by (Ashburner, 2007). To this effect, a customized DARTEL template as available in the vbm8-toolbox was used, based on 550 healthy adults. The thus-derived spatial normalization parameters were then applied to the functional images. This step allows to compare and summarize functional image results on a group level.

2.4.6 Detrending

There are a variety of global effects of no interest that might interfere with the detection of BOLD signals (Aguirre et al., 1998). Such global effects may be caused by long-term instabilities of the scanner baseline or by physiological fluctuations, such as pulsations, swallowing, breathing, change of blood pressure or subject movements. Global effects are difficult to measure directly and often are estimated from the global signal, the spatial average of local signals from all cerebral voxels. If the global signal is highly correlated with experimental conditions, a substantial ambiguity ensues with regard to the sensitivity and specificity of the observable signal changes and their interpretation (Aguirre et al., 1998). In order to remove such global effects, the time course of each voxel was modeled to the global signal, using linear regression. The thus gained global component was removed from each voxel's time course (Macey et al., 2004). This step allows to factor out global effects that are of no interest.

2.4.7 Spatial smoothing

Imaging data does not necessarily follow a normal distribution, potentially disallowing for the use of standard (parametrical) statistical approaches. To this effect and to create a pooled local average over adjacent voxels, spatial smoothing is done (Friston et al., 1995). The contribution of each voxel is determined by a three-dimensional Gaussian filter, with the maximum contribution coming from the central voxel (Friston et al., 1995). Also, even after spatial normalization there is still a considerable inter-subject variability left on the voxel-level; here, smoothing improves comparability between subjects (Friston et al., 1995; Wohlschläger et al., 2007). We smoothed our functional images with a 9 mm full-width-at–half-maximum (FWHM) Gaussian filter.

This step improves the starting estimates for statistical analyses and contributes to an improvement of inter-subject comparability.

2.5 Statistical analysis

For statistical analyses of demographic or performance variables, Student's t-tests were used. Significance was assumed at $p \leq 0.05$, Bonferroni-corrected for multiple comparisons where appropriate.

Statistical analyses of neuroimaging data were performed within the framework of the general linear model (Friston et al., 1995). On the single-subject level, we conducted several multivariate analyses of covariance, including individual realignment parameters as nuisance variables (Friston et al., 1996). Covariate of interest was word-order. On the group level, we applied an initial voxelwise threshold of $p \leq 0.001$ (uncorrected), followed by a cluster-wise correction for multiple comparisons as recently recommended (Woo et al., 2014), achieving a corrected $p \leq 0.05$ by using the false discovery rate.

For the truth-value judgement task, we analyzed the image data acquired during the time spans in which participants had to decide whether to press the button or not (2.5 seconds). For the sentence repetition task, we analyzed the image data acquired during the time spans in which the participants were presented the auditory sentences (4 seconds).

For each task, contrasts assessing non-canonical > canonical word order were calculated. The resulting individual statistical parameter estimates (con-images) were then entered into a second-level random effects group analysis, treating age, gender, and PPVT-score as covariates of non-interest.

In a region of interest (ROI) analysis (Hammers et al., 2003) we focused on frontal and temporal cortex, as these were the regions within which we expected activation differences for our different grammatical conditions (Ben-Shachar et al., 2004; Obleser and Kotz, 2010; Friederici et al., 2006; Obleser et al., 2011).

3 Results

3.1 Error Rates during SR task

The sentence repetition task was performed without grammatical errors by all participants.

3.2 Error rates and average reaction times during TVJ task

The following table shows the error rates and average reaction times during the truth-value judgment task for each sentence type over all participants. When statistically assessing performance in this task, reaction times were not significantly different (*p* = 0.37, t-test). However, error rates were significantly different, with more errors in the topicalization conditions (*p* = 0.006, t-test).

Sentence type	**Errors/Condition**	**Mean reaction time [ms]**	**SD reaction time [ms]**
A)Topicalization (case)	31/252 (12,3%)	784,76	208,65
B) Topicalization (case and number)	29/252 (11,5%)	759,5	180,96
A) and B)	**60/504 (11,9%)**	**772,13**	**193,33**
C) Simple canonical sentence	17/252 (6,6%)	775,6	159,46
D) Coordinated canonical sentence	14/252 (5,5%)	725,61	173,73
C) and D)	**31/504 (6,1%)**	**750,6**	**166,63**
A), B), C) and D)	91/1008 (9,0%)	761,37	179,71

Table 5: Error rates and reaction times

3.3 Activation patterns

A significant effect of non-canonical versus canonical word order on the group level was detected in our data as follows.

3.3.1 Sentence repetition task

For the sentence repetition task, assessing the time span while listening to the acoustically presented sentences, we found significant activation in the left medial superior frontal gyrus (Figure 6), in the right precentral gyrus (Figure 7), and in the left parahippocampal gyrus (Figure 8). Results are also summarized in Table 6.

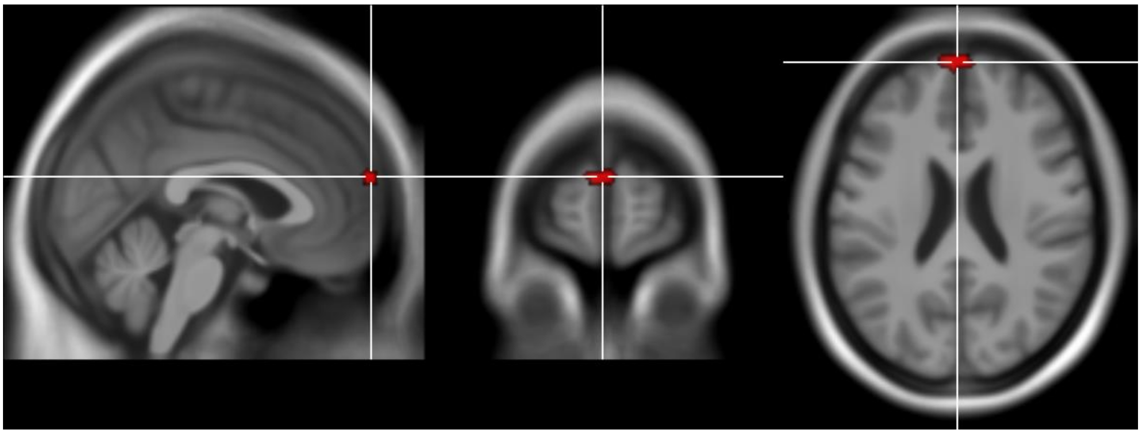

Figure 6: SR-task, left superior frontal gyrus. Activation overlaid on the DARTEL template as available in the vbm8-toolbox.

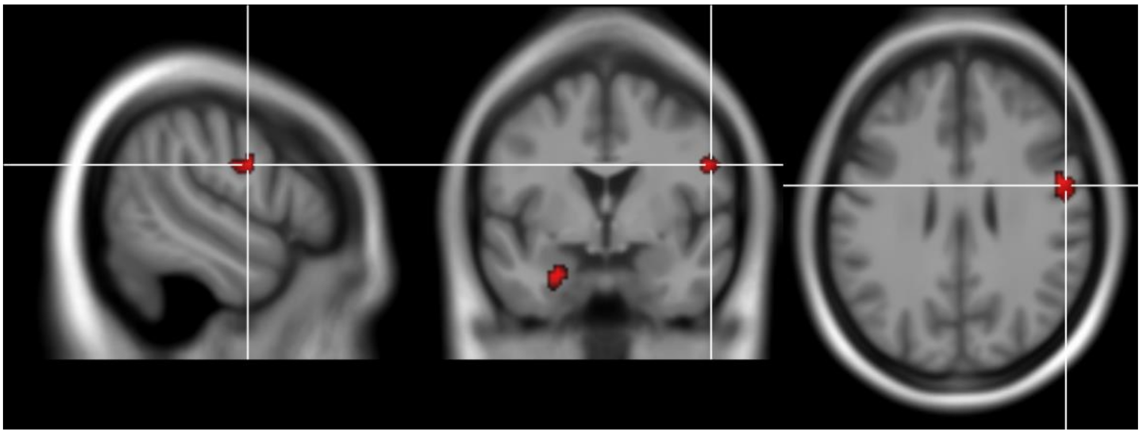

Figure 7: SR-task, right precentral gyrus. Activation overlaid on the DARTEL template as available in the vbm8-toolbox.

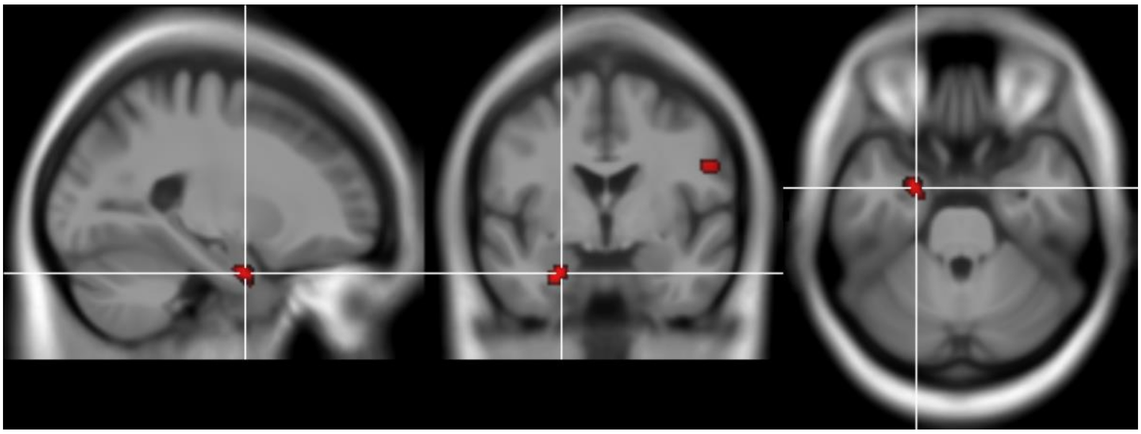

Figure 8: SR-task, left parahippocampal gyrus. Activation overlaid on the DARTEL template as available in the vbm8-toolbox.

Region	**Coordinates**	**Cluster extent**	**T (peak level)**	**$P_{FDR\text{-}corr}$ (cluster-level)**
Left superior frontal gyrus	0 63 21	22	5.67	0.044
Right precentral gyrus	54 0 27	20	5.59	0.044
Left parahippo-campal gyrus	-24 -3 -30	23	5.41	0.044

Table 6: Results – sentence repetition task. Coordinates are mm coordinates in standard space.

3.3.2 Truth-value judgment task

For the truth-value judgement task, assessing the mean time span of decision making, we found significant activation in the left insula (Figure 9), in the left inferior frontal gyrus (pars opercularis; Figure 10), in the right inferior frontal gyrus (pars orbitalis; Figure 11) and in the left middle cingular gyrus (Figure 12). Results are also summarized in Table 7.

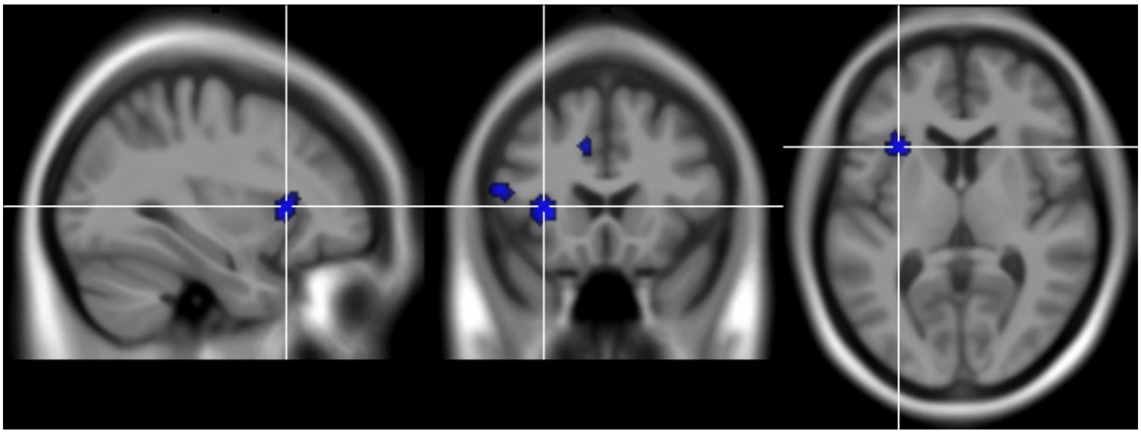

Figure 9: TVJ-task, Left insula. Activation overlaid on the DARTEL template as available in the vbm8-toolbox.

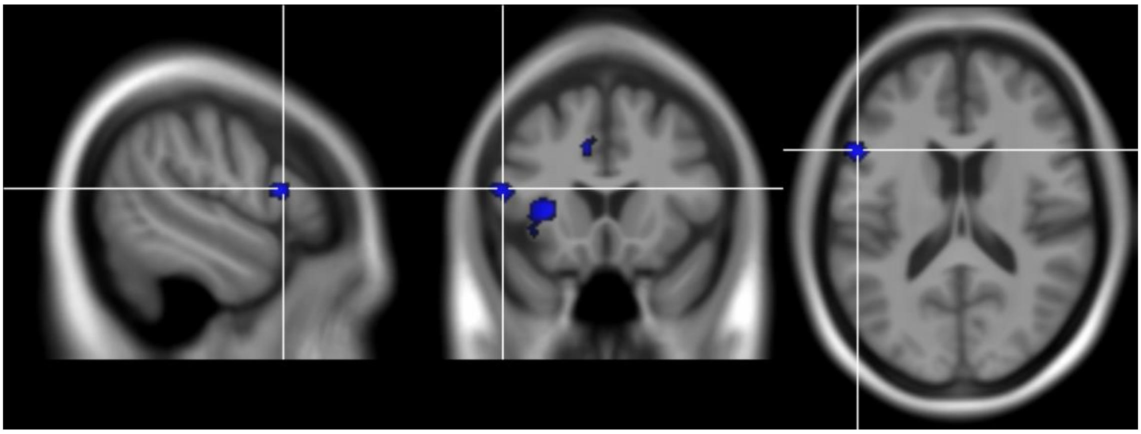

Figure 10: TVJ-task, Left IFG – pars opercularis. Activation overlaid on the DARTEL template as available in the vbm8-toolbox.

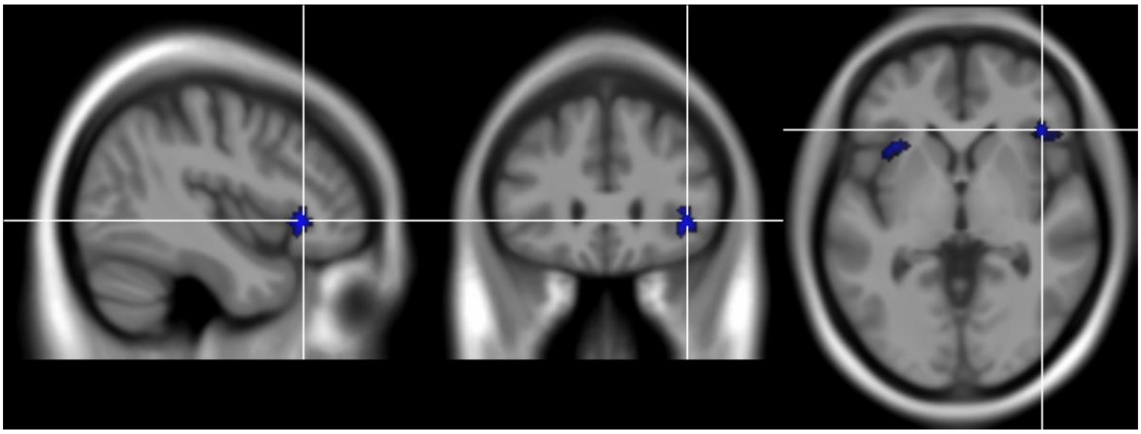

Figure 11: TVJ-task, right IFG - pars orbitalis. Activation overlaid on the DARTEL template as available in the vbm8-toolbox.

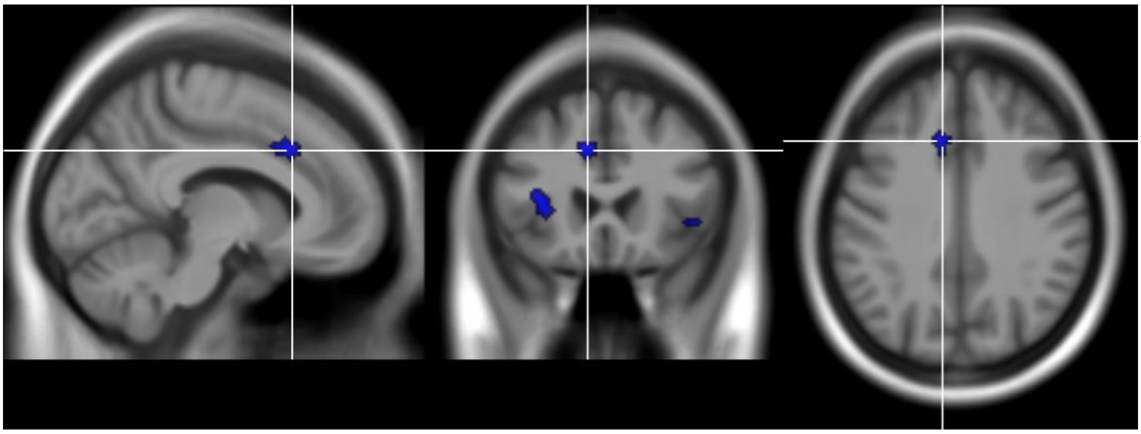

Figure 12: TVJ-task, left cingular gyrus. Activation overlaid on the DARTEL template as available in the vbm8-toolbox.

Region	**Coordinates**	**Cluster extent**	**T (peak level)**	**$P_{FDR\text{-}corr}$ (cluster-level)**
Left Insula	-30 18 3	49	8.01	0.008
Left IFG – pars opercularis	-54 15 15	20	5.92	0.041
Right IFG – pars orbitalis	42 27 -3	26	5.58	0.041
Left cingulate gyrus	-9 21 33	20	5.56	0.043

Table 7: Results – truth-value judgment task. Coordinates are mm coordinates in standard space.

4 Discussion

This study was conducted to develop and evaluate a child-friendly fMRI paradigm for the investigation of complex grammar processing. To this effect, we aimed at contrasting object-first non-canonical to subject-first canonical sentences. A language production and a language comprehension task were embedded into a mixed block and event-related design. The task was implemented using short playmobil® stop-motion movies and acoustically presented sentences. Two canonical and two non-canonical sentence structures were tested.

In summary, the processing of grammatically complex non-canonical sentences was associated with a bilateral network of fronto-temporal brain regions. For the sentence repetition task, activation was found in the left superior frontal gyrus, the right precentral gyrus and the left parahippocampal gyrus. For the truth-value judgement task, word-order variation was associated with activation in the left insula, the left pars opercularis, the right pars orbitalis and the left cingulate gyrus. These results and general aspects relevant to this study shall now be discussed in more detail.

4.1 Complexity of the developed task

Despite the seemingly complicated study design, the task was quickly explained and easily understood by all participants. None of the participants showed difficulties in the correct repetition of all sentence conditions, confirming good audio delivery. The error rate during the truth-value judgement task was low (9 % over all conditions), indicating that the task is easy to do for adults. However, the decisions on the complex non-canonical sentence conditions showed significantly more errors than on the canonical sentence conditions, indicating that a different difficulty level was successfully achieved by the different conditions within the task.

It must be stated that the performance observable in this group shows a certain ceiling effect (Table 5). This may have contributed to a lower effect size observable in the resulting contrast images. On the other hand, the high performance during the truth-value judgement task suggests that this task is not too difficult for children. Further, the differences in performance for the non-canonical compared to the canonical sentence conditions will probably be stronger in children with early left-hemispheric brain lesions (Schwilling et al., 2012).

4.2 Sentence repetition task

During the sentence repetition task, the acoustically-presented sentence accompanying the information shown in the stop-motion movie has to be understood and memorized. We here analyzed the image data acquired during the time span when participants were listening to the sentences. Afterwards, its articulation has to be planned and performed correctly. This was accomplished without any grammatical errors by all participants. The level of difficulty of storing the exact sentence before repeating it is dependent on the length of the sentence (Tewes and Rossmann, 2000; Grimm, 2001). By identifying all words or components of the sentence in their relations, and assembling them to their semantic meaning, the amount of information (or number of words) to store in short-term memory is increased (Tewes and Rossmann, 2000; Grimm, 2001).

In the literature, a large body of evidence indicates that the medial temporal lobe, including the hippocampus, parahippocampus and perirhinal/entorhinal regions, is strongly involved in memory processes, more precisely in the encoding of perceived information (for a review, see Squire et al., 2004). Yet, the exact anatomical allocation of different memory functions is still difficult. Although there have been reports dissociating memory functions in terms of anatomy, findings so far do not reveal a clear distinction between the hippocampus and its adjacent regions (Squire et al., 2004). Both hippocampal and parahippocampal cortex are shown to be involved in both recollective memory and the encoding and retrieval of associations (Squire et al., 2004). This has been shown for spatial information (Wixted and Squire, 2011), for the encoding and retrieval of paired pictures (Pihlajamaki et al., 2003), for the encoding of complex scenes or line drawings into memory and retrieval from memory of previously studied line drawings or words (Gabrieli et al., 1997). A study of (Santi and Grodzinsky, 2007) investigated brain activity related to syntactical movement and found bilateral clusters in parahippocampal/fusiform gyrus as a linear effect of distance of sentence constituents, interpreted as an involvement in working memory functions. These results suggest, that the encoding and/or retrieval of sentences with object-first word order depends on more support by the parahippocampal region than the encoding of subject-first sentences (Squire et al., 2004). This could either be explained by the difference of familiarity and frequency of using in daily language (Gorrell, 2000), or by the complexity of object-topicalization structure (Bahlmann et al., 2007; Friederici et al., 2006; Lidzba et al., 2013), likely requiring more effort during the encoding procedure.

The precentral gyrus is where the primary somatomotor cortex is located (Trepel, 2008). Every part of the musculoskeletal system under voluntary motor control is represented contralaterally in the precentral gyrus (Trepel, 2008). As the central hub for motor functions, it is connected with the corresponding spinal interneurons via the corticospinal tract (Trepel, 2008). In a study by Wilson et al., 2004, participants showed strongly overlapping activation clusters in the primary motor cortex during the listening and the production of the same monosyllables. A process of auditory-to-articulatory mapping was assumed to underlie this similar activation pattern (Wilson et al., 2004). This effect may also be an explanation for the activation we found in the right precentral gyrus. The cluster is in close proximity to the brain regions responsible for orofacial muscles (Trepel, 2008). This seems to indicate that the process of auditory-to-articulatory mapping is more difficult, and thus requires more neural resources, for the more complicated non-canonical compared to the common canonical sentence structure. Yet, the question remains why activation was only found in the right hemisphere. In the study of (Wilson et al., 2004), four out of ten participants activated bilaterally, two activated left-more-than-right, and four activated right-more-than-left; however, at lower thresholds bilateral activation was seen in all participants. This suggests that a simple thresholding effect may underlie this lateralized activation, but as motor activation was not the primary aim of this study, this was not explored here further.

Activation was also seen in the very anterior portion of the superior frontal gyrus. This is a region highly sensitive to movement artefacts (Zaitsev et al., 2015). On the other hand, it has been shown to be involved in semantic processing (Sharp et al., 2010; Binder et al., 2009). In his review, (Binder et al., 2009) refers to dorsomedial prefrontal cortex as “largely overlooked in reviews on semantic processing” and lists it as one of seven regions activating during semantic processing tasks. In a study by (Mazoyer et al., 1993), the superior medial prefrontal area activated when participants were listening to meaningful stories compared to speech in an unknown language, therefore arguing further for its involvement in language processing. Other studies found superior prefrontal activation in an inductive reasoning task (Goel et al., 1997), or in a task where participants had to judge coherent compared to incoherent sentence pairs (Ferstl and von Cramon, 2001). (Fletcher et al., 1995) linked frontomedian/frontodorsal structures to “theory of mind” functions. Despite the frequent activation of the superior medial prefrontal region during different language tasks, the available literature does not reveal a clear structure-function relation for this region; instead, various functions were ascribed to it, likely indicating a multimodal role of this region. Activation of the superior frontal gyrus in the comprehension or production of complex sentence structures has not been described before, making it difficult to relate our results to the existing body of literature. Hence, weighing the weak neurobiological plausibility of this cluster of activation against the high propensity of this edge region to show motion artefacts (Zaitsev et al., 2015), we decided to not discuss this region in more depth.

4.3 Truth-value judgement task

When executing the truth-value judgement task, participants had to process the acoustically-presented sentences and asses the distribution of the roles. Only by decoding syntactic structures participants could decide whether the contents of sentence and movie matched or not. In order to recognize hierarchal dependencies, participants had to judge cues such as word order and case marking (Bates and MacWhinney, 1987).

As expected from the results of previous studies (Friederici et al., 2006; Bahlmann et al., 2007; Ben-Shachar et al., 2004), a significant word-order-effect was found in the left inferior frontal gyrus, pars opercularis. Activation was stronger for the (more difficult) object topicalization, compared to the (more simple) canonical sentence structure. In previous studies, pars opercularis has frequently been associated with complex language comprehension tasks demanding semantic or syntactic skills, for example when the meaning of a word or sentence is difficult to extract (Price, 2010). In terms of semantic comprehension, this could be shown for sentences with ambiguous versus unambiguous meanings (Bilenko et al., 2009), for novel metaphoric versus literal meanings (Mashal et al., 2009), for speech supported by incongruous versus congruous gestures or pantomimes (Willems et al., 2009), and for grammatically correct sentences with implausible versus plausible meanings (Tyler et al., 2010). Closer to our study, syntactic movement requires both semantic and syntactic processing for correct comprehension (Ben-Shachar et al., 2004; Richardson et al., 2010). For example, involvement of pars opercularis was indicated by (Richardson et al., 2010) for sentences in which the meaning depends on the order of subject and object, versus sentences where subject and object cannot be exchanged. Generally, as grammatical structures become more complex and therefore complicate the comprehension of a sentence, left pars opercularis seems to be involved (Just et al., 1996; Caplan et al., 1998, 1999; Röder et al., 2002; Ben-Shachar et al., 2003; Ben-Shachar et al., 2004). Friederici et al., 2010 reported activation for sentences with syntactic errors, Raettig et al., 2010 for violations in the verb-argument structure. Most relevantly for the future application of this task in children, inferior frontal gyrus activation for non-canonical versus canonical sentence structure was shown by Friederici et al., 2006, Bahlmann et al., 2007, Ben-Shachar et al., 2004 for adults and by Knoll et al., 2012 for children. This is also in line with the findings of the Tübingen group, showing that sentences with missing nouns also induce left inferior-frontal activation in an otherwise primarily passive listening task (Wilke et al., 2005). Our results are thus consistent with the findings of previous studies and indicate that Broca's area is an important component for the processing of complicated sentence structure, such as object topicalization, and their interpretation.

Interestingly, we also found activation in the right inferior frontal gyrus, pars orbitalis. In the literature, additional right-hemispheric activation is reported as tasks become more complicated (Beeman et al., 1994; Sachs et al., 2011; Passeri et al., 2014; Argyriou et al., 2015; Bookheimer, 2002). Of note, though, this right-hemispheric activation is most commonly accompanied by left-hemispheric activation, suggesting that the right hemisphere works in an inter-hemispheric manner (Vigneau et al., 2011). This assumption is consistent with split brain studies that show a limited role of the right hemisphere for lexical and phonological processing, but its support during the processing of context (Bogen, 1997; Gazzaniga, 2000). More specifically, inferior frontal gyrus in the right and left hemisphere are interpreted to make top-down predictions on a sequence of events, meaning the use of prior knowledge of language, combined with the context in which it is being used, in order to form expectations (Price, 2010). This strategy may be applied to single words, to phonation, to syntactic, or to semantic cues (Price, 2010). Snijders et al., 2009 documented right inferior frontal activation for a task comparing ambiguous versus unambiguous sentences. In a study by Dick et al., 2009, semantically incongruent, relative to congruent hand movements of a story teller evoked activation in the right IFG. A series of sentences with conflicting information (Peelle et al., 2009), as well as metaphoric compared to literal sentences (Schmidt and Seger, 2009), were shown to induce increased right inferior frontal activation.

As most studies so far investigated the right IFG in general and not specifically the right pars orbitalis, the role of left pars orbitalis shall also be discussed. The left pars orbitalis seems not to be related explicitly to syntax processing, but rather to semantic constraints. Left pars orbitalis activation was associated with auditory sentences with implausible versus plausible meanings (Tyler et al., 2010), (Ye and Zhou, 2009), and with pseudowords compared to words (Kotz et al., 2010). Aarts et al., 2009 conducted a study in which participants were presented the written words "right" or "left", combined with arrows in the same or opposite direction. Left pars orbitalis showed increased activation for the mismatch, meaning the written direction being incongruent with the direction of the arrow. It therefore seems that left pars orbitalis is involved in semantic retrieval and evaluation processes. Regarding our study, the aggravated semantic demands induced by the movement of the object to the beginning of the sentence might explain the activation we found in right pars orbitalis. Finding increased activation in inferior frontal gyrus in the left and right hemisphere for object-topicalization compared to canonical sentences indicated that object-first sentences are difficult structures to process and, in our group, induced bilateral activation.

It must be mentioned that the distinction between anatomically small structures is inherently difficult in fMRI. For example, we found activation in left pars opercularis (BA 44) and right pars orbitalis (BA 47). Due to the Gaussian smoothing applied to our data (using a filter with FWHM = 9 mm), there is an inherent spatial uncertainty (Reimold et al., 2006). Factoring in common sources of variance in fMRI studies, such as inaccuracies during spatial normalization, possible artefacts of movement as well as the uncertain structure-function relationship in the brain, the labelling of the above-noted clusters to left pars opercularis and right pars orbitalis must be interpreted cautiously. Therefore, our results should be understood as a bilateral activation in inferior frontal gyrus. Yet interestingly, (Knoll et al., 2012), employing a study design similar to ours with pictures instead of stop-motion movies to indicate the given action, revealed object-initial-structure related activation in left pars opercularis in a pilot-study with healthy adults. Therefore, while an exact anatomical ascription cannot be made, our finding of activation in left pars opercularis and right pars orbitalis are in very good agreement with the literature (Price, 2010).

The strongest activation cluster was found in the left insula. This region was not found in the above-mentioned previous studies contrasting non-canonical to canonical word order (Friederici et al., 2006; Ben-Shachar et al., 2004; Obleser and Kotz, 2010; Obleser et al., 2011; Knoll et al., 2012). On the single word level, the left insula has been reported to activate for the repetition of pseudowords more than words (Shuster, 2009) and for the repetition of pseudowords with novel syllables more than for pseudowords with familiar syllables (Moser et al., 2009). Brown et al., 2009 speculated that the left insula is involved in orofacial movement in general, such as lip movement, tongue movement or vocalization. This speculation is consistent with the findings that insular activation is not specific to verbal functions, but also activates for syllable singing compared with oral reading (Brown et al., 2009), and for tone (pitch) information, compared with verbal information (Koelsch et al., 2009). The studies of Moser et al., 2009 and Shuster, 2009 also suggested that the insula is more involved in unfamiliar vs. familiar motor plans.

Important for our study is the finding that activation of the insula related to language is not dependent on whether speech is overt or covert, i.e., if speech is actually produced or not (Fridriksson et al., 2009). This information can be taken to indicate that the insula is rather responsible for the planning, but not for the execution, of orofacial movement during speech production. In the light of this, our activation could be interpreted to reflect planning of articulation, even if the task doesn't require actual speech output. As this effect is stronger for the more difficult object topicalization structure, one interpretation could be that planning the articulation (thinking about how a sentence is actually phrased), helps the participant to understand contents that are difficult to extract.

The cingulate has been associated with cognitive control (Barch et al., 2001; Carter et al., 1999; van Veen and Carter, 2002). A common test to evoke activation in cingulate gyrus is the Stroop test. In this test, potentially incongruent information is presented via different channels: for example, words of colours are presented in either the written colour (congruent) or another colour (incongruent). In such tasks, the cingulate gyrus is consistently more active in the incongruent condition (Pardo et al., 1990). Studies of bilinguality show a role for the cingulate for switching between languages (Hervais-Adelman et al., 2011; Garbin et al., 2011). Binder et al., 2009 reviewed the role of the cingulate for functions such as working memory, response conflict, and error detection (Carter et al., 1999; Duncan and Owen, 2000; Owen et al., 2005; van Veen and Carter, 2002; Barch et al., 2001). Especially for the latter, the anterior cingulate gyrus seems most important.

In the context of our study, the cingulate gyrus appears to be more active controlling the reply during the truth-value judgement task for non-canonical than for canonical sentence structure. Since the non-canonical object-first structure is not as commonly used in everyday language (Gorrell, 2000), verifying the correctness of a sentence is more complicated. Only the identification of the case-marking reveals the distribution of the roles. This additional processing step requires a higher level of cognitive control, likely explaining the activation seen in this structure. Another explanation could be as discussed by (Knoll et al., 2012) for an anterior cingulate activation evoked by a similar study design, a “violation of an expectancy of a canonical subject-initial sentence structure”. Both interpretations would be in line with the observable activation in our study, underlining the role of the cingulate for cognitive control functions.

4.4 Lack of activation in expected brain regions

Complex grammar processing has constantly been associated with superior and middle temporal gyrus activation in previous studies (Friederici et al., 2009; Richardson et al., 2010; Cooke et al., 2002; Friederici et al., 2010). Thus, the fact that we did not find comparable results is puzzling. This paragraph is aimed to discuss this lack of expected activation.

In the literature, superior temporal gyrus has been associated with language comprehension, including prelexical-, word- and sentence-level (Leaver and Rauschecker, 2010; Specht et al., 2009; Cooke et al., 2002; Price, 2010). During language comprehension, activation was linked to phonological (Specht et al., 2009), lexical-semantic, and syntactic processing (Baumgaertner et al., 2002; Friederici et al., 2009). As for our tasks we don’t assume differences in the difficulty of phonological processing of the different sentence conditions, the focus of this discussion shall be on semantic and syntactic processing aspects. Involvement of left or bilateral posterior temporal regions in semantic processing was shown for lexical decision making in sentences requiring semantic integration processes by (Baumgaertner et al., 2002; Friederici et al., 2009), and for grammatically correct sentences with semantically plausible versus implausible meanings (Mashal et al., 2009). Regarding syntactic processing, Grodzinsky and Friederici, 2006 and Cooke et al., 2002 found posterior superior and middle temporal regions as syntactical movement complicates sentence structures. Further, Friederici et al., 2009 found such activation for hierarchal more than for linear sentence structure. While Grodzinsky and Friederici, 2006 and Friederici et al., 2009 suggested that this region subserves the integration of syntactic information, the study of Leff et al., 2009b interpreted its involvement in auditory short term-memory functions.

Looking at preceding object topicalization studies, activation in superior temporal gyrus and sulcus was identified by Ben-Shachar et al., 2004, Obleser et al., 2011 and Knoll et al., 2012. While Ben-Shachar et al., 2004 interpreted this activation as engagement in keeping the moved element in memory, Obleser et al., 2011 and Knoll et al., 2012 assumed its contribution to be relevant for abstracting syntactic information.

Comparing our study to the study of Ben-Shachar et al., 2004, differences in study design might be responsible for the different pattern of activation. These authors used long, complex sentences with two objects, varying between subject-initial and object-initial structure. Participants did not have to decide for each sentence on the distribution of the roles, but had to answer questions referring to different information transported in the sentence, not necessarily related to actions. Obleser et al., 2011 used sentences with one direct and one indirect object, varying between one canonical and two non-canonical grammatically correct word orders. The sentence conditions were developed for adults and were therefore distinctly more complex than ours. The sentences were presented acoustically and had to be matched to accompanying pictures. The participants had to decide for a match or mismatch via two push-buttons in the right and left hand. Comparing their study (Experiment 1) to ours, we believe that the less complex sentences in our study explain why we didn’t find a corresponding cluster in posterior superior temporal region. It is also important to note that these sentences also do not differ much from our truth-value judgement task (Obleser et al., 2011). This effectively reduces the effect size between the conditions, making the detection of differences less likely. The study of Knoll et al., 2012 was more similar in study design to ours, but examined preschool children. In their preceding pilot study with healthy adults, only Broca's area was investigated using a predefined region of interest. Thus, the different results of our study and previous studies investigating the processing of non-canonical and canonical word-order might be explained by differences in study design, complexity of sentence conditions, and the population under study.

4.5 Limitations

As this study was designed to develop a task to be applied in healthy children and in children with left-hemispheric brain lesions, these constraints limited our options in several respects. For one, the selection of stimulus material needed to be appropriate for such a population, which we tried to achieve using familiar objects (playmobil® figures). Further, the time constraints on how long a task can be are more pressing when investigating children (Thomas and Casey, 2000; Wilke et al., 2003). The level of difficulty was adapted for children in such a way that the task should be challenging, but not frustrating to perform. This, of course, implies the task to be rather simple for healthy adults with above-average language abilities. Nevertheless, we were able to observe a clear effect of difficulty in various brain regions, suggesting that the ceiling effect did not completely preclude drawing inferences from this task in this population.

As overt language production during fMRI data acquisition automatically implies increased movement artefacts (Birn et al., 2004), especially when working with children (Thomas and Casey, 2000), we wanted to additionally evaluate another option. To this effect and for the purpose of investigating both speech production and comprehension, we mixed blocks of sentence repetition with blocks of the truth-value judgement task, therefore diminishing the strength of our results for both tasks in terms of a reduced scanning time per task. The randomizing of sentence conditions within the blocks offered the opportunity to separately evaluate the data of all four sentence conditions, but additionally sacrificed power for each sentence condition in this event-related statistical analysis.

Finally, using fMRI imposes limits on the conclusions to be drawn from our results, due to the drawbacks discussed in the introduction. A multimodal imaging approach (in combination with behavioural studies) would be an alternative for future studies.

4.6 Conclusion

Our newly-designed language production and comprehension task was successfully implemented and applied in a sample of healthy adults. It revealed new insights into the processing of object topicalization (as a complex grammatical structure) as compared to the (more simple) canonical sentence structure.

The activation pattern in several previously-described core language regions in the truth-value judgement task suggests that this is an interesting approach to investigating the language system. Simultaneously, the high performance in adults supports the notion that it is both suitable and promising for the investigation of word-order effects in children and adolescents affected by early left-hemispheric brain lesions.

5 Abstract

Following left-hemispheric lesions occurring in the pre- or perinatal time period, reorganization of language into homotopic brain regions in the right hemisphere can be observed. This compensatory mechanism allows for the later development of language abilities without clinically-obvious deficits. However, when investigating these children closer, specific language deficits can be detected. A behavioral pilot-study by Schwilling et al., 2012 found significant differences between patients with reorganized (right-hemispheric) language representation and healthy controls in the understanding of non-canonical, object-first sentence structure. Inspired by these results, we aimed to develop a paradigm for the exploration of the neural underpinnings of these differences. Specifically, we were interested in the representation of the processing of complex non-canonical, compared to simple canonical sentence structures. The paradigm should be suitable for children, adolescents, and young adults with reorganized language. This work describes how such a paradigm was developed, implemented, and successfully piloted in 23 young, healthy adults (12 females; mean age: m = 24.39 ± 3.39 years). It consisted of 12 child-friendly, short scenarios with two non-canonical and two canonical acoustic sentence conditions each. The 48 sentences were recorded by a professional female speaker. Each sentence was visualized in a playmobil® stop-motion movie. As a non-invasive imaging method, functional magnetic resonance imaging was used. A sentence-repetition (SR) task and a truth-value-judgement (TVJ) task were embedded into a mixed block- and event-related design. During the SR-task, subjects were instructed to repeat the acoustically-presented sentences (100% concordance of video and sentence). During the TVJ-task, subjects had to decide whether acoustically-presented sentences and the stop-motion movies corresponded in content or not (50% concordance of video and sentence). Within the alternating blocks, the two non-canonical and two canonical sentence conditions were pseudo-randomized. In both tasks, the non-canonical sentence conditions were contrasted with the canonical sentence conditions.

Subjects had no difficulties in repeating the different sentence conditions. Activation during the SR-task was seen in the left superior frontal gyrus, in the right precentral gyrus, and in the left parahippocampal gyrus. During the TVJ-task, error rates for the non-canonical sentence conditions were higher than for the canonical sentence conditions (11,9% non-canonical; 6,1% canonical; p = 0,0063). Activation during the TVJ-task was seen in the left insula, in the left inferior frontal gyrus (pars opercularis), in the right inferior frontal gyrus (pars orbitalis), and in the left cingulate gyrus.

Activation during the SR-task in the left parahippocampal region is interpreted to indicate that object-first sentences depend on more support for the encoding and/or retrieval compared to subject-first sentences. This could either be explained by the difference of familiarity and frequency of occurrence in daily language, or by their complexity. Activation in the right precentral gyrus could point to a higher demand of auditory-to-articulatory mapping for the non-canonical sentence structure. During the TVJ-task, activation in the left insula could reflect motor planning of covert speech which is known to support understanding complex content. Left cingulate activation likely reflects a more active cognitive control of the reply during the non-canonical sentences of our task. An explanation could be the difference of familiarity or a violation of the expectation of the more commonly-used subject-first sentences. The involvement of both left and right inferior frontal gyrus (left pars opercularis, right pars orbitalis) suggests higher syntactic and semantic processing demands for the non-canonical compared to the canonical sentence structure.

The high performance of our participants in both tasks points to a certain ceiling effect, which might have lowered the observable effect sizes. However, this should be less of a problem when investigating children and adolescents. The higher error rate for the more complex non-canonical sentence structure, combined with an activation pattern in core language regions, suggests that this task is an interesting approach to investigate this very particular aspect of the language system. Taken together, this supports the notion that it is both suitable and promising for the investigation of word-order effects in children and adolescents affected by early left-hemispheric brain lesions.

5.1 Zusammenfassung

In der Folge von links-hemisphärischen Hirnläsionen in der Prä- und Perinatalzeit kann eine Reorganisation von Sprachfunktionen in homotope Hirnareale der rechten Hemisphäre beobachtet werden. Dieser Kompensationsmechanismus ermöglicht später eine Sprachentwicklung ohne klinisch offensichtliche Schwächen. Wenn man die betroffenen Kinder jedoch genauer untersucht, können durchaus distinkte Sprachdefizite gefunden werden. Eine Verhaltensstudie von Schwilling et al., 2012 entdeckte signifikante Unterschiede zwischen Patienten mit reorganisierter (rechts-hemisphärischer) Sprachorganisation und einer gesunden Kontrollgruppe im Verstehen von nicht-kanonischen, objekt-topikalisierten Satzstrukturen. Inspiriert durch diese Ergebnisse war es unser Ziel ein Paradigma zu entwickeln, um die neuronalen Grundlagen dieser Unterschiede zu untersuchen. Insbesondere interessierte uns hierbei die Repräsentation der Verarbeitung von komplexen (nicht-kanonischen) im Vergleich zu einfachen (kanonischen) Satzstrukturen. Das Paradigma sollte geeignet sein für die Untersuchung von Kindern, Jugendlichen und jungen Erwachsenen mit reorganisierter Sprache. Diese Arbeit beschreibt, wie solch ein Paradigma entwickelt, umgesetzt und an 23 jungen Erwachsenen Probanden (12 Frauen; Durchschnittsalter: $m = 24{,}39 \pm 3{,}39$ Jahre) erfolgreich pilotiert wurde. Es wurden 12 kindgerechte Szenarien mit jeweils 2 nicht-kanonischen und 2 kanonischen Satzbedingungen entwickelt. Die 48 Sätze wurden durch eine professionelle Sprecherin aufgenommen. Die visuelle Umsetzung erfolgte anhand kurzer Playmobil® stop-motion Filme. Als nicht-invasive bildgebende Methode wurde die funktionelle Magnetresonanztomographie (fMRT) genutzt. Eine Satz-Wiederholungs- („sentence repetition“, SR) und eine Wahrheits-Beurteilungs-Aufgabe („truth value judgement“, TVJ) wurden in ein gemischtes Block- und Event-Related Design eingebettet. Während der SR-Aufgabe mussten die Probanden den über Kopfhörer dargebotenen Satz laut und deutlich wiederholen (100% Konkordanz von Satz und Film). Während der TVJ-Aufgabe mussten die Probanden entscheiden, ob akustischer Satz und stop-motion Film inhaltlich übereinstimmten (50% Konkordanz von Satz und Film). Innerhalb der Aufgaben waren die 4 Satzbedingungen pseudorandomisiert. In beiden

Aufgaben wurden die 2 nicht-kanonischen gegen die 2 kanonischen Satzbedingungen kontrastiert.

Die Probanden zeigten keine Fehler bei der Wiederholung der Satzbedingungen. In der SR-Aufgabe zeigten sich Aktivierungen im linken superioren frontalen Gyrus, im rechten präzentralen Gyrus und im linken parahippocampalen Gyrus. Während der TVJ-Aufgabe waren die Fehlerraten für die nicht-kanonischen Satzbedingungen signifikant höher als für die kanonischen Satzbedingungen (11,9% nicht-kanonisch; 6,1% kanonisch; $p = 0{,}0063$). In der TVJ-Aufgabe zeigten sich Aktivierungen in der linken Insel, im linken inferioren frontalen Gyrus (pars opercularis), im rechten inferioren frontalen Gyrus (pars orbitalis) und im linken Cingulum.

Die Aktivierung während der SR-Aufgabe im linken parahippocampalen Gyrus wird interpretiert als Hinweis darauf, dass das Merken und/oder Reproduzieren von objekt-topikalisierten Sätze auf mehr Unterstützung dieser Struktur angewiesen ist als bei kanonischen Satzstrukturen. Dies könnte durch das seltenere Auftreten von nicht-kanonischen Sätzen im Alltag oder durch deren höhere Komplexität zu erklären sein. Die Aktivierung im rechten präzentralen Gyrus könnte auf eine erschwerte auditorisch-zu-artikulatorische Planung hinweisen. Während der TVJ-Aufgabe könnte die Aktivierung in der linken Insel die motorische Planung von verdeckter Sprache widerspiegeln, welche zum Verstehen komplexer Inhalte genutzt wird. Die Aktivierung im linken Cingulum reflektiert wahrscheinlich eine ausgeprägtere kognitive Kontrolle bei der Bearbeitung der nicht-kanonischen Satzbedingungen. Dies könnte durch die unterschiedliche Vertrautheit der Strukturen oder durch ein nicht-Erfüllen der Erwartung der häufigeren kanonischen Struktur zu erklären sein. Die Beteiligung von linkem und rechtem inferiorem frontalen Gyrus (linker pars opercularis, rechter pars orbitalis) deutet auf höhere syntaktische und semantische Anforderungen für die Verarbeitung von nicht-kanonischen im Vergleich zu kanonischen Satzbedingungen hin.

Das gute Abschneiden unserer Probanden in beiden Aufgaben deutet auf einen gewissen Deckeneffekt, welcher die resultierende Effektstärke limitiert haben könnte. Dies dürfte allerdings bei Kindern und Jugendlichen ein geringeres

Problem sein. Die signifikant höhere Fehlerrate bei der nicht-kanonischen Satzstruktur, verbunden mit einem Aktivierungsmuster in Kern-Sprachregionen, deutet darauf hin, dass diese Aufgabe einen interessanten Ansatz für die Untersuchung dieses speziellen Aspektes des Sprachsystems bietet. Zusammenfassend lässt sich ableiten, dass dieses Paradigma sowohl geeignet wie auch vielversprechend ist für die Untersuchung der spezifischen Defizite bei Kindern und jungen Erwachsenen mit links-hemisphärischen Hirnläsionen.

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Die statistische Auswertung erfolgte eigenständig nach Anleitung durch PD Dr. med. Marko Wilke und PD Dr. rer. nat. Karen Lidzba.

Ich versichere, die Arbeit selbständig nach Anleitung durch PD Dr. med. Marko Wilke und PD Dr. rer. nat. Karen Lidzba verfasst zu haben und keine weiteren als die von mir angegebenen Quellen oder Hilfsmittel verwendet zu haben.

Welzheim, den 02.08.15

Christina Schlegel

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