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Resting-state functional connectivity in the brain and its relation to language development in preschool children

Der Fakultät für Biowissenschaften, Pharmazie und Psychologie

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Cogito ergo sum.

I think, therefore I am.

- René Descartes

To the scientific spirit.

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Resting-state functional connectivity in the brain and its relation to language development in preschool children

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Dissertation

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Human infants have been shown to have an innate capacity to acquire their mother tongue. In recent decades, the advent of the functional magnetic resonance imaging (fMRI) technique has made it feasible to explore the neural basis underlying language acquisition and processing in children, even in newborn infants (for reviews, see Kuhl & Rivera-Gaxiola, 2008; Kuhl, 2010).

Spontaneous low-frequency (< 0.1 Hz) fluctuations (LFFs) in the resting brain have been shown to be physiologically meaningful in the seminal study (Biswal et al., 1995). Compared to task-based fMRI, resting-state fMRI (rs-fMRI) has some unique advantages in neuroimaging research, especially in obtaining data from pediatric and clinical populations. Moreover, it enables us to characterize the functional organization of the brain in a systematic manner in the absence of explicit tasks. Among brain systems, the language network has been well investigated by analyzing LFFs in the resting brain.

This thesis attempts to investigate the functional connectivity within the language network in typically developing preschool children and the covariation of this connectivity with children's language development by using the rs-fMRI technique. The first study (see Chapter 2.1; Xiao et al., 2016a) revealed connectivity differences in language-related regions between 5-year-olds and adults, and demonstrated distinct correlation patterns between functional connections within the language network and sentence comprehension performance in children. The results showed a left fronto-temporal connection for processing syntactically more complex sentences, suggesting that this connection is already in place at age 5 when it is needed for complex sentence comprehension, even though the whole functional network is still immature. In the second study (see Chapter 2.2; Xiao et al., 2016b), sentence comprehension performance and rs-fMRI data were obtained from a cohort of children at age 5 and a one-year follow-up. This study examined the changes in functional connectivity in the developing brain and their relation to the development of language abilities. The findings showed that the development of intrinsic functional connectivity in preschool children over the course of one year is clearly observable and individual differences in this development are related to the advancement in sentence comprehension ability with age.

In summary, the present thesis provides new insights into the relationship between intrinsic functional connectivity in the brain and language processing, as well as between the changes in intrinsic functional connectivity and concurrent language development in preschool children. Moreover, it allows for a better understanding of the neural mechanisms underlying language processing and the advancement of language abilities in the developing brain.

Contents

1 General introduction

Language is one of the unique human capacities. Human infants learn their mother tongue in the first years of life easily and efficiently (for reviews, see Dehaene-Lambertz & Spelke, 2015; Friederici, 2005; Kuhl & Rivera-Gaxiola, 2008; Kuhl, 2010). A large body of research has shown the inherent competence of infants in language perception and acquisition. For example, early studies have observed that infants as young as 1 month of age are able to respond to speech sounds (Eimas et al., 1971) and they are also able to discriminate the acoustic cue underlying the phonemic distinction between voiced and voiceless stop consonants independent of relevant linguistic exposure at the age of 2 months (Streeter, 1976). Infants show a preference for phonemes in their native language by the age of 6 months, suggesting that the phonetic perception is shaped by the specific language that infants are exposed to, and it is detectable in the first half year of life (Kuhl et al., 1992). Language acquisition was found to be closely related to the statistical properties of the language input in 8-month-old infants (Saffran et al., 1996). Another study further investigated the statistical learning effect in language acquisition, and unveiled that infants aged 6 and 8 months are sensitive to the statistical distribution of speech sounds in the input language and this sensitivity influences speech perception (Maye et al., 2002). These findings demonstrate that infants are capable of distinguishing speech sounds and learning familiar speech patterns very quickly before the end of the first year.

The innate ability to acquire the mother tongue is regarded as a most fascinating puzzle in understanding the neural underpinnings of language, and a large number of theoretical and empirical studies have been presented to solve the mystery of language acquisition in young children. Over the past decades, with the advent of non-invasive neuroimaging techniques, there have been numerous findings of the workings of the brain, which have allowed for a more comprehensive understanding of language acquisition and development in the early years of life.

The neural basis of language comprehension and production has been associated with superior temporal (Wernicke's) and inferior frontal (Broca's) cortical areas respectively. But, recent studies have reported a wide range of regions involved in language processing by employing blood oxygen level dependent (BOLD) functional magnetic resonance imaging (fMRI) (for a review, see Price, 2010). A recent study using the functional connectivity approach suggested a more extended network, including not only cortical regions in prefrontal, temporal, and parietal cortices but also subcortical regions in bilateral caudate, left putamen/globus pallidus, and subthalamic nucleus (Tomasi & Volkow, 2012). So far, most of the fMRI studies with regard to language processing have focused on adults, and fMRI data to characterize language processing in young children are still limited, not to mention data describing language-brain relationship in infants and young children (Skeide & Friederici, 2016).

In the past two decades, the resting-state fMRI (rs-fMRI) technique has been extensively used as a powerful tool to understand brain functions after the seminal study (Biswal et al., 1995). Different from traditional BOLD fMRI technique, no specific task is required for rs-fMRI, and data obtained in a relatively short scan length (as brief as 5 min) appear to be valid and reliable (Van Dijk et al., 2010). Thus, rs-fMRI has great advantages in acquiring data from pediatric and clinical populations who are not able to perform complex tasks or stay long in the scanner (for reviews, see Power et al., 2010; Uddin et al., 2010). Moreover, it provides an elegant way to characterize functional organizations of the brain in a systematic manner and to study various systems simultaneously (Cole et al., 2014; Smith et al., 2009). Among others, the language network has been well investigated by the analysis of low-frequency (< 0.1 Hz) fluctuations

(LFFs) in the resting brain (Tomasi & Volkow, 2012; Xiang et al., 2010). Xiang et al. (2010) first showed perisylvian language networks in a resting-state functional connectivity study, and Tomasi & Volkow (2012) demonstrated a widespread language network and its characterizations. These findings provide new insights into our understanding of the brain organizations involved in language functions.

So far, however, our knowledge of the functional brain connections within the language network with regard to language processing and their changes during the course of typical development in children is still very sparse, which does not allow us to relate the development of language abilities to brain maturation with age. Therefore, in the present thesis, using the rs-fMRI technique, I aimed to investigate the functional connectivity in the network of language-relevant brain regions and its relation to language processing in preschool children on the one hand, and to explore the developmental changes in this intrinsic connectivity and its response to language development in the typically developing brain on the other hand.

1.1 A theoretical psycholinguistic framework of sentence processing

Human language is not simply naturally acquired devoid of any context or pressure. Instead, language acquisition is a dynamic process interacting with multiple factors, including auditory patterns, articulatory patterns, social patterns, patterns implicit in the input, and pressures arising from general aspects of the cognitive system (for a review, see MacWhinney, 1998). Under this conception, the Competition Model was proposed based on cross-linguistic studies of sentence processing in young children, and it treats language learning as an emergent process with the goal of investigating the competitive relationships between lexical items, phonological forms, and syntactic patterns during language processing (Bates & MacWhinney, 1982, 1989; Bates et al., 1984; MacWhinney, 1987). The term “competition” refers to the competition of assigning the actor’s role among several nouns in a sentence. For example, consider the sentence “The boy is petting the cat”: two nouns are involved in this sentence, and the competition occurs while deciding which one is the actor. In a sentence, the thematic roles could be basically characterized by proto-agent and proto-patient, and an agent carries more agentivity property than a patient based on the degree of agentivity (Dowty, 1991). Because of the contrary relationship between the agent and patient, there commonly exists a direct competition for the agent and patient identification.

The main focus of the Competition Model is the use of different cues for sentence comprehension. The cue is an information source that can be used by the language user to understand sentences in a language. When multiple cues are available for sentence interpretation, either competition or convergence between different cues will happen, which is dependent on the directions that different cues point toward. For instance, in the sentence “the carrot bites the cat”, word order and animacy cue point to different nouns as the agent of the action (word order implies “the carrot” while animacy cue suggests “the cat”) where competition occurs, but in the sentence “the cat bites the carrot”, both word order and animacy cue point to the same noun – “the cat” – as the agent where convergence happens.

An earlier study found that in case-inflected languages such as German, utterances of children rely on the dominant word order that serves as a cue in sentence comprehension before they have mastered the morphology of their language (Brown, 1973). However, findings from a cross-linguistic study concluded that it is not a universal predisposition for children to use word order as a cue to comprehend sentences. Rather, the use of a cue is dependent on the regularity and consistency of the language (Slobin & Bever, 1982), which is consistent with the claims of the

Competition Model. According to this model, learning of language forms is closely associated with the accurate recording of multiple exposures to words and patterns in different contexts, and sentence interpretation is supported by linguistic cues (Bates & MacWhinney, 1982; Bates et al., 1984; MacWhinney, 2012).

The model claims that the acquisition of a certain cue strategy during the course of language development is based on competition between the strength of cues, reflecting the extent of cues dominating or controlling language comprehension. The cue strength is primarily determined by cue validity, which is characterized by both availability and reliability. According to the model, the reliability of cues is defined as the proportion of times that the cue is correct over the total number of occurrences of the cue, and the availability of the cue is the proportion of times that the cue is available over the times the cue occurring; the product of cue reliability and cue availability is cue validity (MacWhinney, 2012). Cue reliability is the basic factor for cue validity, indicating that a presented cue is not misleading or ambiguous, and a cue with high reliability will lead to a correct functional choice. The availability of a cue represents to what extent it is available whenever needed, and a cue with high availability always exists for use. The most valid cues are those with both high reliability and availability, but cues with low reliability are not valid anymore even when they are highly available.

Previous behavioral results from cross-linguistic studies provide evidence for the different cue strategies in adults from different language backgrounds. In English, the dominant cue is the word order, i.e., subject-verb-object order; in German, case marking is the strongest cue, and the article serves as a cue to identify an agent; in Italian, agreement is the dominant cue; in Russian, case-marking, the case suffix in nouns, is the major cue; in Chinese, animacy cue is mostly used to point out the agent (Kempe & MacWhinney, 1998; Li et al., 1993; MacWhinney, 2001;

MacWhinney et al., 1984). Besides, the Competition Model has often been applied to the prediction of cue usage and its changes in young children. Given their immature language ability, cues are still inadequately processed in young children, but they can make full use of the cues to which they are frequently exposed, thereby showing different cue strategies across languages. For example, English-speaking children tend to use word order while Italian-speaking children tend to use animacy cue as young as 2 years of age (Bates et al., 1984), and Turkish-speaking children prefer case markers as cues with exposure to more reliable markers (Slobin & Bever, 1982). Moreover, ample behavioral evidence has shown that the factor affecting the cue strength varies with language development. At the very beginning, the acquisition of a cue is mainly dependent on cue availability because infants are only familiar with cues that are frequently presented in the language input, but with the increase of simultaneously presented multiple cues in the expanding language input, cue reliability becomes more important than cue availability and even dominant in the cue strength based on the proficiency level (MacWhinney, 2012).

Among languages, German is the focus of this thesis, which has been widely studied in order to confirm the validity of the Competition Model because of the language's complexities of declension. The results successfully matched the model and showed the crucial role of cues in the acquisition of German declension (MacWhinney et al., 1989). Cues in German include case marking, subject–verb agreement, animacy, and word order, and among these cues case-marking is the strongest in adults (MacWhinney et al., 1984). In contrast to English, German has a relatively free word order and therefore cues other than word order are often needed to comprehend sentence information for early learners. The following example illustrates this:

(1) Canonical subject-initial sentence:

Der$_{[NOM]}$ Tiger zieht den$_{[ACC]}$ Fuchs.

“The tiger pulls the fox.”

(2) Non-canonical object-initial sentence:

Den$_{[ACC]}$ Fuchs zieht der$_{[NOM]}$ Tiger.

“The tiger pulls the fox.”

The functions of the noun phrases in the sentences above are marked by the nominative case (NOM) as a subject or the accusative case (ACC) as an object. The nominative case article “der” indicates “der Tiger” as the agent (actor) of the sentence, while the accusative case article “den” points to “den Fuchs” as the patient (receiver) of the action. As shown in the example sentences, the order of the noun phrases does not affect their functions, but the case marking (nominative or accusative) of the noun’s article conveys the information. In this example, flexible word order does not carry reliable cue for comprehending these sentences, but instead, case-marking cue has high availability. Based on the Competition Model, cue reliability is the main determinant of the cue strength, and low reliability of word order in German makes it hardly a dominant cue, whereas case-marking cue is a more practical candidate due to its high availability (MacWhinney et al., 1984). As mentioned earlier, however, a cue with high availability is not valid at all if its reliability is low.

Previous research has found that, compared to English and Italian, German has a strong preference for animate actors, indicating animacy serving as an important extra cue to rely on except for case marking (MacWhinney et al., 1984). A second-language learning study observed that learners of German rely more on animacy information to supplement the case-marking cue when it is weak owing to the syncretism in the nominative and accusative cases of German feminine, neuter, and plural nouns (Kempe & MacWhinney, 1998). Research on German children 2-7 years showed that 2- to 3-year-olds rely mainly on the animacy cue and the case-marking cue is dominant from age 4 on, but agreement is the strongest cue afterward even in adults (Lindner, 2003). These empirical findings in the early stage of acquisition of German suggest that case-marking, despite its high availability, is not a valid cue under certain conditions because of its low reliability, and the animacy cue comes into play until the case-marking cue becomes more reliable.

1.2 A neuroscientific model of language development

During the past decades, the application of neuroimaging techniques, including electroencephalography (EEG)/event-related potentials (ERP), magnetoencephalography, fMRI, and near-infrared spectroscopy, has made it possible to explore the brain mechanisms underlying early language acquisition (for reviews, see Kuhl & Rivera-Gaxiola, 2008; Kuhl, 2010). Among these techniques, ERP has been the most widely used in investigating speech and language processing in infants and young children due to its operability and validity. Findings from ERP studies provide evidence for quantitative changes in language processing, demonstrating neurophysiological correlates of language acquisition in early childhood. In a review study, Friederici (2005) summarized the trajectory of language acquisition in infants from a number of previous ERP studies: infants are able to discriminate different phonemes in the first 2 months of life; they learn knowledge of stress patterns and phonotactic rules between 5–12 months; they develop phonotactic knowledge associated with lexical-semantic processes between 12–14 months and they are able to process semantics of words in picture contexts at 14 months; infants process words in sentential contexts around 30 months and they show electrophysiological response patterns to syntactic violations at 32 months. With respect to syntax acquisition, research has shown that 2-year-old toddlers are able to process syntactic information of sentences during listening to spoken sentences (Bernal et al., 2010), and they are also sensitive to syntactic errors in the form of phrase structure violations (Oberecker & Friederici, 2006).

Due to its relatively high spatiotemporal resolution, fMRI has been employed prevalently in adults and has even been applied to infants. However, given the difficulties of obtaining data from such young populations, only a few fMRI studies concerning language processing have been conducted in infants (Dehaene-Lambertz et al., 2002; Dehaene-Lambertz et al., 2006; Perani et al., 2011). Dehaene-Lambertz et al. (2002) performed an fMRI experiment in awake and sleeping 3-month-old infants to examine their brain responses while listening to sentences of their native language presented either forward or backward. The authors observed activations in adult-like left-lateralized regions, such as superior temporal and angular gyri. Another fMRI study investigated 3-month-old infants' BOLD response to short sentences of their mother language presented in a slow event-related paradigm (Dehaene-Lambertz et al., 2006). This study observed slow BOLD responses in the bilateral superior temporal regions and Broca's area, and found activations in Broca's area engaged in processing repeated sentences. Perani et al. (2011) examined brain activations in 2-day-old newborns during listening to a story presented in three different conditions (i.e., normal speech, hummed speech, and flatted speech) and found strong activations in the bilateral superior temporal gyrus (STG) and inferior frontal gyrus (IFG) for both normal and hummed speech as reported in adults. In addition, this study confirmed activations in both hemispheric auditory cortices for normal speech, but with a right predominant activation in the right hemisphere. These findings demonstrated primary evidence for the brain mechanisms of early language processing.

Recently, Skeide & Friederici (2016) proposed a model of the ontogeny of the cortical language network based on neuroimaging data from EEG and fMRI studies describing the acquisition of language in early years of life (Figure 1.1). According to this model, there are two main developmental stages. The first stage, referring to bottom-up processing, is primarily implemented in the bilateral temporal cortices and acquired in the early childhood. In this stage, with the exposure to language inputs and the pruning of neurons, infants are gradually able to deal with phonological, prosodic, and semantic information. The second stage is to develop the ability of sentence-level syntactic processing in a top-down manner, mainly involving the left inferior frontal and superior temporal cortices. By 2 years of age, children can already process semantic relations in a sentence (Friedrich & Friederici, 2010). At age 3, they are able to process syntactic information in sentences, but still inadequately. Thus, young children make use of semantic information in sentences as a cue to understand syntactically complex sentences until around 9 years of age (Skeide et al., 2014). This ability continues to increase into adulthood, as it is related to the cortical specialization of the left IFG and left posterior STG and it is also associated with the maturation of their underlying structural connection. More details on this point will be outlined in the following section.

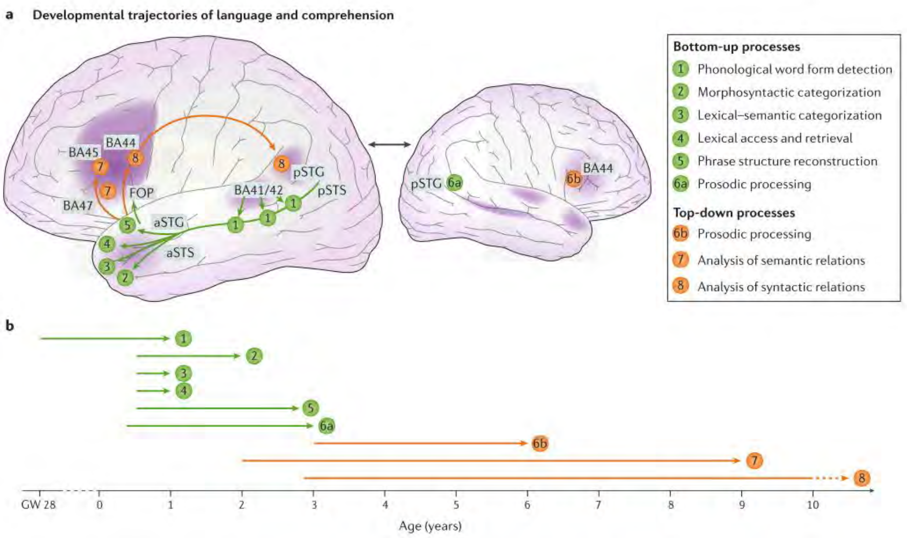

Figure 1.1 The model of the ontogeny of the cortical language network (a), including two stages: bottom-up processes (colored in green) and top-down processes (colored in orange); the corresponding timeline of language acquisition (b; age in years). Arrows indicate the assumed flow of information along interconnecting white matter fiber tracts. aSTG: anterior superior temporal gyrus; aSTS: anterior superior temporal sulcus; pSTG: posterior superior temporal gyrus; pSTS: posterior superior temporal sulcus. (Figure adapted from Skeide & Friederici (2016)).

1.3 Neural basis underlying language processing

1.3.1 Ventral and dorsal pathway

The language processing framework was suggested to be characterized by two divergent processing streams (Hickok & Poeppel, 2000) and subsequently, it was extended to describe the functional anatomy of language (Hickok & Poeppel, 2004). In this extended framework, a ventral pathway connecting the left superior temporal sulcus (STS) and posterior inferior temporal regions (i.e., parts of the middle temporal gyrus (MTG) and inferior temporal gyrus) is involved in sound-to-meaning mapping, and a dorsal pathway connecting the left inferior parietal and ventral frontal cortices is engaged in sound-to-motor mapping (Hickok & Poeppel, 2004). These two pathways have been widely acknowledged as the brain basis of language processing (e.g., Friederici, 2012a; Hickok & Poeppel, 2007; Rauschecker, 2012; Rauschecker & Scott, 2009; Saur et al., 2008). Combining fMRI and a diffusion tensor imaging approach, this model was further tested in terms of its neuroanatomical basis, which was identified to comprise a dorsal pathway connecting the superior temporal lobe and premotor cortices in the frontal lobe via the arcuate and superior longitudinal fasciculus (AF/SLF) and a ventral pathway connecting the middle temporal lobe and the ventrolateral prefrontal cortex via the extreme capsule (Saur et al., 2008).

On the basis of numerous functional and anatomical neuroimaging studies, the dual-pathway model was refined and subdivided into double ventral and dorsal pathways with distinct functions in language processing (for reviews, see Friederici, 2011, 2012a) (Figure 1.2). One ventral pathway connecting BA 45 and the temporal cortex via the extreme capsule fiber system is related to sound-to-meaning mapping, while the other ventral pathway connecting the anterior STG and IFG is assumed to support processes of local syntactic structure building. One dorsal pathway connecting the posterior STG/STS to the premotor cortex via the AF/SLF is engaged in auditory-to-motor mapping, and the other dorsal pathway connecting the posterior STG/STS to BA 44 via the AF/SLF is involved in processing syntax, especially processing complex syntactic information.

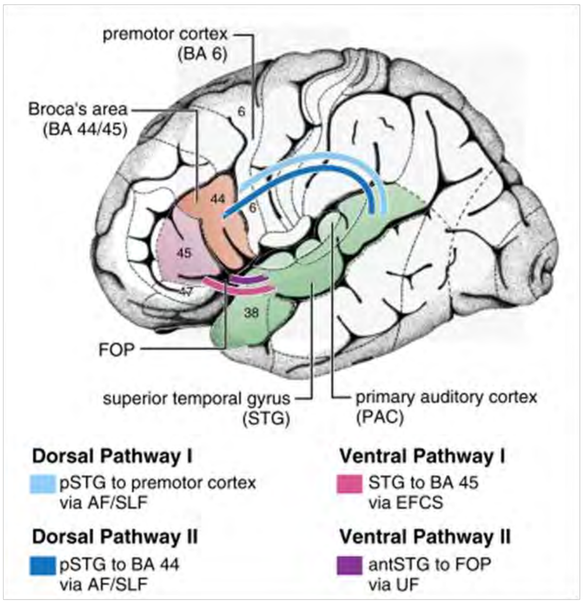

Figure 1.2 Language processing pathways on the basis of structural connectivity, including two ventral and two dorsal pathways. BA: Brodmann area; p: posterior; ant: anterior; FOP: frontal operculum; AF: arcuate fasciculus, SLF: superior longitudinal fasciculus; EFCS: extreme fiber capsule system; UF: uncinate fasciculus. (Figure adapted from Friederici (2011)).

With regard to brain maturation, previous studies in newborn infants and young children have offered primary evidence for the different developmental rates of fiber tract connections underlying the ventral and dorsal pathways (Brauer et al., 2011; Brauer et al., 2013; Broce et al., 2015; Perani et al., 2011). It has been demonstrated that the ventral pathway is already present at birth and matures rapidly; however, one part of the dorsal pathway, connecting the temporal cortex to Broca's area, is still underdeveloped at the age of seven years, while the other part of the dorsal pathway connecting the temporal to the premotor cortices is already present at birth (for a review, see Friederici, 2012b). The immature fiber connection between the temporal cortex and Broca's area is regarded to be associated with the inability of processing syntactically complex sentences in young children (for a review, see Friederici, 2012b). The close relationship between brain maturation and the concurrent development of sentence comprehension in children will be described in detail, and prior to this, the brain basis of sentence processing in adults will be introduced.

1.3.2 Sentence processing in adults

Over the last two decades, the neural mechanisms underlying sentence processing in adults have been well investigated using the fMRI technique. As the core of sentence comprehension, the process of syntactic information has been of a particular interest to researchers and has been studied thoroughly by different paradigms (e.g., word lists, sentence-level violations, and manipulation of word order).

In pioneering studies, it has been shown that sentence reading with varying syntactic complexity selectively activated Broca's area in the left IFG by using positron emission tomography (PET) (Caplan et al., 1998; Stromswold et al., 1996). An early fMRI study, using three types of sentences that differ in structural complexity, revealed a modulation effect of sentence complexity in activations of Broca's and Wernicke's areas as well as their right homologs, but activations were much stronger in the left hemisphere (Just et al., 1996). These results showed primary brain networks involved in sentence-level syntactic processing; however, sentence-level semantic information, which generally interacts with sentence syntax, had not been taken into account yet. In order to differentiate the brain regions engaged in auditory language comprehension, Friederici et al. (2000) varied the speech input in the presence or absence of semantic and syntactic information. The authors observed activations in the bilateral STG across different types of auditory language input, and additional activations in both left and right frontal cortices in violation conditions (i.e., syntactic speech and two word-list conditions) but not in the processing of normal speech. Moreover, the increase of activations in the bilateral anterior portion of the STG and deep portion of the left frontal operculum (FOP) was exclusively found in the focus of syntactic processes, suggesting an involvement of the left frontal and bilateral temporal cortices when processing syntactic information in sentences (Friederici et al., 2000). The differentiation of brain regions involved in processing sentence-level semantic and syntactic information was further investigated by using a violation paradigm, and it was demonstrated that semantic violations activated mainly the bilateral mid STG and the insular cortex, whereas the left anterior STG, the left posterior FOP, and the putamen were engaged in parsing syntactic violations (Friederici et al., 2003). Taken together, these findings suggest a temporo-frontal network related to both semantic and syntactic processes, but with distinct regions specialized for each process, such as the anterior STG specifically for syntactic processing (for a review, see Friederici, 2002).

ERP findings in adults suggest that the processing of syntactic violations can be divided into an early stage corresponding to processing phrase structure or agreement violations and a late stage corresponding to processing syntactic violations requiring syntactic repair or where temporarily ambiguous sentences require syntactic reanalysis (for reviews, see Friederici, 2002; Friederici & Kotz, 2003). Moreover, data from a number of experimental studies showed separable brain systems responsible for the early and late syntactic processes: the left anterior STG and left IFG are engaged in the early structure building processes, and the posterior STG and basal ganglia are involved in late syntactic revision and integration processes (for a review, see Friederici & Kotz, 2003).

It has been demonstrated that the ability to deal with hierarchically structured sequences such as embedded structures like A[AB]B is unique in human, although non-human primates can also process and learn simple sequences like ABAB (Fitch & Hauser, 2004). The ability of comprehending the hierarchical structure is crucial for humans to understand more complex sentence information in language, but it requires additional computation compared to simple sequences and thus non-human primates are not able to process embedded structures (Fitch & Hauser, 2004). Following this study, Friederici et al. (2006a) investigated the functional differentiation of the brain regions responsible for comprehending these two grammars of different complexity and observed that the left FOP was involved in parsing both grammar types while BA 44 was additionally engaged in hierarchical information processing. This study also revealed differential structural connectivity that the left FOP is connected to the left anterior temporal lobe via the fasciculus uncinatus, whereas BA 44 is connected to the posterior STG in the left hemisphere via the fasciculus longitudinalis superior (Friederici et al., 2006a).

In order to further appreciate the brain basis of syntactically complex sentence processing, several studies have been performed by manipulating the argument hierarchies in sentences, such as the order of the arguments. In the examples shown in Chapter 1.1, reproduced here for convenience: “Der$_{[NOM]}$ Tiger zieht den$_{[ACC]}$ Fuchs” and “Den$_{[ACC]}$ Fuchs zieht der$_{[NOM]}$ Tiger”, the first one with a sentence-initial nominative argument is considered a canonical subject-initial sentence, whereas the second one with a sentence-initial accusative argument is considered a non-canonical object-initial sentence. The object-initial sentence is syntactically more complex than the subject-initial sentence because of the non-canonical structure. Röder et al. (2002) used syntactically easy and difficult sentences by varying the word order of nominal phrases in German, and reported the strongest effect of syntactic difficulty in the left IFG, i.e., BA 44/45. Friederici et al. (2006b) manipulated the complexity and grammaticality of sentences within the domain of word order variations in German, and observed that the pars opercularis of the left IFG (left IFGoper; BA 44) was especially involved in processing structural complexity of such sentences. Another study on sentence embedding (nested structures) in German also showed the activation in BA 44 that was independent of working memory load (Makuuchi et al., 2009). Furthermore, although the complexity of sentence structures is accompanied invariably by increasing working memory or task difficulty, it has been confirmed that the involvement of the left BA 44 in processing syntactically complex sentences is attributed to the hierarchical structure of sentences rather than the increasing working memory demand (Grewe et al., 2005; Makuuchi et al., 2009).

Notably, the activation in the left posterior STG/STS has been widely reported for complex syntactic processing (Bornkessel et al., 2005; Friederici et al., 2006a; Friederici et al., 2010; Friederici et al., 2009; Kinno et al., 2008; Newman et al., 2010; Santi & Grodzinsky, 2010). For example, it was found that the left posterior STG/MTG showed more enhanced responses to non-canonical object-initial sentences, the syntactically more complex sentence type, than canonical subject-initial sentences (Kinno et al., 2008). Friederici et al. (2009) observed activations in the bilateral posterior superior temporal cortex (i.e., left posterior STG/STS and right posterior STS) during complex sentences processing, implying the importance of the posterior superior temporal regions for processing sentential syntactic information. Comparing sentences containing a syntactic violation with syntactically correct sentences, it was observed that syntactic phrase structure violations engendered strong activation in the mid to posterior STG/STS (Friederici et al., 2010). A meta-analysis based on a number of language-related neuroimaging studies revealed that higher syntactic processing demands primarily activate regions including BA 44/45 and the posterior STG/MTG in the left hemisphere (Hagoort & Indefrey, 2014).

Collectively, BA 44 together with the posterior STG/STS, constitutes a brain network in the left hemispheric inferior frontal and superior temporal areas for processing syntactic complexity of sentences (for a review, see Friederici, 2011). These findings have greatly enriched our understanding of the brain mechanisms underlying syntactic processing in adults, which could be regarded as a model of sentence processing in the human brain. Therefore, it provides a basis for studying typically developing children who are undergoing rapid development as their brains mature with age. Furthermore, it enables us to investigate the trajectory of language development from childhood to adulthood.

1.3.3 Sentence processing in young children

So far, mounting studies have investigated sentence processing in young children. However, research regarding different cues for sentence comprehension in early childhood is still sparse. As mentioned above, young children are still in the process of learning the valid cues for sentence comprehension, which has been examined by several behavioral studies (Chan et al., 2009; Dittmar et al., 2008; Gertner & Fisher, 2012; Lindner, 2003; Noble et al., 2011). For example, using a forced-choice pointing paradigm in English-learning children, Noble et al. (2011) found that, 2-year-olds can interpret agent and patient roles correctly in transitive sentences even with causal events, but cannot assign the conjoined agent in intransitive sentences with noncausal events until age 3. Dittmar et al. (2008) investigated cue usage in German children, and observed that 2-year-olds can understand sentences correctly when both word order and case marking are valid cues and that 5-year-olds can use word order alone but not case marking alone; the latter became a dominant stand-alone cue only in 7-year-olds. An ERP study by Schipke et al. (2012) focused on the processing of case-marking and argument structures in German children aged 3, 4.5, and 6 years. The results showed that children at the age of 3 and 4.5 years use mainly a word-order strategy, although children at 4.5 years are already sensitive to case-marking cue; at the age of 6 years children can use case-marking cues, but still need extra effort for correct thematic role assignment. These studies indicate that the cue strategy in young children varies with the cue strength at different stages, which in turn reflects the development of sentence comprehension abilities with age.

In recent years, fMRI studies investigating the neural basis of sentence processing in young children have emerged. Brauer & Friederici (2007) studied sentence comprehension in terms of semantic and syntactic processes using violations in sentences, and observed function-specific activations in the left FOP and bilateral STG in adults for violations. Instead, children showed no specific activations in the bilateral STG for different language conditions, but compared to adults, they additionally engaged areas in the left IFG to support higher demanding processes. This study suggests that perisylvian regions, especially the left IFG and STG, play a crucial role in sentence comprehension, and these regions have not yet specialized in 5- to 6-year-old children whose brains are still immature. Further, Brauer et al. (2008) examined the time courses of the BOLD hemodynamic responses in fMRI during sentence processing, involving the bilateral inferior frontal cortex (IFC) and superior temporal cortex (STC). This study showed an overall later peak of BOLD responses and a temporal primacy of right over left hemispheric activations in children compared to adults. Moreover, it observed much later IFC responses than STC responses in children, but the difference is less pronounced in adults. These findings indicate, due to slower and less automatic language processes, children need higher processing costs to comprehend sentences than adults, especially in the bilateral IFC. By using a multimodal approach and a syntactic processing task, Nuñez et al. (2011) showed a negative correlation between cortical thickness and the activation extent in the right IFG with age. The authors also reported a positive relationship between better syntactic performance and increased activation in the left IFG regardless of age, which suggests a decreased involvement of the right IFG for syntactic processing with age and an increased engagement in the left IFG with improved language skills.

The acquisition of case-marking cues for sentence interpretation was investigated by Knoll et al. (2012). This study tested typically developing German preschool children aged 6 years using auditorily presented short sentences which were either canonical subject-initial or non-canonical object-initial sentences. The results demonstrated that the left IFG was only activated for object-initial sentences but not for subject-initial sentences. In addition, individual differences showed a trend towards greater activation in the left IFG for object-initial sentences than for subject-initial sentences, but only in children with high grammatical performance. Yeatman et al. (2010) examined the brain activation network in response to increasing demands of complex sentences in children and adolescents aged 10-16 years using a cross-modal sentence-picture verification paradigm. This study reported greater activation of the IFG in response to increasing task demands in children with better language skills than children with average language abilities. In a recent study, sentence processing in children aged 3 to 4, 6 to 7, and 9 to 10 years was investigated using a paradigm that combined syntactic complexity and semantic plausibility (Skeide et al., 2014). Results found the syntax-semantics interaction in the left mid to posterior STG in 3- to 4- and 6- to 7-year-old children due to the reliance on semantic plausibility cues, whereas children at 10 years of age were able to process syntax independent of semantics and showed adult-like activation in the left IFGoper. These findings suggest that the processing of syntax becomes gradually separated from the processing of semantics, and they also present a functional specification of cortical regions that support complex syntax processing with age. Subsequently, the relation between brain function and language performance as well as between brain structure and language performance was tested in the same cohort of children (Skeide et al., 2015). The authors observed that enhanced performance in processing syntactically complex sentences was not only positively correlated with activations of core language processing regions – left IFGoper and posterior STG, but also associated with the maturation of AF connecting these two regions (Skeide et al., 2015).

Taken together, these findings show that language-related regions, mainly the left hemispheric IFG and posterior STG, are related to the processing of sentential syntactic complexity in developing children and that, noteworthily, activations in these regions can predict children's abilities to parse syntactically complex sentences (Skeide et al., 2015). It indicates that the investigation of individual differences might be useful for elucidating the neural mechanisms of language development in children.

1.4 Methodologies in brain research

In this section, I will firstly give an overview of the physical and physiological underpinnings of BOLD fMRI. On this basis, rs-fMRI will be introduced in detail as it is the main technique applied in the studies included in this thesis. Finally, I will outline several approaches used to analyze rs-fMRI data presented in Chapter 2.

1.4.1 BOLD functional magnetic resonance imaging

In the early 1990s, a seminal study by Ogawa et al. (1990) discovered that the BOLD contrast can provide maps of blood oxygenation in the brain by scanning anesthetized rodents at 7.0 Tesla MRI scanner. Shortly afterward, the BOLD contrast was firstly utilized in human neuroimaging and showed increases of the local signal during visual and motor stimulation, suggesting that the functional brain mapping is feasible by using intrinsic blood-tissue contrast (Kwong et al., 1992). At this time, other research independently published and reported similar findings in the human brain (Bandettini et al., 1992; Ogawa et al., 1992). These early studies consistently revealed that functional activation increases the regional cerebral blood flow (CBF), which results in an increased engagement of oxygenated blood.

Certain properties of blood hemoglobin in a magnetic field can explain the mechanisms behind the BOLD contrast. Continuing the pioneering study by Michael Faraday on the magnetic properties of hemoglobin (Faraday, 1846), Linus Pauling and Charles Coryell observed distinct magnetic susceptibilities of oxyhemoglobin and deoxyhemoglobin in a magnetic field (Pauling & Coryell, 1936). Specifically, they found that deoxygenated hemoglobin in veins disrupts the magnetic field like a little magnet because of the presence of iron in hemoglobin molecule, whereas oxygenated hemoglobin in arteries does not because oxygen neutralizes the effect of the iron (Pauling & Coryell, 1936). Several decades later, a breakthrough study by Thulborn et al. (1982) eventually bridged the gap between magnetic susceptibility of oxy- and deoxyhemoglobin and the fMRI signal reflected by brain oxygen consumption, paving the way for the successful application of fMRI in human neuroimaging.

In general, the process of the fMRI BOLD signal production contains several key constituents (Figure 1.3). Neural activity responds to a stimulus presented externally, which triggers changes in the BOLD contrast, characterized by the hemodynamic response (HR). The link between neural activity and HR is known as neurovascular coupling, the nature of which remains largely unknown (for a review, see Villringer & Dirnagl, 1994). HR assumes the BOLD contrast depending on the dynamic deoxygenated hemoglobin amount of neuronal activity, but research has found that the BOLD signal could be better predicted by local field potentials (LFPs) rather than single- and multi-unit activity that occurs only transiently at the onset of the stimulus but do not persist over time, whereas LFPs not only occur transiently but also persist over time (Logothetis et al., 2001).

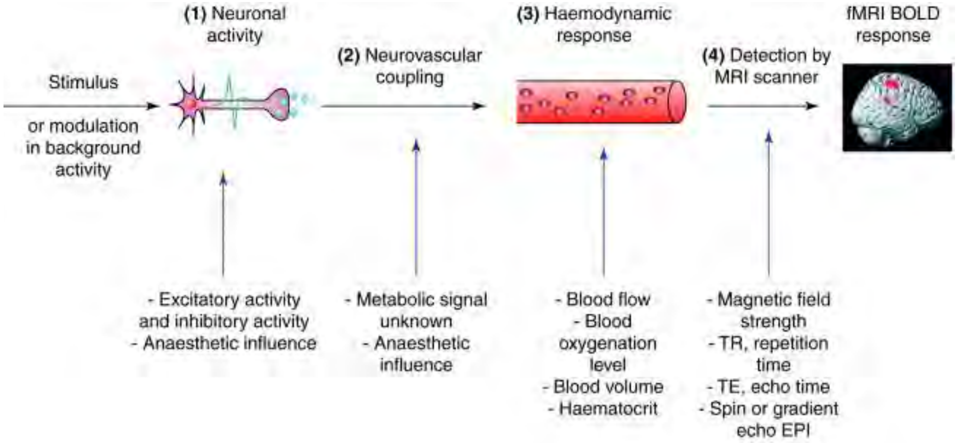

Figure 1.3 The process of the fMRI BOLD signal production. (1) neuronal activity induced by a stimulus or modulation in background activity, with the engagement of both excitatory and inhibitory activity; (2) neurovascular coupling, characterized by the relationship between neuronal activity and hemodynamic response; (3) haemodynamic response with different representations, such as blood flow, blood oxygenation level, and blood volume; (4) fMRI signal detection by MRI scanner with multiple related

parameters, including the magnetic field strength, repetition time, echo time, spin or gradient echo echo-planar imaging. (Figure adapted from Arthurs & Boniface (2002)).

Despite the discovery of the linear correlation between neuronal activity and HR (Logothetis et al., 2001), in reality, it is still difficult to quantify HR because other physiological factors that are even harder to measure can also contribute to changes in deoxyhemoglobin concentration, such as vascular geometry, hematocrit, and basal oxygenation levels (Ogawa et al., 1993). Moreover, HR can vary widely across cortical areas (Soltysik et al., 2004). It has been recognized that the BOLD signal occurs at large draining veins as well as close by at the capillary level, and even possibly a few centimeters downstream from the neuronally active regions (Ogawa et al., 1993). In addition, the amount of the BOLD signal per se is potentially affected by many experimental parameters in fMRI scanning, including the magnetic field strength, echo time, repetition time, and imaging techniques such as spin- or gradient-echo echo-planar imaging. The quality of BOLD images is also susceptible to various artifacts, especially head motion and field non-homogeneities (Turner & Ordidge, 2000). These factors further affect the amount of the BOLD response that reflects a given HR.

The nature of HR has been found to be related to changes in both CBF and cerebral blood volume (CBV) (Mandeville et al., 1999) (Figure 1.4). During HR, an initial dip occurs after the onset of neuronal activity due to the initial oxygen extraction out of nearby capillaries that results in a local increase in paramagnetic deoxyhemoglobin, hence a decrease in MR image intensity (Menon et al., 1995). After compensatory oxygen supply caused by increased neural activity, an increased inflow of oxygenated blood occurs. Continuous oxygen delivery results in a decrease of deoxygenated hemoglobin and a rise of the BOLD signal that reaches to a maximum value after about five seconds, referred to as the peak of the HR function, and then extends to a plateau. The BOLD signal decreases quickly after neuronal activity stops, until below the baseline level where the signal lingers for an interval, known as post-stimulus undershoot. Based on a balloon model, the post-stimulus undershoot in the BOLD signal exists because CBF decreases more rapidly than CBV, and CBF returns to the baseline when the CBV remains elevated, leading to the presence of more deoxygenated hemoglobin (Buxton et al., 2004). When CBV slowly returns to the baseline level, the BOLD signal synchronously increases to the baseline, and the undershoot ends.

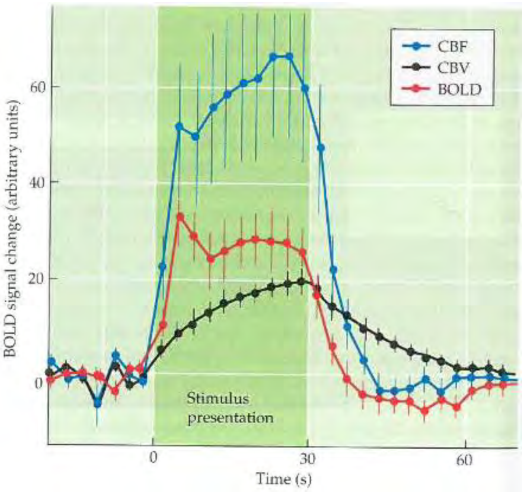

Figure 1.4 The hemodynamic response and its relationship with cerebral blood flow (CBF) and cerebral blood volume (CBV). In the experiment, CBF and CBV were measured when stimulating the forepaw of a rat (Mandeville et al., 1999). Following the stimulus onset, the BOLD signal showed changes associated with both CBF and CBV. After the stimulus offset, a post-stimulus undershoot was observed, which might be due to the temporal mismatch between changes in CBF and CBV, leading to an increase of deoxyhemoglobin and thereby decreasing the BOLD signal. (Figure adapted from Huettel et al. (2009)).

Regarding fMRI experiments, two other properties of the BOLD signal are relevant here: spatial resolution and temporal resolution. As the currently mainstay non-invasive neuroimaging technique, fMRI has great advantages over other functional imaging techniques, especially its excellent spatial resolution and reasonable temporal resolution. The spatial resolution of fMRI refers to its ability of distinguishing differences between nearby tissues, measured by the voxel size; a voxel is a three-dimensional cube. The spatial specificity of the fMRI signal could be improved by increasing the magnetic field strength (Logothetis, 2008). The temporal resolution is very important for many fMRI research questions, which is associated with the ability to accurately detect brain activity in response to a stimulus and depends on the applied repetition time. As mentioned above, the fMRI BOLD signal is detected from HR that is the result of neuronal activity, but hemodynamic changes do not occur following neuronal activity within tens of milliseconds; rather, they occur until after one to two seconds with a short delay because the BOLD signal estimates activity of slower changes in the vascular system. By resampling the BOLD signal into smaller repetition time, it allows for a better estimation of vascular changes and in turn, improves the interpretation of neural activity.

To date, as a valuable tool for the investigation of the human brain function, BOLD fMRI has been overwhelmingly employed in cognitive neuroimaging studies to broaden our understanding of the functional organization of the human brain.

1.4.2 Resting-state fMRI

In the early years of fMRI studies, the vast majority of task-based experiments only presented findings of activity increases and ignored activity decreases, although task-induced deactivations have been frequently observed (Gusnard & Raichle, 2001). Moreover, with regard to the brain's energy metabolism, early work found little impact of cognitive processing on CBF and oxygenation consumption in the brain (Sokoloff et al., 1955). For an adult, the brain represents about 2% of the total body weight while it consumes 20% of the whole energy (Clarke & Sokoloff, 1999), with just 1-10% of extra energy consumption for task performance (Shulman et al., 2014). These findings clearly show that the brain consumes most of its energy during rest rather than task state, suggesting a fundamental role of the intrinsic activity in the brain (Raichle & Mintun, 2006).

After the seminal study by Biswal et al. (1995), rs-fMRI quickly became prominent and shed new light on the brain mechanisms underlying human cognition. By using PET, decreased activations in a set of regions have been consistently observed during task performance in healthy human adults, independent of particular tasks (Shulman et al., 1997). These regions were further identified with a decrease of activation during externally oriented tasks while an increase of activation during the resting baseline, suggesting a baseline or default state of the brain, termed as “default mode” (Raichle et al., 2001). The identification of a default mode of the brain function demonstrated rs-fMRI as a powerful technique for exploring LFFs of the resting brain, and triggered broader and deeper investigations concerning the intrinsic functional system in the brain, which led to rapid development in the field of cognitive neuroimaging since the new millennium.

So far, there is no strict definition for “resting state”, but technically, it refers to the subject lying quietly but awake in the scanner, without performing an explicit task. In specific situations, subjects are asked to keep the eyes closed or open with or without visual fixation during scanning. Compared to traditional task-based fMRI research, in which external stimuli are presented to measure the neural activity and the subject’s response, rs-fMRI has some unique advantages in terms of acquiring neuroimaging data from pediatric and clinical populations who are not able to perform complicated tasks in the scanner. Though still limited, novel findings have been reported in studies of infants and young children using the rs-fMRI technique (e.g., Cao et al., 2016; de Bie et al., 2012; Fair et al., 2008; Fransson et al., 2011; Fransson et al., 2007; Gao et al., 2009; W. Lee et al., 2013; Liu et al., 2008; Muetzel et al., 2016; Power et al., 2010; van den Heuvel et al., 2015; van den Heuvel et al., 2009), which expand our knowledge of functional changes during the early years of brain development. With the rs-fMRI technique, large samples of clinical populations with different diseases could be obtained for scientific research, although most of these patients may not be available or suitable for task-based fMRI studies (for a review, see Uddin et al., 2010). Moreover, rs-fMRI also allows for investigating the functional organization of the brain in a valid and relatively simple way and studying various systems in the brain, whereas only one specific system is usually examined in a task-based fMRI study. For instance, the intrinsic organization of the brain could be characterized by the default mode network (DMN) and its anti-correlated network in the absence of overt task performance (Fox et al., 2005). In independent component analysis (ICA)-based studies, 10 resting-state networks were found in adults, involving motor, visual, executive control, auditory, and memory regions besides the DMN, and these networks were reproducible across datasets (Damoiseaux et al., 2006); 5 unique networks were observed in infants, encompassing visual, sensorimotor, and auditory regions as well as an incomplete DMN (Fransson et al., 2007). Furthermore, first results have identified the functional architecture in very young infants (Fransson et al., 2011; Fransson et al., 2007) and even the topological development patterns prior to birth in the preterm infants brain (Cao et al., 2016). Importantly, rs-fMRI also provides the possibility of exploring developmental changes in the brain’s functional architecture (Fair et al., 2008; Fair et al., 2009; Fair et al., 2007).

Despite the absence of explicit tasks, it has been widely demonstrated that brain networks that are engaged in cognitive tasks can also be reliably identified during resting state (Cole et al., 2014; Smith et al., 2009), suggesting a strong overlapping between the intrinsic functional connectivity and task-evoked activations in the brain. Notably, resting-state networks have been proved to be reliable and reproducible. For example, a persistent DMN was detected in different consciousness states (Greicius et al., 2008). The resting-state networks were still discernible during sleep and did not require active cognitive processes or conscious awareness (Fukunaga et al., 2006). Lately, a longitudinal study acquiring rs-fMRI data from a healthy subject weekly over 3.5 years reported high reproducibility of resting-state networks (Choe et al., 2015). Moreover, in a large sample (n = 536) of rs-fMRI data from children, resting-state networks were obtained by using ICA, and most of these networks were highly reproducible across different subsamples (Muetzel et al., 2016).

Intriguingly, recent research has revealed that an individual’s intrinsic connectivity can be used to distinguish that individual’s fundamental cognitive behavior (i.e., fluid intelligence) (Finn et al., 2015), and that the intrinsic activity in the resting brain can even predict individual differences during task performance (Tavor et al., 2016). These findings suggest the robust individual variability of the functional brain organization and therefore provide a critical foundation for correlating an individual’s intrinsic activity in the brain with that individual’s cognitive trait and the response to external task stimuli.

To date, most of the rs-fMRI studies have been performed in adults, but rs-fMRI studies in young children are still limited due to difficulties of data acquisition. In the present thesis, rs-fMRI data were acquired from typically developing children to investigate the intrinsic functional connectivity within the language network with respect to language processing as well as the development of the functional brain network over a one-year period and its behavioral relevance.

1.4.3 Approaches for rs-fMRI data analysis

As mentioned above, the rs-fMRI technique has some unique advantages in exploring the functional organization of the brain. During the past two decades, a growing body of neuroimaging research has focused on novel hypotheses by employing this powerful tool, and along this technique, increasing analytic methodologies for data analysis have also been developed in recent years (Margulies et al., 2010). Several approaches used for rs-fMRI data analysis in this thesis, including resting-state functional connectivity (RSFC), amplitude of low-frequency fluctuation (ALFF), and degree centrality, will be introduced in detail.

1.4.3.1 RSFC and RSFC–behavior correlation analysis

RSFC measures the level of synchronized activity of spontaneous fMRI time series recorded during rest, reflecting the level of functional connections between those spatially separated regions (Figure 1.5). In RSFC, high correlations indicate regions in the same system and selective correlations between regions are used to map the organization of brain systems. RSFC is particularly useful for featuring large-scale brain systems of widely distributed regions and connection strengths, offering new insight into the connectional architecture of the human brain (Van Dijk et al., 2010).

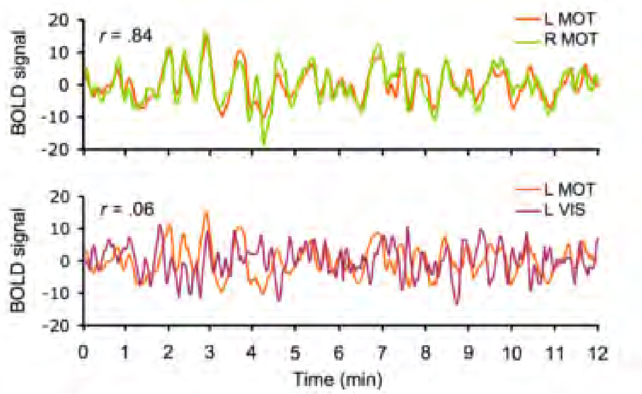

Figure 1.5 The basis of resting-state functional connectivity. These two figures depict different levels of synchronized activities of spontaneous low-frequency fluctuations in the fMRI BOLD signal: a strong functional correlation (*r* = 0.84) between left and right motor cortex over time (above) and a weak functional correlation (*r* = 0.06) between motor and visual regions over time (below). L: left; R: right; MOT: motor; VIS: visual. (Figure adapted from Van Dijk et al. (2010)).

Seed-based functional connectivity calculates the correlation between the average time series of an a priori defined seed (or region of interest) and the time series of all other regions in the brain. This approach was initially applied to rs-fMRI data by Biswal et al. (1995). In this pioneering study, the premotor region was defined as a seed and a high degree of temporal correlations was observed between the time courses of this seed region and the time courses of other regions associated with motor functions. The coupling between the correlation pattern detected from LFFs in the resting brain and activated regions during a finger tapping task suggested the correlation of LFFs as a manifestation of functional connectivity of the brain (Biswal et al., 1995). Thereafter, functional connectivity analysis has been employed in a large number of studies (e.g., Biswal et al., 1997; Cordes et al., 2000; Greicius et al., 2003; Hampson et al., 2010; Hampson et al., 2002; Lowe et al., 1998; Xiong et al., 1999) and widely used to explore resting-state functional networks (for a review, see van den Heuvel & Pol, 2010). For example, in the study by Cordes et al. (2000), four seeds were selected according to the maximal activations in different tasks (i.e., sensorimotor, visual, language, and auditory tasks), and RSFC maps of these seeds turned out to be similar to activation patterns in each task. The functional connectivity analysis was also utilized to identify the presence of the language-related network and the connection strength within the network (Hampson et al., 2002). Furthermore, RSFC in the whole brain can serve as a predictor of individual brain maturity with age (Dosenbach et al., 2010).

Basically, there are two methods to define seeds: one is on the basis of anatomical landmarks (e.g., AAL, Brodmann area) and the other is based on a priori empirical evidence provided by task-based fMRI studies. As for regions defined by anatomical landmarks, they are usually very large and represent a mixture of different functions rather than a single function related to this region. More importantly, it is unknown to what extent anatomical seeds indeed represent a specific function. By contrast, seeds defined by the peaks of activation regions from previous task-based fMRI studies are assumed to better represent brain regions involved in a specific cognitive process. So far, considerable studies have used activation peaks of previous task-evoked fMRI studies to explore related networks, such as the DMN (e.g., Fox et al., 2005), the language network (e.g., Hampson et al., 2002; Muller & Meyer, 2014), the attention control network (e.g., Dosenbach et al., 2007; Fair et al., 2007), the emotional processing network (e.g., Alaerts et al., 2015), and the voice-selective network (e.g., Abrams et al., 2013).

As mentioned above, RSFC measures the strength of the functional connection between two regions, which can be obtained from individual subjects and has been proved to covary with the behavioral performance in subjects (Hampson et al., 2006b). The study by Hampson et al. (2006b) revealed significant correlations between the reading abilities of subjects and the strength of the function connection between language-related regions (i.e., BA 39 and Broca's area), suggesting that RSFC–behavior correlation analysis is a valid and powerful approach to investigate correlations between behavioral performance and functional brain connections. To date, this approach has been widely used to explore the neural basis of individual differences in a variety of cognitive abilities, such as working memory (Hampson et al., 2010; Hampson et al., 2006a; Wang et al., 2010; Zou et al., 2013), reading (Koyama et al., 2011; Zhang et al., 2014), personality (Adelstein et al., 2011), face processing (Zhu et al., 2011), executive control (Seeley et al., 2007), and intelligence (Song et al., 2008). Moreover, it is also a useful tool to identify brain dysfunctions associated with various clinical disorders (for a review, see Stevens & Spreng, 2014).

In practice, there are two variations for RSFC–behavior correlation analysis. One is based on the strong prior hypothesis, firstly calculating the connection strength of two predefined seeds and then correlating the connection strength with behavioral performance across subjects; by contrast, the other is more data-driven, firstly computing individual functional maps for each predefined seed and then correlating the RSFC strength in the whole brain with behavioral performance across subjects. For the former, a positive relationship suggests that stronger correlation strength between two seed regions relates to better behavioral performance in subjects; for the latter, the positive correlation with a brain region indicates that the RSFC strength between the predefined seed and this region can serve as a predictor of better behavioral performance.

In the present thesis, seed-based RSFC was utilized to investigate brain connections within the language network. Language-related regions were selected as seeds and correlated with other regions of the brain. On the basis of RSFC maps, the connectivity strength in the brain was correlated with the language performance across subjects. RSFC–behavior correlation analysis provides deeper insight into brain function and its relation to individual differences in behavioral performance.

1.4.3.2 Amplitude of low-frequency fluctuations

Although functional connectivity between two regions can provide comprehensive and integrative LFFs information with respect to temporal synchronization, it is not capable of detecting differences in specific regions for different populations nor is it able to reflect information from the domain of frequency synchronization. A previous study has reported the activation in the primary visual cortex induced by LFFs at 0.034 Hz (range 0.025–0.041 Hz) using the power spectrum method, indicating that LFFs might be an index of regional spontaneous neuronal activity (Kiviniemi et al., 2000). Inspired by this interesting finding, ALFF was initially proposed to measure spontaneous fMRI activity in the resting brain by Zang et al. (2007). In this study, ALFF was used to investigate the baseline brain function of attention deficit hyperactivity disorder. The study reported altered ALFF in some brain regions in children with this disorder compared to a group of control children, suggesting that ALFF as a local method could serve as a marker of rs-fMRI to detect abnormal brain functions underlying pathophysiology in patients (Zang et al., 2007).

For the calculation of ALFF, time series is firstly transformed to the frequency domain signal (i.e., power spectrum) by the fast Fourier transform, and then the averaged square root of each frequency of the power spectrum is computed across certain frequency (e.g., 0.01–0.08 Hz) at each voxel (Figure 1.6). So far, ALFF has been extensively used in fMRI studies to investigate abnormal brain functions by comparing clinical populations with healthy controls (e.g., Hoptman et al., 2010; Jiang et al., 2011; H. Liu et al., 2014; J. Liu et al., 2014; Turner et al., 2012; Zhang et al., 2010). In healthy participants, a study found distinct ALFF values in different resting states (i.e., eye open and eye closed) in the visual cortex, implying that ALFF could also be a biomarker for physiological states of the brain (Yang et al., 2007). Moreover, test-retest reliability of ALFF has been examined in both healthy adults (Zuo et al., 2010) and patients with chronic schizophrenia (Turner et al., 2012).

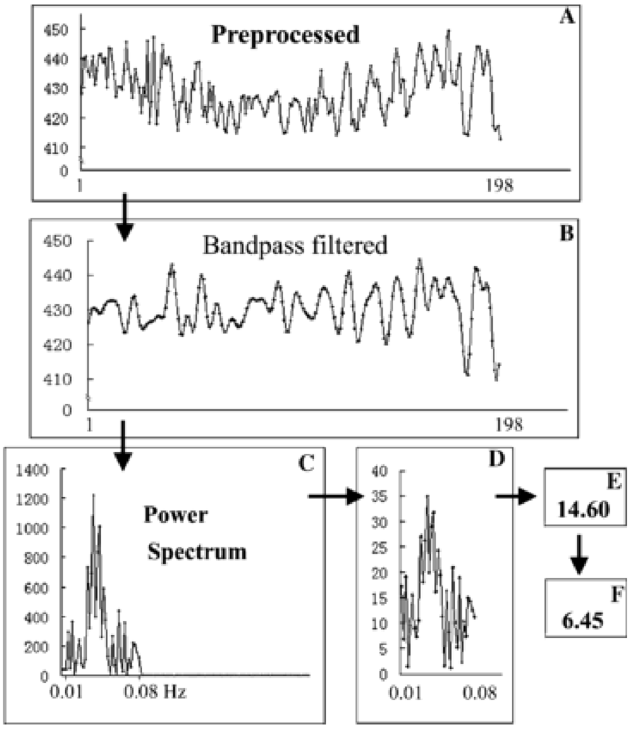

Figure 1.6 The illustration of ALFF analysis. Specifically, the analysis comprises: (A) fMRI data preprocessing; (B) bandpass filtering (e.g., 0.01–0.08); (C) obtaining the power spectrum by transforming the filtered time series to the frequency domain with a fast Fourier transform; (D) calculating the averaged square root of each frequency of the power spectrum across 0.01–0.08 Hz at each voxel; (E) computing the average value of ALFF (14.60) and (F) the standardized ALFF value (6.45). (Figure adapted from Zang et al. (2007)).

The strong coupling of the ALFF pattern and the DMN was consistently shown in previous studies (e.g., Yang et al., 2007; Zang et al., 2007; Zuo et al., 2010). Moreover, recent research, for instance, demonstrated an overlap between changes in ALFF and functional connectivity in several brain regions in patients who stutter (Xuan et al., 2012) and in seasonal affective disorder (Abou Elseoud et al., 2014). It was observed that ALFF within the DMN was related to the DMN functional organization in Alzheimer's disease patients (Weiler et al., 2014). These findings indicate a relationship between ALFF and functional connectivity. Lately, a novel method was developed to investigate the interaction and association between ALFF and network-based functional connectivity in depression, defined as ALFF-based functional connectivity (Tadayonnejad et al., 2015). This method combines both ALFF and functional connectivity and thus provides new insight into the correlations of local measures (i.e., ALFF) and large-scale measures (i.e., functional connectivity).

1.4.3.3 Degree centrality

Recently, graph theoretical analysis has been introduced into the neuroimaging field as a new approach to characterize functional and structural networks in the human brain, and it has certain advantages in elucidating complex neural network organizations. In a graph, brain regions are regarded as nodes, and connections between brain regions are taken as edges. It has been found that a combination of different measures, such as degree, betweenness, and closeness centrality, allows for reliable identification of hub regions in the brain (Sporns et al., 2007). The node degree is defined as the number of edges that connect this node with the rest of the network. In the human brain, hubs refer to brain regions that have a high degree of connectivity and play a critical role in information integration underlying diverse aspects of cognitive processes (van den Heuvel & Sporns, 2013).

Among measures of graph theory, degree centrality is the most fundamental and often used centrality measure, and thus was firstly applied to mapping the degree of intrinsic functional connectivity across the whole brain (Buckner et al., 2009). Following this, other voxel-based centrality measures were also introduced to characterizing brain networks, such as: eigenvector centrality that particularly weights nodes based on their degree of connection within the network (Lohmann et al., 2010b); betweenness centrality that measures how often a voxel locates in the shortest path between pairs of other voxels in the brain (Fransson et al., 2011); and leverage centrality that measures the extent of connectivity of a node relative to the connectivity of its neighbors and therefore can identify neighborhood hubs more accurately than other centrality measures (Joyce et al., 2010). Among these measures, however, degree centrality is of special interest to the present thesis because it is the most basic measure for the network and most other measures are ultimately linked to it (Bullmore & Sporns, 2009).

Degree centrality is a data-driven approach, taking each voxel as a seed to calculate functional connectivity in the whole brain (Figure 1.7). Two types of graphs are used to characterize the brain network: binarized and weighted graphs. For binarized graphs, a threshold is given to correlation maps generated for each voxel, and all connections below the given threshold are set to zero while all remaining connections are set to 1. The given threshold is usually 0.25 which has been shown to represent a good compromise in previous studies (e.g., Buckner et al., 2009; Hampson et al., 2012; Martuzzi et al., 2011), though degree centrality maps are rather robust against different thresholds (Buckner et al., 2009; Hampson et al., 2012). By comparison, weighted graphs maintain all information regarding the strength of existing connections, but binarized graphs discard connections below the threshold which might also contain valuable information. Nonetheless, most previous studies used binarized graphs to compute functional brain networks (e.g., Buckner et al., 2009; Cole et al., 2010; Di Martino et al., 2013; Fransson et al., 2011; Li et al., 2016; Tusche et al., 2014). Some studies also examined both types of graphs and confirmed highly similar results from different graph methods (Hampson et al., 2012; Zuo et al., 2012).

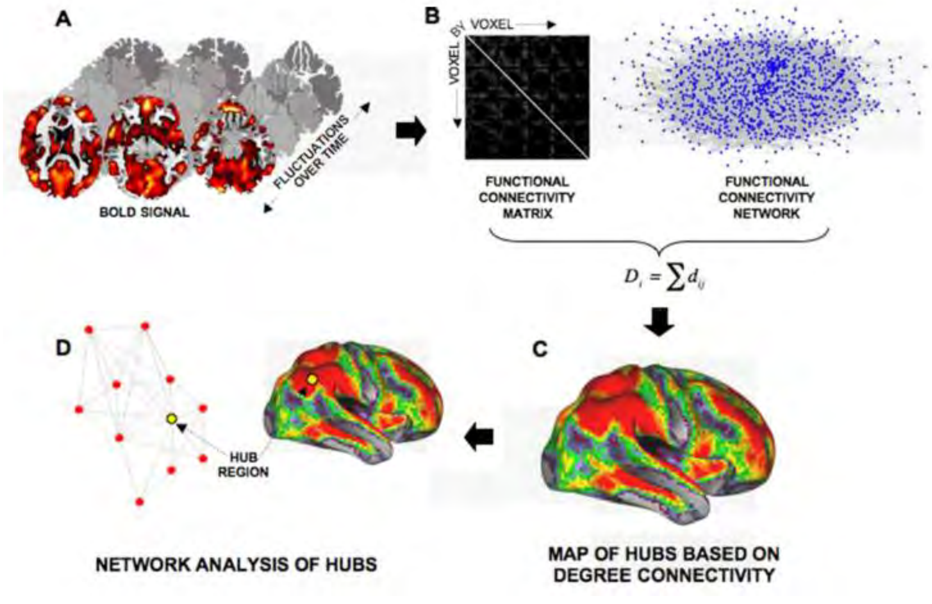

Figure 1.7 The illustration of degree centrality analysis. (A) Functional connectivity between intrinsic BOLD signal fluctuations is calculated at the voxel level; (B) the functional connectivity matrix and network for each subject are constructed; (C) the degree of connectivity map is calculated on the basis of degree of voxels in the network; (D) the degree centrality map with hub regions is identified by the peak of regions involved in the degree connectivity. (Figure adapted from Buckner et al. (2009)).

As a prevailing graph measure, degree centrality has been widely employed to identify brain networks with hub regions (Cole et al., 2010; Fransson et al., 2011; Martuzzi et al., 2011), to explore the changes in degree of connectivity with age (Hampson et al., 2012), to highlight the hub regions associated with cognitive performance (Tusche et al., 2014), and to detect the network abnormalities in patients (Buckner et al., 2009; Di Martino et al., 2013; Li et al., 2016). Notably, evidence has shown that degree centrality is physiologically meaningful (Liang et al., 2013; Tomasi et al., 2013). For example, the degree of connectivity of brain regions was found to be related to the cerebral metabolic rate of glucose, reflecting the energy cost of neural communication (Tomasi et al., 2013). Another study observed a tight coupling of functional brain hubs and the brain's metabolism, suggesting hub regions in the brain relevant to the distribution of regional CBF (Liang et al., 2013).

Given the solid physiological basis and data-driven feature, degree centrality is a suitable candidate to investigate the intrinsic connectivity patterns in the brain. Different from aforementioned seed-based RSFC, the calculation of degree centrality does not require a predefined seed; instead, each voxel is serving as a seed to compute its correlations with other voxels in the brain. Therefore, this approach can avoid potential bias from the prior hypothesis. In the thesis, this approach was applied to explore the changes in the connectivity patterns at a one-year interval in typically developing children. For the interpretation of results, a region showing positive changes indicates increasing connectivity between this region and other regions of the brain, suggesting an enhanced role of this region in the whole brain network as a function of age, whereas a region showing negative changes indicates its decreasing connectivity with other regions of the brain and a reduced role of this region with age.

1.5 The intrinsic language network

Inspired by the analysis of LFFs in the resting brain, an alternative approach towards the investigation of the functional brain network of language processing was employed to explore specific tasks or functional domain information underlying LFFs signals. A consistent correlation pattern (involving left inferior frontal and posterior superior temporal regions) was identified based on the analysis of LFFs from four language-related fMRI experiments (Lohmann et al., 2010a). This general framework underlying language studies was independent of specific tasks and thus called the default language network (Lohmann et al., 2010a). In a follow-up study, using an identical approach, the development of the language network was characterized by strong functional interhemispheric connectivity in young children at ages of 5 to 7 years and strong intrahemispheric connectivity between inferior frontal and superior temporal cortices in adults (Friederici et al., 2011). Moreover, the LFFs analysis across different speech conditions (i.e., normal speech, hummed speech, and flatted speech) in newborns also showed strong interhemispheric connectivity and weak intrahemispheric connectivity as observed in young children (Perani et al., 2011). These findings demonstrate not only the presence of a language-specific functional connectivity pattern in the brain but also the development of this language network with age.

In recent years, research exploring the language network using LFFs in rs-fMRI data has progressed (Muller & Meyer, 2014; Tomasi & Volkow, 2012; Xiang et al., 2010; Zhu et al., 2014). For example, Xiang et al. (2010) initially observed the functional connectivity topology in the perisylvian language networks by seeding in three subregions of Broca's area and their right homologs. When seeding in Broca's and Wernicke's areas, Tomasi & Volkow (2012) observed that the intrinsic language network has a predominance of short-range functional connectivity in general except for a predominance of long-range connectivity in the posterior Wernicke's area. This language network was found to be highly reproducible across different languages (Tomasi & Volkow, 2012) and also across short- and long-term scan sessions (Zhu et al., 2014). Moreover, the functional asymmetry of the language network was also investigated, and it demonstrated left lateralized connectivity in Broca's area and right lateralized connectivity in Wernicke's area (Tomasi & Volkow, 2012; Zhu et al., 2014). These results suggest that, on the one hand, seed-based functional connectivity is a feasible and valid approach to identify the language network in the resting brain, and on the other hand, this language network is highly reliable and reproducible.

So far, the language network has been described mainly in adults and its developmental changes from childhood to adulthood have also been studied, but it is still unknown how the language network in the brain is related to sentence comprehension performance and how the changes of this language network are associated with the language development in typically developing children. The scarcity of knowledge on these points led to research questions in this thesis:

(1) How is the intrinsic functional connectivity within the language network related to children's performance in sentence comprehension?

(2) Can 5-year-olds make use of the adult-like fronto-temporal connection to process syntactic complexity?

(3) How does the intrinsic functional connectivity change over a one-year period in typically developing children? Are the changes in functional connections related to concurrent language development?

(4) Are individual differences in children's language development associated with their functional brain connectivity?

In order to address these questions, two studies were conducted in which both rs-fMRI data and the off-line sentence comprehension performance were obtained from typically developing German preschool children. In the following chapter, two publications reporting these two studies will be presented, the first one with the focus of the brain basis underlying sentence processing and the second one exploring developmental changes in functional connectivity within the language network and its response to the development of language abilities in preschool children.

2 Publications

2.1 Development of a selective left-hemispheric fronto-temporal network for processing syntactic complexity in language

Xiao, Y., Friederici, A.D., Margulies, D.S., & Brauer, J. (2016a). Development of a selective left-hemispheric fronto-temporal network for processing syntactic complexity in language comprehension. *Neuropsychologia 83*, 274–282.

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Development of a selective left-hemispheric fronto-temporal network for processing syntactic complexity in language comprehension

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ABSTRACT

The development of language comprehension abilities in childhood is closely related to the maturation of the brain, especially the ability to process syntactically complex sentences. Recent studies proposed that the fronto-temporal connection within left perisylvian regions, supporting the processing of syntactically complex sentences, is still immature at preschool age. In the current study, resting state functional magnetic resonance imaging data were acquired from typically developing 5-year-old children and adults to shed further light on the brain functional development. Children additionally performed a behavioral syntactic comprehension test outside the scanner. The amplitude of low-frequency fluctuations was analyzed in order to identify the functional correlation networks of language-relevant brain regions. Results showed an intrahemispheric correlation between left inferior frontal gyrus (IFG) and left posterior superior temporal sulcus (pSTS) in adults, whereas an interhemispheric correlation between left IFG and its right-hemispheric homolog was predominant in children. Correlation analysis between resting-state functional connectivity and sentence processing performance in 5-year-olds revealed that local connectivity within the left IFG is associated with competence of processing syntactically simple canonical sentences, while long-range connectivity between IFG and pSTS in left hemisphere is associated with competence of processing syntactically relatively more complex non-canonical sentences. The present developmental data suggest that a selective left fronto-temporal connectivity network for processing complex syntax is already in functional connection at the age of 5 years when measured in a non-task situation. The correlational findings provide new insight into the relationship between intrinsic functional connectivity and syntactic language abilities in preschool children.

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1. Introduction

The maturation of the brain during childhood is vital for normal development of language abilities. So far, however, functional magnetic resonance imaging (fMRI) data are still rare to describe the developing language–brain relationship during early development (for review see Friederici, 2006). Therefore, the available data do not allow us to relate certain stages of language development to particular aspects of brain maturation.

In adults, the neural basis of language comprehension has been investigated both using electrophysiological measures (Deutsch and Bentin, 2001; Friederici, 2002; Hagoort, 2003) as well as hemodynamic measures (for a review see Price, 2010; Vigneau et al., 2006). Language comprehension has been associated with activation in the inferior frontal cortex (Broca's area) and the superior temporal cortex (Wernicke's area). Hemodynamic studies indicate that the left inferior frontal gyrus (IFG) and the posterior part of the left superior temporal gyrus and sulcus (pSTG/pSTS) subserve the processing of complex syntactic sentence structures in particular (for reviews see Friederici, 2011, 2012). These two areas showed stronger selective activation for sentences with syntactically more complex non-canonical word order than for sentences with syntactically less complex canonical word order (e.g., Friederici et al., 2006; Kinno et al., 2008; Obleser et al., 2011).

In recent years, efficient connectivity analysis such as dynamic causal modeling (DCM) was employed to further identify the connections within language-relevant brain regions during language processing. By using activation peaks associated with object-cleft sentences over syntactically less complex subject-cleft sentence processing, including IFG, pSTS, and other perisylvian cortical areas, the IFG was identified as the input where syntactic complexity modulated the flow of information from IFG to pSTS (den Ouden et al., 2012). A recent study by Makuuchi and Friederici (2013) showed converging results. In this study, four regional clusters were identified from the activation of syntactically

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more complex object-first sentences created by dislocating object-noun phrases from their original position of the basic subject-first sentences to a new position: IFG and the inferior frontal sulcus (IFS), the inferior parietal cortex (IPC) and the posterior part of the temporal cortex including pSTG/pSTS; the prevailing model indicated information flow from IFG via IFS and inferior parietal cortex to the pSTS. These findings provided evidence for the importance of this connection for the parsing of complex syntactic sentences. A study with adults and 7-year-old children combined information about structural nerve fiber connections from diffusion-weighted imaging (DWI) data and fMRI data from a language task, and found that adults make use of a more confined fronto-temporal language network than children because of a still ongoing maturation of the structural fronto-temporal connection in children (Brauer et al., 2011).

Since the seminal findings of Biswal et al. (1995) describing spontaneous low frequency (<0.1 Hz) fluctuations (LFFs) in the resting human brain, a line of research has been opened into characterizing functional connectivity and, more specifically, resting-state networks. Lohmann et al. (2010) have shown that default network information can be extracted from task-dependent fMRI data by removing specific experimental stimulation using low-frequency filtering. This method provides insight in domain-selective default networks such as the so-called default language network. As shown in this study, the default language network indicated low-frequency fronto-temporal correlations in fMRI data obtained from language studies independent of task and experimental specifics (Lohmann et al., 2010). Furthermore, the development of this default language network was shown to be characterized by a trend from interhemispheric connectivity in 7-year-old children to more confined intrahemispheric connectivity in adults (Friederici et al., 2011).

In the present study, we first employed a seed-independent, voxel-wise functional resting-state MRI measure (amplitude of low-frequency fluctuation, ALFF) to calculate the intensity of regional spontaneous brain activity in order to examine the correlations among the amplitude of low-frequency blood oxygen level-dependent (BOLD) fluctuations. ALFF is a regional measure for detecting the frequency of BOLD oscillations, and it provides information of regional spontaneous activity. Such an approach was proposed by Zang et al. (2007) and successfully applied as a measure of functional connectivity (Tadayonnejad et al., 2015). For ALFF, the square root of power spectrum is integrated in a low-frequency range for detecting the regional intensity of spontaneous fluctuations in BOLD signal. In the present study, we chose four regions as regions of interest (ROIs), including IFG and pSTS in both hemispheres. Activation peaks of task-evoked fMRI have previously been employed on resting-state fMRI data in order to explore related functional networks in various domains such as attention control (e.g., Dosenbach et al., 2007), emotional processing (e.g., Alaerts et al., 2015), voice-selective processing (e.g., Abrams et al., 2013), among others. The coordinates of ROIs selected for the current analysis were based on seeds from language networks that previously had been successfully applied to describe LFF language networks (Friederici et al., 2011), and both left regions have been reported relevant for processing syntactic information in numerous studies (e.g., Bahlmann et al., 2007; Ben-Shachar et al., 2003; Bornkessel et al., 2005; Friederici et al., 2006; Makuuchi et al., 2009; Moro et al., 2001; Musso et al., 2003; Newman et al., 2010; Röder et al., 2002). Since previous research showed right hemispheric regions to be additionally involved in young children when processing sentence-level information (Brauer and Friederici, 2007; Brauer et al., 2008; Holland et al., 2001), the right homolog areas were included in the analysis allowing to investigate potential interregional within- as well as cross-hemispheric correlations and also developmental differences in the interhemispheric connectivity between 5-year-olds and adults. The current study reports correlations in ALFF and relates them to findings on the language network in LFF as reported previously (Friederici et al., 2011).

We expected to find developmental differences in interregional connectivity within language-relevant regions from 5-year-olds to adults. Next, focusing on 5-year-olds data, we explored to what extent behavioral performance for processing syntactic complexity tested outside the scanner is related to resting-state functional connectivity (RSFC). Seed-based functional connectivity is an approach by which correlations are obtained between the time course of a given seed and the time course of all the other regions within the mask, thereby providing a detailed map of specific connectivity for a brain area of interest. RSFC-behavior correlations across subjects have been widely employed to investigate the neural basis of individual differences in performance (e.g., Hampson et al., 2006; Kelly et al., 2008; Koyama et al., 2011; Seeley et al., 2007; Wang et al., 2010; Zou et al., 2013). The left IFG was chosen as seed in functional connectivity (FC) analysis and the relationship between FC maps and performance in distinct syntactically complex sentences was analyzed. We hypothesized a selective left frontal-to-temporal connectivity for adults which should not yet be present for children at this age, while for children we expected stronger interhemispheric correlations. Furthermore, the left-hemispheric long-range connectivity from left IFG to left pSTS was expected to be associated with the ability to parse syntactically complex information in children.

2. Materials and methods

2.1. Participants

Forty-six typically developing preschool children aged 5 years (23 males; mean age 5.5 years, range 5.0–5.9 years) and thirty-three adults (17 males; mean age 25.06 years, range 20–32 years) participated in the study. Prior to participation, the children's parents and adult participants gave written, informed consent, and children gave verbal assent for attendance. All children were assessed for their nonverbal intelligence quotient (IQ) using the German version of the Kaufman Assessment Battery for Children (K-ABC) (Melchers and Preuss, 2003). Raw scores were converted into age-dependent standardized scores (sample mean ± SD: 107.66 ± 9.26, range 88–126). All participants were right-handed, monolingual German speakers with no history of neurological, medical, or psychological disorders. The study was approved by the ethical review board of the local university.

2.2. Behavioral testing

All children completed a picture-sentence matching test outside the scanner as used in previous studies (Knoll et al., 2012; Schipke et al., 2012) which comprised of two syntactic conditions: simple canonical subject-initial sentences (SO) and syntactically more complex non-canonical object-initial sentences (OS). Noun phrases in sentences were case marked by nominative case (NOM, subject) or accusative case (ACC, object). There were 75 sentences in each syntactic condition. Stimulus examples are as follows:

(1) Subject-initial sentence (SO):
[der Tiger]$_{\text{(NOM)}}$ zieht [den Fuchs]$_{\text{(ACC)}}$
[the tiger]$_{\text{(SBJ)}}$ pulls [the fox]$_{\text{(OBJ)}}$
The tiger pulls the fox.
(2) Object-initial sentence (OS):

[den Fuchs]$_{\text{(ACC)}}$ zieht [der Tiger]$_{\text{(NOM)}}$

[the fox]$_{\text{(OBJ)}}$ pulls [the tiger]$_{\text{(SBJ)}}$
The tiger pulls the fox.

Sentences contained animate (animals) as well as inanimate nouns (things) to increase semantic variation. Although behavioral performance was taken for each subcondition separately, sentences were pooled into the two syntactic conditions of SO and OS sentences. This was done for two reasons: firstly, animacy of nouns was not the main focus of the present research question on syntactic sentence processing of subject-initial and object-initial sentence structures, and secondly, a 2×3 repeated-measures ANOVA including syntax (SYN) conditions (subject-initial, object-initial) and semantics (SEM) sub-conditions (subject animate: SA, object animate: OA, both animate: BA) revealed only a significant main effect of SYN ($F(1,40)=33.91$, $p<.001$), whereas the main effect of SEM did not reach significance ($F(2,39)=3.02$, $p=.06$) nor was there a significant SYN × SEM interaction ($F(2,39) < 1$). Behavioral performance in each of the sub-conditions in percent was: OS–BA: 78.05, SO–BA: 93.60, OS–SA: 82.93, SO–SA: 96.04, OS–OA: 82.01, SO–OA: 96.04.

All items were spoken by a trained female native speaker in a well-pronounced, child-directed manner. All sentences were recorded and digitized at 44.1 kHz, 16-bit mono. They had an average length of approximately 3.3 s. Children were asked to point to one of two presented pictures, one of which corresponded to the auditorily presented sentence. The corresponding picture appeared in 50% of the trials on the right/left side of the screen, and actions were performed in 50% of the trials from left-to-right/right-to-left. The number of hit was recorded for each condition. Two children failed to complete the test.

2.3. MRI scanning

All data were acquired using a 3T magnetic resonance scanner (Siemens Tim Trio) with a 12-channel head coil. During resting-state acquisition, children were instructed to lie as still as possible with eyes open while watching a calm screensaver showing a lava lamp in order to reduce potential mind-wandering. Resting-state fMRI whole-brain volumes were acquired by a T2*-weighted gradient-echo echo-planar imaging (EPI) sequence, TR 2000 ms, TE 30 ms, flip angle 90°, slice thickness 3 mm, gap 1 mm, FOV 19.2 cm, matrix 64×64, 28 slices, 100 volumes, duration 3.3 min. High-resolution 3D structural images were acquired with a T1-weighted, magnetization prepared rapid gradient echo (MPRAGE) sequence, TR 1480 ms, TE 3.46 ms, flip angle 10°; slice thickness 1.5 mm, gap 0 mm; matrix 250×250; spatial resolution $1 \times 1 \times 1.5$ mm^3, duration of 6 min.

2.4. Preprocessing

Data preprocessing was carried out using the Data Processing Assistant for Resting-State fMRI (DPARSF) (Chao-Gan and Yu-Feng, 2010, http://www.restfmri.net) based on Statistical Parametric Mapping (SPM8) (http://www.fil.ion.ucl.ac.uk/spm) and Resting-State fMRI Data Analysis Toolkit (REST) (Song et al., 2011, http://www.restfmri.net). Preprocessing included: (1) discarding the first 3 EPI volumes from each resting-state scan to allow for signal equilibration; (2) slice timing by shifting the signal measured in each slice relative to the acquisition of the slice at the mid-point of each TR; (3) 3D motion correction using a least squares approach and a 6 parameter (rigid body) spatial transformation; (4) reorienting functional images, and then co-registering MPRAGE image to the mean functional image of each participant; (5) segmenting MPRAGE images into gray matter, white matter (WM) and cerebrospinal fluid (CSF), and creating a study-specific template via diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL) (Ashburner, 2007). In order to account for head size differences between children and adults, the template was generated using all participants to reduce warping amount differences between groups. DARTEL is a high-dimensional image registration technique, allowing for optimal mapping between subjects; it registers all subjects into a common space, where the degree of applied deformation is the same for each individual (Ashburner, 2007). The study-specific template was firstly normalized to Montreal Neurological Institute (MNI) space with 6 mm full-width-at-half-maximum (FWHM) Gaussian kernel, and all functional images were normalized to this template and resampled to voxel size $3 \times 3 \times 3$ mm^3.

Nuisance regression was implemented by using a component based noise correction method (CompCor) (Behzadi et al., 2007). Specifically, regressors included principal components (PC) extracted from subject-specific WM and CSF mask (5 PC parameters) as well as Friston 24-parameter model (6 head motion parameters, 6 head motion parameters one time point before, and 12 corresponding squared items) (Friston et al., 1996). CompCor procedure included detrending, variance normalization, and PC analysis (PCA) according to Behzadi et al. (2007). Compared to mean signal regression, where average signals are extracted from WM and CSF mask, signals captured by principal components derived from these noise ROIs can better account for voxel-specific phase differences in physiological noise due to the potential of PCA to identify temporal pattern of physiological noise (Thomas et al., 2002). The Friston 24-motion-parameter model was used as head motion regressor because it has been found to likely become a standard for the field given its statistical superiority over smaller sets of motion parameters (Power et al., 2014; Satterthwaite et al., 2013; Yan et al., 2013a).

Given recent concerns regarding the confounding influence of micromovements in intrinsic functional connectivity analyses (Power et al., 2012; Satterthwaite et al., 2012; Van Dijk et al., 2012), time series of framewise displacement (FD) (Jenkinson et al., 2002) were computed as it is preferable for its consideration of voxel-wise differences in its derivation (Yan et al., 2013a). Three children were excluded because of head motion (mean FD Jenkinson) greater than mean+2*SD (threshold 0.483 mm) (after Yan et al., 2013b). For the remaining data, the mean volumes below the threshold of FD=0.5 mm was 96.15 (SD 5.42) for children 99.76 (SD 0.79) for adults with no significant within-group variance. The threshold of FD=0.5 mm is slightly higher than suggested for adult data (Power et al., 2014), but appropriate for child data and hence used for both groups. The average of mean FD in children was 0.15 mm (SD=0.11 mm, range=0.05–0.45 mm), and in adults 0.08 mm (SD=0.03 mm, range=0.03–0.15 mm), which reached significance between groups ($t(72)=-3.69$, $p<.001$). Therefore, FD was used as a covariate in subsequent analyses.

Neither scrubbing (Power et al., 2012) nor interpolation (Carp, 2013) was implemented here to ensure the reliability of results (Yan et al., 2013a; Zuo et al., 2013) and to avoid alteration of data frames. ALFF calculation is based on Fast Fourier transform (FFT) which cannot be applied to scrubbed data due to alteration of its temporal structure by removal of frames (Yan et al., 2013a). Except for ALFF calculation, temporal filtering was performed with a band-pass of 0.01–0.1 Hz as recommended by previous studies (Lohmann et al., 2010; Yan et al., 2013a,b).

2.5. ALFF and correlation calculation

ALFF analysis was done using REST (Song et al., 2011, http://www.restfmri.net). The procedure was the same as used in previous studies (Liu et al., 2014; Yang et al., 2007; Zang et al., 2007; Zhang et al., 2010). The time series for each voxel were first transformed to the frequency domain using FFT. The square root was calculated at each frequency of the power spectrum and the averaged square root was calculated across 0.01–0.1 Hz at each voxel, obtaining the ALFF (Zang et al., 2007). Finally, z transformation was implemented by subtracting global mean and dividing by standard deviation of all ALFF in the given brain gray mask.

For correlation analysis, two core regions of the language network (left IFG, left pSTS) as well as their right-hemispheric counterparts were selected as ROIs as identified in a previous study (Friederici et al., 2011), 'tal2mni' routine (http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach) was applied and results anatomically verified. This resulted in the following ROIs: left IFG at -58, 17, 20; rigth IFG at 58, 17, 20; left pSTS at -57, -44, 12; right pSTS at 57, -44, 12 (all coordinates in MNI space). For each participant, mean ALFF values within each ROI (voxel level) were computed and entered into Pearson's correlation analyses between these ROIs.

2.6. RSFC–behavior correlation analysis

RSFC analysis was performed for children using REST software and focusing on left IFG ROI connectivity as it is a major cortical hub relevant for processing syntactic complexity. For RSFC calculation, the mean time series of left IFG was first computed for each participant by averaging the time series of all the voxels in the left IFG (radius 6 mm), and then individual level RSFC correlation maps (r-map) were produced for the whole brain.

Next, r-maps were converted into z-maps with application of Fisher's r-to-z transformation to obtain normal distribution. Subsequently, RSFC–behavior correlation analysis was conducted using 'REST Correlation Analysis' command in the REST software. Pearson's correlation coefficients between Fisher-z-transformed RSFC strength and performance in the two task conditions (SO, OS) as well as their direct comparison were calculated within a volume of interest (VOI) of the perisylvian language regions, including the inferior frontal as well as middle and superior temporal cortices within both hemispheres (Fig. 1) according to Friederici et al. (2011). Additionally, left V1 (BA 17) served as a language-unrelated control region, which was abstracted from Brodmann template in the REST toolbox. Analysis procedure was the same as outlined above. All group level statistical analyses were controlled for age, gender, mean FD, and IQ. Finally, all statistical r-maps were transformed into z maps by implementing 'rest_TFRtoZ' function in the REST toolbox (Song et al., 2011, http://www.restfmri.net) and further corrected for multiple comparisons using Gaussian Random Field (GRF) theory ($Z > 2.3$, cluster-wise $p < .05$, GRF corrected) with minimal a cluster size of 40 voxels.

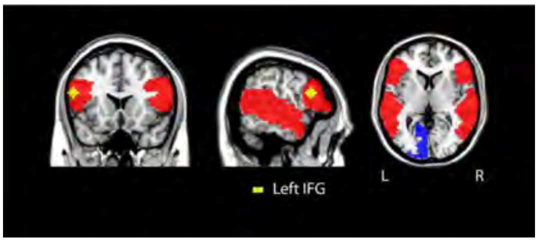

Fig. 1. Volume of interest (VOI) mask (red) used for correlation analysis. The VOI comprises a total of 6532 voxels (176,364 mm^3) covering right and left perisylvian language regions. Left IFG (yellow) served as a seed region of interest for resting-state functional connectivity (RSFC). Left BA 17 (blue) served as a language-unrelated control region for RSFC. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

3. Results

3.1. Behavioral results

Children's performance in the picture-sentence matching test resulted in a mean accuracy for SO=95.22% (SD 7.04) and for OS=81.00% (SD 16.31), suggesting a significant advantage for SO sentences ($t(40)=5.82$, $p < .001$). Both SO and OS showed significant performance above chance (SO: $t(40)=40.61$, $p < .001$, OS: $t(40)=12.02$, $p < .001$). Accuracy for both SO and OS was not significantly correlated with age, sex, or IQ.

3.2. ALFF-based functional connectivity

The results showed significant correlation between left IFG and left pSTS for adults, but not for 5-year-old children (Fig. 2A). At the same time, there was a significant correlation between left and right IFG for children, but not for adults (Fig. 2A). No other correlations were significant. The correlations for the two groups are depicted in Fig. 2B with BrainNet Viewer (Xia et al., 2013, http://www.nitrc.org/projects/bnv).

Interhemispheric connectivity as illustrated in Fig. 2 shows the quasi-comparison between adults' and children's network connectivities with strong interhemispheric connectivity for children compared to long range intrahemispheric connectivity for adults.

3.3. RSFC–behavior correlation analysis

In a next step, functional connectivity was associated with children's performance in sentence processing. By correlating RSFC maps of left IFG with scores from behavioral conditions (SO and OS), we found divergent correlation patterns for SO and OS performances. As shown in Fig. 3, correlation between the left IFG seed and SO performance was observed in bilateral but strongly left-lateralized anterior STG/STS (aSTG/aSTS). Correlation between the left IFG seed and OS performance was found in the left pSTG/pSTS. The individual variation in the contribution to correlation between left IFG and left pSTG/pSTS with OS performance is shown in Fig. 4. The direct contrast between two correlation maps revealed stronger correlation in bilateral pSTG/pSTS for OS performance, and stronger correlation within bilateral IFG for SO performance, both dominant within the left hemisphere. Peak coordinates of both correlations as well as the contrast are reported in Table 1. When seeded in the control region BA 17, no correlation within the VOI was observed.

4. Discussion

The present study set out to investigate the functional connectivity of language-relevant brain regions during resting state and its relation to syntactic language performance. Correlations among intrinsic BOLD oscillations in predefined language-relevant ROIs revealed long-range functional association between IFG and pSTS within the left hemisphere for adults, whereas interhemispheric association between bilateral IFG was observed for 5-year-old children, suggesting immaturity of the left fronto-temporal functional network within the perisylvian region in children at 5 years of age. Furthermore, an association with language performance in children was found. Long-range intrinsic connectivity between left IFG and left pSTG/pSTS was correlated with the performance in syntactically relatively more complex non-canonical sentences (OS), whereas no such fronto-temporal connectivity was associated with performance in processing syntactically less complex canonical sentences (SO). In previous studies, a selective network connecting the language-relevant frontal and

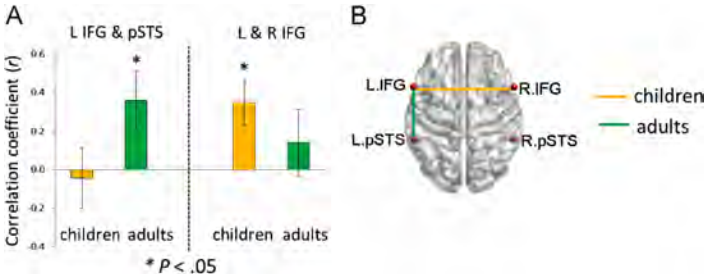

Fig. 2. Correlations of amplitudes of low frequency fluctuations between language areas for children and adults. (A) Shows a significant correlation in ALFF between left IFG and left pSTS for adults, whereas significant correlation between left and right IFG was observed for children. Error bars represent standard error of the mean. The map in (B) illustrates the regions of interests and their correlational relationships. Significant correlations are indicated with lines (orange: children, green: adults). No other correlations were significant. L: left hemisphere; R: right hemisphere; IFG: inferior frontal gyrus; pSTS: posterior superior temporal sulcus. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

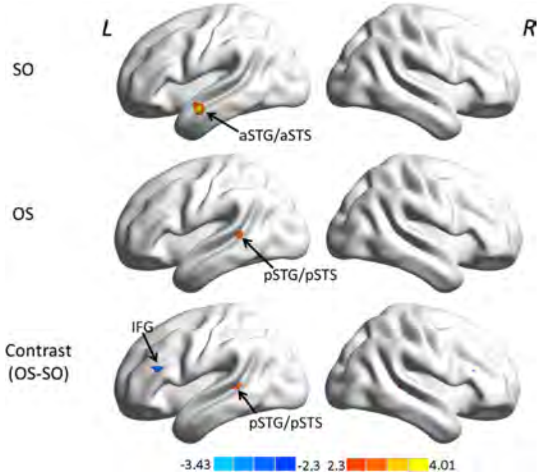

Fig. 3. Resting-state functional connectivity in its relation to sentence comprehension performance in children. Statistical maps of the correlation between functional connectivity of the left IFG (−58, 17, 20) and performance in simple syntax (SO) (first row), complex syntax (OS) (second row), as well as the direct contrast (third row, blue for SO, yellow-red for OS), $Z > 2.3$, cluster-wise $p < .05$, GRF corrected. SO performance is associated with connectivity to aSTG/aSTS as well as local connectivity within the IFG as seen in the direct contrast, while OS performance is associated with stronger long-range connectivity to the pSTG/pSTS, mainly in the left hemisphere. L, left hemisphere; R, right hemisphere; aSTG/aSTS, anterior superior temporal gyrus and sulcus; pSTG/pSTS, posterior superior temporal gyrus and sulcus; IFG, inferior frontal gyrus. Results are illustrated with BrainNet Viewer (Xia et al., 2013, http://www.nitrc.org/projects/bnv). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

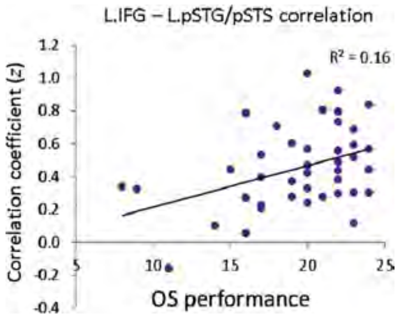

Fig. 4. Individual variation in the contribution to correlation between left IFG and left pSTG/pSTS with OS performance in children as shown in Fig. 3.

Table 1
MNI peak coordinates of RSFC–behavior correlation.

RSFC–behavior correlation	Cluster location	Cluster size (voxels)	Peak (MNI) *X*	*Y*	*Z*	Peak *Z*
SO	L.aSTG/aSTS	142	−51	−6	−15	4.01
	R.aSTG/aSTS	43	48	−9	−12	3.75
OS	L.pSTG/pSTS	52	−51	−42	6	3.43
Contrast (OS–SO)	L.pSTG/pSTS	67	−51	−39	6	3.27
	R.pSTG/pSTS	42	51	−39	6	2.74
	L.IFG	59	−39	24	15	−3.43
	R.IFG	41	36	18	18	−2.86

Notes: L: left hemisphere; R: right hemisphere; aSTG/aSTS: anterior superior temporal gyrus and sulcus; pSTG/pSTS: posterior superior temporal gyrus and sulcus; IFG: inferior frontal gyrus.

temporal regions, particularly the inferior frontal and superior temporal areas, has been described for adults in numerous fMRI experiments on syntactic processing (for reviews see Friederici, 2011, 2012; Price, 2010). The current findings imply that the network of these areas is already associated with the processing of complex syntax at the age of 5 years, even though the entire functional network is not yet fully mature, as indicated by ALFF-based functional connectivity between language-related regions in children and adults (Friederici et al., 2011).

Behavioral results of the present study suggest that children at 5 years of age are able to process syntactic information even in non-canonical OS sentences already above chance. Still, they performed significantly better on simple SO compared to syntactically more demanding OS sentences. The results show that young children at age 5 years are already developing the ability to comprehend syntactically complex utterances. The very good performance of 5-year-old children on SO sentences may be due to the fact that they may apply an agent-first strategy rather than performing a full syntactic analysis (Kamide et al., 2003). Better performance for subject-initial over object-initial sentence structures is in line with previous behavioral results from children at age 5 and 6 years (Knoll et al., 2012) or 7 years (Dittmar et al., 2008). It is, moreover, consistent with other recent findings of significant above chance accuracy for object-relative sentences in children at age 6 years (Skeide et al., 2015). But these results stand in contrast to other studies (e.g., Lindner, 2003; Schipke et al., 2011), in which children at about this age were found to perform not significantly above chance level for object-initial sentences. A number of factors might contribute to this inconsistency such as word familiarity or alternatively available linguistic cues for sentence interpretation. According to the competition model of language processing, sentence interpretation is supported by linguistic cues, among them case marking, word order, and animacy, with a language-specific weighting of these various factors (Bates and MacWhinney, 1982; MacWhinney, 2013). In the current study, in addition to unambiguous case marking, the varying animacy information of nouns across sentences might have drawn attention to the availability of such additional cues for sentence interpretation. Previous studies have often used material with only animate nouns thereby providing no additional semantic cues (Dittmar et al., 2008; Schipke et al., 2012). The availability of animacy cues in the current study might have contributed to the relatively good performance of children in comprehending sentences, although animacy did not significantly interact with the syntax.

The current analyses revealed significant correlations of low-frequency BOLD oscillation power between left IFG and left pSTS in adults, but not so in children who rather showed strong correlations between left IFG and its right-hemispheric homolog. In other words, these correlation patterns reveal a selective fronto-temporal functional association between the left hemispheric language-relevant regions in adults. For children, on the other hand, this left-hemispheric long-range network association is not yet established as in adults. For children rather interhemispheric association is observed which is in line with previous task-based fMRI findings (Brauer and Friederici, 2007; Szaflarski et al., 2006). The right hemisphere had been shown to have an important role in prosodic aspects of sentence processing, and a stronger role of prosody in early language processing had been proposed (Wartenburger et al., 2007). The stronger involvement of the right hemisphere had been discussed as a resource that supports language processing when left-hemispheric fronto-temporal connectivity is not yet mature as in early childhood (Holland et al., 2007) or decreasing as in elder age (Antonenko et al., 2013; Holland et al., 2007; Wartenburger et al., 2007). Models of structural brain development propose a stronger bilaterality in the maturing brain and relate this phenomenon to language development (Broce et al., 2015). The increasing correlation strength from left IFG to left pSTS with age is in line with the interpretation that a selective fronto-temporal functional connectivity characterizes a developmental trend within the default language network from childhood to adulthood (Friederici et al., 2011). Moreover, the interhemispheric connectivity in 5-year-olds is consistent with LFFs results of fMRI data (Friederici et al., 2011; Perani et al., 2011) and also resting-state functional connectivity (Fox et al., 2009; Fransson et al., 2011), and contrasting the prominent left-intrahemispheric functional connectivity in adults (Lohmann et al., 2010; Perani et al., 2011).

Seed-based functional connectivity was conducted with a seed in the left IFG (BA 44) which has been identified a main hub for processing complex syntax in numerous studies (for review see Friederici, 2011). For example, the brain activation in left IFG increases systematically as syntactic complexity increases (Friederici et al., 2006). The left IFG is involved in sentence embedding (nested structures) in German (Makuuchi et al., 2009) and activated in embedding and syntactic movement (Santi and Grodzinsky, 2010). Moreover, an enhanced activation in the left pSTG/pSTS has been reported for the processing of syntactic information in syntactically complex sentences (Friederici et al., 2006; Kinno et al., 2008; Röder et al., 2002). The present results revealed stronger coupling of RSFC between left IFG and left pSTG/pSTS for OS performance, but not for SO performance in 5-year-old children, indicating that competence of processing syntactically complex sentences is positively associated with selective RSFC strength between these regions. Notably, the present results are consistent with findings from task-dependent fMRI experiments (Kinno et al., 2008; Knoll et al., 2012; Thompson et al., 2010), which consistently reported enhanced selective activation in both left IFG and left pSTG/pSTS when processing syntactically complex sentences. The coherent overlapping correlation between left IFG and left pSTG/pSTS in the present LFF data are taken to reflect the inherent relationship between intrinsic brain activity and syntactic processing competence. On the basis of the present results we infer that correlations between frontal and temporal language-relevant regions in the perisylvian cortex are selectively modulated by the ability to process syntactically complex utterances.

In contrast, we found that SO performance was positively correlated with RSFC between IFG and aSTG. The aSTG has been referred to as a brain region for local, less complex syntactic and combinatorial processes. Previous research has associated increased activation in the aSTG during task fMRI employing simple dependencies in artificial grammar sequences (Friederici et al., 2006), syntactic violation tasks (Friederici et al., 2003), as well as natural language listening paradigms (Brennan et al., 2012). The IFG is structurally connected to the aSTG via a ventral fiber pathway, while the connection to the pSTG/pSTS is implemented via a dorsal pathway, which have been shown to be associated to the ability to process either simple (ventral pathway) or more complex (dorsal pathway) syntactic dependencies (Friederici et al., 2006). From the perspective of brain maturation, the ventral pathway matures earlier than the dorsal pathway (Brauer et al., 2013). We also observed stronger local correlation within the IFG for SO performance compared to OS performance. This local connectivity included the involvement of pars triangularis (BA 45) and IFS. As a subregion of IFG, BA 45 plays a role in language processing, such as syntactic movement (Grodzinsky, 2000; Santi and Grodzinsky, 2010) and semantic processes (Friederici, 2002; Hagoort, 2005). The left IFS had been argued to serve a function for supporting syntactic working memory (Makuuchi et al., 2009). Thus, both BA 45 and IFS are involved in processing sentences. The stronger local and ventral connectivity for SO performance suggests attributions to the processing of syntactically less complex sentences, while the long-range connectivity is regarded crucial for the processing of more complex syntactic structures (Skeide et al., 2015).

As observed in a previous study, the left dorsal fronto-temporal structural connection between the language-relevant areas in IFG and pSTG/pSTS develops as the brain matures and is still structurally underdeveloped at the age of seven years (Brauer et al., 2011). This is in line with our present ALFF-based functional connectivity findings of an immature left fronto-temporal functional association at age five years. Importantly, competence of parsing syntactically complex OS sentences was related to left fronto-temporal functional connectivity. Together with the structural findings from 7-year-olds, it can be interpreted that although the structural connection between left IFG and pSTG/pSTS is still immature, yet resting-state functional connectivity is at least already partly in place already at age five when it is required for the processing of syntactically complex utterances.

We should, however, note a few limitations when interpreting the results described in this paper. First, considering the difficulties of data acquisition from young children, only 100 volumes of resting-state data were collected for the current study with a total duration of 3.3 min. Van Dijk et al. (2010) observed stable correlation strengths at acquisition times of about 5 min. Moreover, recent studies found good inter-session reliability for functional homogeneity analyses with scan durations as brief as 3 min (Zuo et al., 2013) as well as high reliability of resting-fMRI measures available for scan durations of 3 min (Yan et al., 2013a). Second, given strong apriori hypotheses for selective perisylvian networks, a ROI-based rather than a whole-brain approach was chosen to examine correlations of low-frequency BOLD oscillation. This is, however, because of strong hypotheses based empirical support from numerous research on the role of these regions for syntactic processes from previous fMRI studies in adults (Friederici et al., 2011; Kinno et al., 2008; Makuuchi et al., 2009; Thompson et al., 2010; Tomasi and Volkow, 2012) and in children (Brauer and Friederici, 2007; Brauer et al., 2008; Knoll et al., 2012; Nuñez et al., 2011; Skeide et al., 2014; Yeatman et al., 2010). A ROI-based approach appeared most appropriate to answer the hypotheses. As a final remark, it is important to keep in mind that the results presented here were based on resting state fMRI data, and did not stem from task fMRI experiments. Hence, the findings should be interpreted in resting-state fMRI context with the assumption that they reflect intrinsic neural activity and in combination with behavioral data reveal relationships between functional connectivity and behavioral ability in syntactic processing. Third, we used a less stringent primary threshold ($p < .01$) with a corresponding cluster-level $p < .05$, which is more liberal than the primary threshold of $p < .001$, suggested for avoiding spanning of clusters across anatomical regions and loosing spatial specificity (Woo et al., 2014). However, that was not the case for the present data. Moreover, other studies have successfully used Gaussian random field theory with the same thresholds as applied in the current study, $Z > 2.3$, cluster-level $p < .05$ (e.g., Alaerts et al., 2015; Pirnia et al., 2015; Salomons et al., 2015).

5. Conclusion

This study revealed the development of the fronto-temporal resting-state connectivity from 5-year-olds to adults by examining the correlation of intrinsic low-frequency BOLD oscillations in language-related regions. Notably, the findings of an interhemispheric coupling of left and right IFG in 5-year-olds and long-range connectivity from IFG to pSTS within left hemisphere in adults are consistent with previous LFFs analyses of fMRI data (Friederici et al., 2011). A stronger long-range connectivity in adults corresponds to a developmental trajectory of a proper selective left-hemispheric language network (Brauer et al., 2011; Friederici et al., 2011). The RSFC–behavior relationships showed stronger long-range IFG connectivity with left pSTG/pSTS for OS performance, but stronger local and ventral correlation within the IFG and to the aSTG for SO performance. In contrast to processing relatively simple syntactic sentences (SO), processing syntactically complex sentences (OS) is associated with stronger long-range coupling between left IFG and left pSTG/pSTS. The present results support the notion that fronto-temporal functional connectivity within the language network in the left hemisphere is crucial for the processing of syntactically complex sentences (den Ouden et al., 2012; Friederici et al., 2011). They indicate that this connectivity is specific for the language network, no connectivity differences were observed for the control seed in BA 17. Although the adult-like left fronto-temporal connection is still not fully structurally developed in 5-year-olds, these two regions are already able to cooperate and correlate with syntactic processes at this age. The findings provide novel insight into the relationship between intrinsic functional connectivity and syntactic language abilities in preschool children.

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2.2 Longitudinal changes in resting-state fMRI from age 5 to age 6 covary with language development

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Longitudinal changes in resting-state fMRI from age 5 to age 6 years covary with language development

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ABSTRACT

Resting-state functional magnetic resonance imaging is a powerful technique to study the whole-brain neural connectivity that underlies cognitive systems. The present study aimed to define the changes in neural connectivity in their relation to language development. Longitudinal resting-state functional data were acquired from a cohort of preschool children at age 5 and one year later, and changes in functional connectivity were correlated with language performance in sentence comprehension. For this, degree centrality, a voxel-based network measure, was used to assess age-related differences in connectivity at the whole-brain level. Increases in connectivity with age were found selectively in a cluster within the left posterior superior temporal gyrus and sulcus (STG/STS). In order to further specify the connection changes, a secondary seed-based functional connectivity analysis on this very cluster was performed. The correlations between resting-state functional connectivity (RSFC) and language performance revealed developmental effects with age and, importantly, also dependent on the advancement in sentence comprehension ability over time. In children with greater advancement in language abilities, the behavioral improvement was positively correlated with RSFC increase between left posterior STG/STS and other regions of the language network, i.e., left and right inferior frontal cortex. The age-related changes observed in this study provide evidence for alterations in the language network as language develops and demonstrates the viability of this approach for the investigation of normal and aberrant language development.

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Introduction

Given the importance of language development during childhood, an increasing number of studies have investigated the neural basis of language acquisition. In recent years, functional magnetic resonance imaging (fMRI) has been widely used to detect the brain mechanisms underlying language processing in adults (Friederici, 2006, 2011; Kinno et al., 2008; Makuuchi et al., 2009), as well as during childhood (Balsamo et al., 2006; Brauer and Friederici, 2007; Brauer et al., 2008; Knoll et al., 2012; Perani et al., 2011; Redcay et al., 2008; Szaflarski et al., 2006a, 2006b).

Studies on language processing using fMRI in adults have consistently reported activation in the left posterior superior temporal gyrus and sulcus (STG/STS) and the left inferior frontal cortex (IFC) as crucial regions for language comprehension (for a review, see Friederici, 2011). Specifically, the left IFC has been constantly reported as being involved in processing syntactically complex sentence structures (Ben-Shachar et al., 2004; Bornkessel et al., 2005; Friederici et al., 2006b; Grewe et al., 2005; Obleser et al., 2011; Santi and Grodzinsky, 2010). Moreover, enhanced activation in the left posterior STG/STS has been reported for the processing of syntactic information in syntactically complex sentences in adults (Friederici et al., 2006a; Kinno et al., 2008; Röder et al., 2002). Developmental research has reported that the superior temporal cortex is required for rapid language acquisition during the second year of life (Redcay et al., 2008). A 10-year longitudinal study reported that bilateral superior temporal cortical activation played an increasing role in narrative comprehension from young children to adolescents (Szaflarski et al., 2012). In addition, the recruitment of left superior temporal cortex was shown for both semantic and syntactic processing in children aged 5 and 6 years (Brauer and Friederici, 2007) and for syntax–semantics interaction effects in 3–4- and 6–7-year-old children (Skeide et al., 2014).

It was furthermore shown that the maturation of structural connectivity correlates with the performance on processing complex sentences (Skeide et al., 2015), and that the structural connectivity is still not adult-like around the age of 7 years when children still have problems with processing such sentences (Brauer et al., 2011). Studies exploring the functional connectivity between the language-related areas so far have mostly been conducted with adults. They indicate a functional connectivity between the IFC and the STG/STS suggesting that these

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brain regions are functionally connected during sentence comprehension (den Ouden et al., 2012; Makuuchi and Friederici, 2013).

Spontaneous low frequency (<0.1 Hz) fluctuations (LFFs) in the human brain at rest have been observed to be related to intrinsic brain activities (Biswal et al., 1995). During the past two decades, a large number of studies have used resting-state functional MRI data to map the brain organization underlying human cognition (e.g., Dosenbach et al., 2010; Fox et al., 2005; Fransson et al., 2011).

Functional connectivity of language regions was observed in LFFs factoring out task dependent activity when seeding in the respective brain regions (Friederici et al., 2011; Lohmann et al., 2010). Data from newborns using the same analysis method reveal that such a functional connectivity is not yet present early in life when infants start to acquire language (Perani et al., 2011). These findings suggest that the analysis of LFFs can serve the investigation of language development. And indeed a number of novel findings have expanded our knowledge on the development of functional and structural connectivity in infants and young children (de Bie et al., 2012; Fransson et al., 2011, 2007; Gao et al., 2009; Lee et al., 2013; Power et al., 2010; van den Heuvel et al., 2014).

The development of the language network from childhood to adulthood was shown to be characterized by a development from inter- to intra-hemispheric connectivities (Friederici et al., 2011). So far, however, research using resting-state fMRI data to identify and explore the language related networks is still very limited (Antonenko et al., 2012; Muller and Meyer, 2014; Tomasi and Volkow, 2012; Turken and Dronkers, 2011; Xiang et al., 2010), and resting-state fMRI data to explore the development of language in children is even more sparse. Recent studies have shown that RSFC–behavior correlations are advantageous to reveal the neural basis of individual variation in cognitive performance (e.g., Hampson et al., 2006; Kelly et al., 2008; Koyama et al., 2011; Seeley et al., 2007; Stevens and Spreng, 2014; Wang et al., 2010; Zou et al., 2013). Given the interesting relation between task-dependent fMRI and seed based task-independent resting-state fMRI data on language processing in adults, we expect to elucidate the development of the functional connectivity networks related to language development by combining behavioral and resting-state fMRI data.

Here, we present an exploratory examination of developmental changes in intrinsic connectivity patterns of children from age 5 to age 6 by using a network measure, which allows an unbiased comparison at a voxel-wise level. The range was chosen since at this age the structural and functional development of the brain is in full progress (Gogtay et al., 2004; Knoll et al., 2012; Skeide et al., 2014) while at the same time performance in language functions increases steadily (Guasti, 2002; Sakai, 2005; Skeide et al., 2014). Combining resting-state functional connectivity (RSFC) with behavioral data on the development of sentence comprehension carries the potential to open new perspectives on the relation between brain maturation and the ontogeny of language in children. In order to explore the developmental changes in intrinsic connectivity patterns, longitudinal resting-state fMRI data were acquired from a cohort of typically developing children aged 5 years and one year later, and subjected to degree centrality analysis. As a measure of graph theory, degree centrality is among the most fundamental and most common centrality measures, and has been widely used to identify hubs in the human brain (e.g., Buckner et al., 2009; Cole et al., 2010; Tomasi and Volkow, 2011). Degree centrality has been found to be physiologically meaningful (Liang et al., 2013; Tomasi et al., 2015, 2013) and has been applied to investigate the changes in network connectivity associated with healthy aging (Hampson et al., 2012) and cognitive functions (van den Heuvel et al., 2009). Hubs, as highly connected central nodes in a network, are thought to play pivotal roles in the coordination of information flow (Sporns et al., 2007) and may also help to minimize wiring and metabolism costs by providing a limited number of long-distance connections that integrate local networks (Bassett and Bullmore, 2006). The approach used here is similar to that shown by Buckner et al. (2009) and Zuo et al. (2012). Binary network measure of degree centrality was computed in a voxel-wise manner and used in order to identify developmental changes in intrinsic connectivity over one year. Subsequently, the result of this analysis was used as a seed to further detect how the connections change with age and, moreover, to what extent the functional resting-state network is related to language abilities. We expected to find growing involvement of core regions of the language network with age, in particular the posterior STG/STS and IFC. The importance of these regions in functional networks supporting language functions should be reflected in a relation between the growing network architecture and language development.

Methods

Participants

Fifty-three typically developing preschool children at age 5 years (27 males; mean age 5.5 years, range 5.0 to 6.0 years) participated in the study, and longitudinal data were obtained in a one-year follow-up measurement (mean age 6.5 years, range 6.0 to 7.1 years). Prior to participation, children's parents gave written, informed consent, and children gave verbal assent for attendance. All participants were right-handed, monolingual German speakers with no history of neurological, medical, or psychological disorders. The study was approved by the Ethical Review Board of the University of Leipzig (Germany).

Behavioral testing

Sentence comprehension was assessed by the standardized German test of sentence-comprehension (Test zum Satzverstehen von Kindern (TSVK); Siegmüller et al., 2011). The test employs a picture matching task with three possible pictures in response to verbally presented sentences at varying syntactic difficulty. Participants were instructed to listen to stories and to select the picture that best fits the story. The number of correct responses was summed (in percent) and converted to standard scores (*T* values).

MRI scanning

All data were obtained at a 3T magnetic resonance scanner (Siemens Tim Trio, Germany) with a 12-channel head coil. During resting-state data acquisition, children were instructed to lie as still as possible, keep their eyes open and watch the visual presentation of a screensaver featuring a lava lamp. Resting-state fMRI whole-brain volumes were acquired with a T2*-weighted gradient-echo echo-planar imaging (EPI) sequence using the following parameters: TR 2000 ms, TE 30 ms, flip angle = 90°, slice thickness 3 mm, gap = 1 mm, FOV 19.2 cm, matrix = 64×64, 28 slices, 100 volumes. High-resolution 3-D structural images were acquired with a T1-weighted, magnetization prepared rapid gradient echo (MPRAGE) sequence using the following parameters: TR 1480 ms, TE 3.46 ms, flip angle = 10°; slice thickness 1.5 mm, gap 0 mm; matrix 250×250; spatial resolution $1 \times 1 \times 1.5$ mm.

Preprocessing

Data preprocessing was carried out using the Data Processing Assistant for Resting-State fMRI (DPARSF) (Chao-Gan and Yu-Feng, 2010, http://www.restfmri.net) which is based on Statistical Parametric Mapping (SPM8) (http://www.fil.ion.ucl.ac.uk/spm) and Resting-State fMRI Data Analysis Toolkit (REST) (Song et al., 2011, http://www.restfmri.net). Before preprocessing, the first three EPI volumes were discarded to avoid possible effects of scanner instability and allow for signal equilibration. Preprocessing steps included: *i*) slice timing by shifting the signal measured in each slice relative to the acquisition of the slice at the mid-point of each TR; *ii*) 3D motion correction using a least squares approach and a 6 parameter (rigid body) spatial transformation; *iii*) reorienting both functional and MPRAGE images and then co-registering MPRAGE image to the mean functional image of each subject; *iv*) MPRAGE images were segmented into gray matter, white matter (WM), and cerebrospinal fluid (CSF) tissue based on the NIH pediatric atlas (NIHPD) (Fonov et al., 2011, http://www.bic.mni.mcgill.ca/ServicesAtlases/NIHPD-obj1), using the asymmetric T1 version of the NIHPD atlas, age range 4.5–8.5 years old (prepuberty), based on 82 subjects; *v*) spatial normalization by using the parameters from the segmentation procedure in each subject and resampling voxel size to $3 \times 3 \times 3$ mm^3; *vi*) spatial smoothing with a 6-mm full-width-at-half-maximum (FWHM) Gaussian kernel; *vii*) nuisance regression, including principal components (PCs) extracted from subject-specific WM and CSF mask (5 PC parameters) using a component based noise correction method (CompCor) (Behzadi et al., 2007), as well as Friston 24-parameter model (6 head motion parameters, 6 head motion parameters one time point before, and the 12 corresponding squared items) (Friston et al., 1996). The CompCor procedure comprised detrending, variance (i.e., WM and CSF) normalization and PC analysis according to Behzadi et al. (2007); *viii*) band-pass temporal filtering (0.01–0.1 Hz). For degree centrality calculation, spatial smoothing was not included in the preprocessing but performed after *Z*-normalization in order to prevent artefactual local correlations between voxels (Zuo et al., 2012).

CompCor was proposed to correct for physiological noise by regressing out PCs from noise regions of interest (ROIs) (Behzadi et al., 2007). Compared with mean signal regression, where average signal were extracted from WM and CSF mask, signals captured by PCs derived from these noise ROIs can better account for voxel-specific phase differences in physiological noise due to the potential of principle component analysis to identify temporal pattern of physiological noise (Thomas et al., 2002).

Given concerns regarding a possible confounding influence of micromovements in intrinsic functional connectivity analyses (Power et al., 2012, 2014; Satterthwaite et al., 2012; Van Dijk et al., 2012), the framewise displacement (FD) of time series (Jenkinson et al., 2002) was calculated as it is preferable for its consideration of voxel-wise differences in its derivation (Yan et al., 2013a). Seven subjects with motion (mean FD) greater than mean + 2 ∗ SD (Yan et al., 2013b) were excluded, with threshold of 0.229 mm for children at age 5 and 0.221 mm at age 6, separately. For the remaining 46 data sets, the average of mean FD at age 5 was 0.101 mm (SD = 0.04 mm, range = 0.037–0.206 mm), and at age 6 was 0.092 mm (SD = 0.039 mm, range = 0.025–0.184 mm). Differences of mean FD were calculated by using paired *t*-test and showed no significant differences ($t(45) = 1.349$, $p = .184$). Nevertheless, the mean FD was controlled as a covariate of no interest in subsequent group-level statistical analyses to reduce any remaining potential effect of head motion.

Calculation of degree centrality maps

Degree centrality maps were computed by using the REST toolbox that employs an approach similar to that shown by Buckner et al. (2009) and Zuo et al. (2012). Specifically, for each voxel i the connectivity between the time course of this given voxel i and the time course of every other voxel within the mask of gray matter of the brain was computed. Then the correlation map of voxel i was converted to a binary map of connectivity thresholded at $r = 0.25$, setting all connections below the threshold to zero while setting all remaining connections to 1. The sum of all non-zero connections in this binary map was calculated to yield the degree centrality of the voxel i. This process was repeated for each voxel in the brain to produce a whole-brain map of the network degree.

The individual-level degree centrality maps were then standardized by converting to *z*-scores and maps were averaged across participants and compared (Buckner et al., 2009; Van Dijk et al., 2012; Zuo et al., 2012). The *z*-score transformation is achieved by subtracting mean degree and dividing standard deviation of degree across all voxels as described in previous studies (Buckner et al., 2009; Zuo et al., 2012). Group-level degree centrality map for each age group was obtained by implementing one-sample *t*-test. Multiple comparisons were corrected at the cluster-level using Gaussian random field theory ($|Z| > 3.5$, cluster-wise $p < .001$, GRF corrected).

The threshold used to compute degree centrality in this study was chosen to be consistent with previous studies (Buckner et al., 2009; Hampson et al., 2012; Van Dijk et al., 2012), and different threshold selections did not qualitatively change the results for the cortex (Buckner et al., 2009; Hampson et al., 2012). For an analysis with alternative thresholds, see Supplementary Fig. S1. Furthermore, the weighted version of degree centrality was also computed, assuring the robustness of the findings with nearly identical results as shown in Supplementary Fig. S2.

Developmental changes in degree centrality

The primary analysis of this study examined intrinsic connectivity differences in the longitudinal data identifying clusters that change their degree centrality with development. Paired *t*-test was performed to detect the developmental changes in voxel-wise connectivity maps from age 5 to age 6 years, controlled for head motion (mean FD).

Seed-based connectivity changes and relation to advances in language performance

However, the aforementioned primary analysis would not provide information about which connections are changing or the relation between the connections and language performance. To explore this, a secondary seed-based analysis was implemented. The resulting clusters from the primary analysis were subjected to a seed-based analysis on functional connectivity.

RSFC analyses were performed at both measurement time points using REST software. For RSFC calculation, the mean time series of the seed were first computed for each participant by averaging the time series of all the voxels in the seed (6-mm-radius sphere), and then an individual level RSFC correlation map (*r*-map) was produced within the whole brain. Next, *r*-maps were converted into *z*-maps with application of Fisher's *r*-to-*z* transformation to obtain approximately normally distributed values for further statistical analysis.

Average functional connectivity maps for both time points (age 5 and age 6) were computed based on *z*-transformed maps to illustrate the connectivity patterns of the cluster. In addition, the comparison of connectivity maps between the two time points was obtained by performing paired *t*-test, controlling for mean FD of each participant, and corrected at the cluster-level using Gaussian random field theory ($Z > 2.3$, cluster-wise $p < .05$, GRF corrected).

In order to model the relationship between changes in functional connectivity and changes in behavioral performance, the absolute changes of both connectivity strength and language comprehension (TSVK) performance were calculated for age 6 subtracting age 5, and results were then entered into a model of RSFC-behavior correlation. For further exploration of behavioral effects, the whole group data were divided into two subgroups by the median of changes in TSVK performance from age 5 to age 6. Participants with change value greater than median were considered to show greater advancement in language abilities (18 participants) whereas participants with change value smaller than median were considered to show less advancement in language abilities (20 participants). Subsequently, RSFC-behavioral correlation was obtained for each of the two subgroups. Finally, all statistical *r*-maps were transformed to *z*-maps and corrected at the cluster-level using Gaussian random field theory ($Z > 2.3$, cluster-wise $p < .05$, GRF corrected).

Results

Behavioral results

Mean accuracy for the sentence comprehension task was 67.7% (SD 11.38) at age 5 years and 78.8% (SD 8.37) at age 6 years. Performance was above chance at both time points (age 5: $t(45) = 10.55$, $p < .001$; age 6: $t(45) = 23.34$, $p < .001$), and there was a significant performance difference between the two measurement time points ($t(45) = -7.53$, $p < .001$) (Fig. 1).

Group-level degree centrality and changes with age

Degree centrality maps indicate that hubs at age 5 and age 6 years covered regions of the default mode network (DMN), including posterior cingulate cortex/precuneus (PCC), lateral temporal cortex, lateral parietal cortex, and medial/lateral prefrontal cortices (Fig. 2) as known from adult data (Buckner et al., 2009). Interestingly, the comparison between the two measurement time points yielded one cluster centered on the left posterior STG/STS (MNI coordinates: −45, −51, 21; peak z: 3.95; 170 voxels) with increased connectivity at age 6 compared to age 5 years (Fig. 3).

Seed-based connectivity changes and relation to advances in language performance

In a next step, the resulting cluster from the degree centrality analysis was used as a seed in order to examine functional connectivity of this cluster. This seeding in the left posterior STG/STS revealed a number of correlated regions at both ages, including middle frontal gyrus, bilateral PCC, dorsomedial prefrontal cortex, bilateral STG/STS and angular gyrus bilaterally (Figs. 4A and B). At age 6 years, the IFC was additionally involved (Fig. 4B). Direct comparison of functional connectivity between the two measurement time points showed developmental changes in the left inferior frontal sulcus (IFS) of the IFC and left angular gyrus from age 5 to age 6 years (Fig. 4C). Individual variations in correlations between left posterior STG/STS and left IFS as well as left angular gyrus are shown in Figs. 4D and E, respectively.

In order to further evaluate behavioral relevance of these functional networks, changes in RSFC were correlated with changes in language comprehension performance from age 5 to age 6 years. Participants were allocated to two subgroups with either greater or less change in language performance based on a median split. RSFC-behavior correlation for each subgroup showed distinct patterns. Specifically, correlations in the left and right IFC were observed in children with greater advancement in language abilities, whereas correlations in bilateral PCC, ventromedial prefrontal cortex and anterior cingulate cortex were observed in children with less advancement in language abilities (Figs. 5A and B; Table 1). All maps are displayed with the BrainNet Viewer (Xia et al., 2013, http://www.nitrc.org/projects/bnv/).

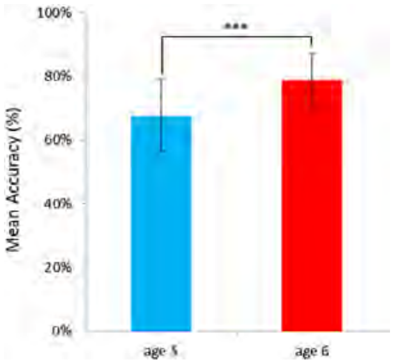

Fig. 1. Mean accuracy of sentence comprehension performance (TSVK) at age 5 and 6 years. Error bars represent standard error of the mean (*** P < .001).

Discussion

The current study investigated the neural basis of language development in longitudinal resting-state functional MRI data in a cohort of typically developing children at age 5 and age 6 years. Using a data-driven approach to investigate degree centrality, we found at both ages a similar pattern of hubs covering regions of the DMN. A significant cluster of stronger intrinsic connectivity at age 6 compared to age 5 was observed in the left posterior STG/STS. The RSFC-behavior correlation revealed connections from this cluster to language-relevant regions in bilateral IFC for children with greater advancement in language abilities, whereas for children with less advancement in language abilities stronger connectivity of DMN regions was observed. These findings demonstrate the development of functional resting-state networks during a one-year period between age 5 and age 6 and its relation to concurrent development of language abilities.

Increased degree centrality in left posterior STG/STS with age

Importantly, we found increased connectivity between ages 5 to 6 years in the left posterior STG/STS. There was no other region that showed connectivity increase above threshold and there were no regions with concurrent decreased connectivity change. Accumulated evidence supports the role of the posterior STG/STS in language comprehension (for a review, see Friederici, 2011). Task-related activation in this region has been reported for processing syntactic information in word list (Humphries et al., 2005; Snijders et al., 2009), complex sentences (Cooke et al., 2002; Friederici et al., 2006a, 2009; Kinno et al., 2008; Röder et al., 2002), and combined syntactic and semantic sentential information (Friederici et al., 2003, 2010) as well as argument processing (Grewe et al., 2007, 2006). Taken together, evidence suggests this region as a central component for the integration of linguistic information at different levels.

Note that the specific functional role of increased degree centrality in the left posterior STG/STS from age 5 to age 6 cannot be concluded directly from resting-state functional brain data alone. These changes can potentially be related to a variety of developmental changes in brain maturation and human development. However, based on the specific location of this increase in connectivity in the posterior STG/STS, we hypothesize that it is related to the central involvement of this region in the language network where changes in the functional network are manifested at that age when language abilities increase prominently (e.g., Guasti, 2002; Sakai, 2005). The posterior STG/STS had been shown a central part of the language network in studies with adults (Friederici, 2011; Hickok and Poeppel, 2007; Vigneau et al., 2006) and with children (Berl et al., 2010; Brauer et al., 2008; Knoll et al., 2012; Skeide et al., 2015). Therefore, a secondary analysis exploring changes in RSFC based on this region was performed to further examine which network connections terminating in this region are changing from age 5 to age 6, whether they are part of the language network, and whether there is a relation to behavioral changes in language abilities.

Frontal-to-temporal connections in children with greater advancement in language comprehension

Previous task-dependent fMRI experiments in adults and children have consistently reported enhanced activation in both left IFC and left posterior STG/STS when processing syntactically complex sentences (Kinno et al., 2008; Knoll et al., 2012; Obleser et al., 2011; Thompson et al., 2010). The left frontal-to-temporal network connection between

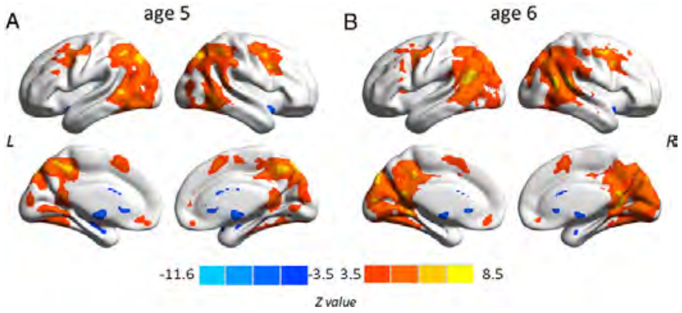

Fig. 2. Voxel-wise degree centrality maps at age 5 (2A) and age 6 (2B). Red–yellow colors indicate positive connectivity, whereas blue colors indicate negative connectivity. *Z* value is the scale of degree centrality. Multiple comparisons were corrected at the cluster-level using Gaussian random field theory ($|Z| > 3.5$, cluster-wise $p < .001$, GRF corrected). L, left hemisphere; R, right hemisphere.

language-relevant brain regions develops as the brain matures and is still structurally immature at the age of 5 to 6 years (Brauer et al., 2011). Furthermore, the common activity of left IFC and posterior STG/STS in the sense of a "default language network" has been observed in LFFs (Lohmann et al., 2010), which was, moreover, shown not yet fully developed at age 6 years (Friederici et al., 2011). Consistent with these findings, we found that RSFC between bilateral IFC (left inferior frontal gyrus and right IFS) and left posterior STG/STS was positively correlated with greater advancement in language comprehension, suggesting that this long-range connection is relevant for the progress in language abilities.

It has been widely acknowledged that the activation of left IFC is crucial for language comprehension (Friederici, 2011; Friederici et al., 2006a; Makuuchi et al., 2009; Santi and Grodzinsky, 2010). Other studies have shown increasing BOLD responses in the left IFC as task difficulty increases and have related this to increased working memory and phonological processing demands (Binder et al., 2005; Desai et al., 2006; Lehmann et al., 2006; Tregellas et al., 2006). A developmental study found that children with better syntactic processing skills showed more prominent activation in the left IFC compared to children with poorer syntactic processing skills (Nuñez et al., 2011). Particularly, mounting evidence from fMRI or behavioral studies has revealed that language performance is closely related with working memory (e.g., Baddeley, 2003; Gathercole and Susan, 2000; Määttä et al., 2014; Montgomery and Evans, 2009; van Daal et al., 2008). It was shown that for both, syntactic processes as well as working memory demands, the IFC is recruited (Makuuchi et al., 2009). The current findings of stronger functional connectivity between IFC and posterior STG/STS could be helpful for syntactic comprehension in a narrow sense but also in a more general sense for working memory related processes.

The involvement of DMN in children with less advancement in language comprehension

The DMN was originally defined as a set of brain areas that consistently show task-induced deactivation in functional imaging studies (Binder et al., 1999; Raichle et al., 2001; Shulman et al., 1997). Recent studies have found that the DMN was widely engaged in internal mentation (e.g., self-referential processing, mentalizing, affective cognition, theory of mind, episodic retrieval, autobiographical thought, mnemonic or prospective processes) (Andrews-Hanna et al., 2010, 2014a, 2014b; Buckner and Carroll, 2007; D'Argembeau et al., 2005; Gusnard et al., 2001; Gusnard and Raichle, 2001; Johnson, 2003; Northoff et al., 2006; Whitfield-Gabrieli et al., 2011).

Mounting evidence has confirmed the opposite relationship between behavioral performance and the suppression of the DMN (Anticevic et al., 2010; Daselaar et al., 2004; Shulman et al., 2007; White et al., 2013). For instance, successful performance on cognitive tasks has been related to a specific recruitment of task-relevant networks while deactivating resting-state networks such as the DMN

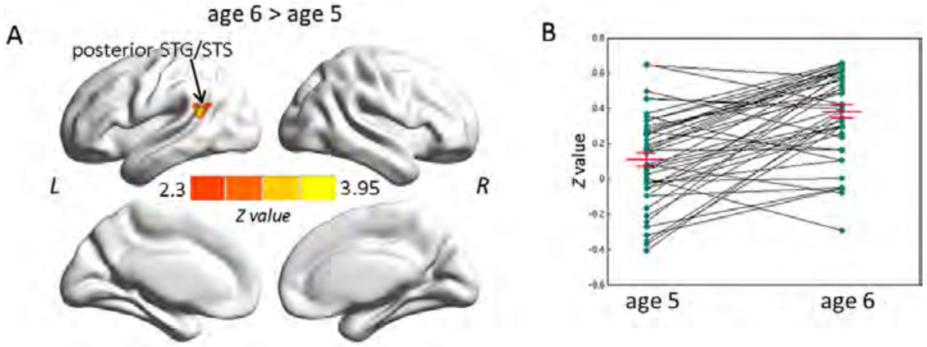

Fig. 3. Comparison of degree centrality maps between age 5 and age 6 years (3A). Red–yellow colors indicates stronger degree centrality at age 6 compared to age 5 in the left posterior STG/STS. Multiple comparisons were corrected at the cluster level using Gaussian random field theory ($Z > 2.3$, cluster-wise $p < .05$, GRF corrected). Figure B illustrates individual variation in degree centrality of left posterior STG/STS and also includes the mean values of the cluster in posterior STG/STS at age 5 and age 6 years, as well as error bars representing standard error of the mean (3B). L, left hemisphere; R, right hemisphere. STG/STS, superior temporal gyrus and sulcus.

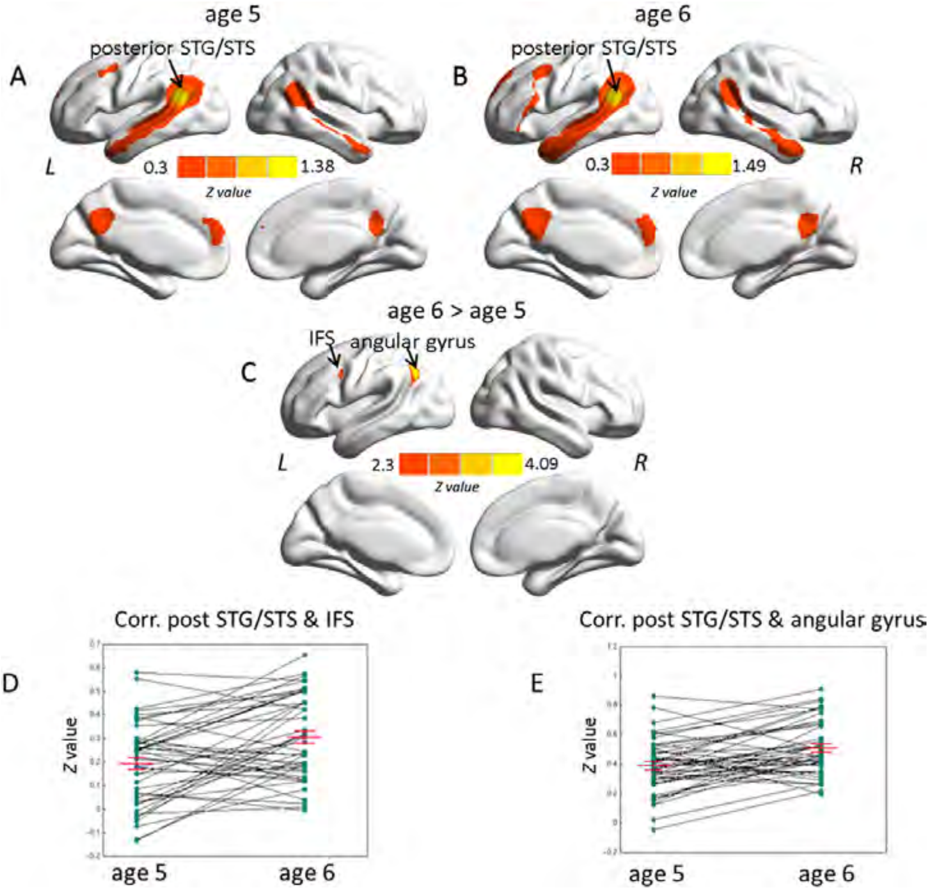

Fig. 4. Average functional connectivity maps seeded in the left posterior STG/STS shown for children at age 5 (4A) and age 6 (4B). Significant correlations to left inferior frontal cortex are only found for age 6 ($Z = 0.3$ with minimal cluster size of 60 voxels). Fig. C depicts the direct contrast between the two time points (4C), with red–yellow colors indicating stronger connections at age 6 ($Z > 2.3$, cluster-wise $p < .05$, GRF corrected). In addition, the individual variation in correlations between left posterior STG/STS and left IFS (4D), as well as between posterior STG/STS and left angular gyrus (4E) are depicted including the mean correlation coefficients at age 5 and age 6. Error bars represent standard error of the mean. L, left hemisphere; R, right hemisphere. IFS, inferior frontal sulcus.

(Anticevic et al., 2012, 2010; Hampson et al., 2010; Kelly et al., 2008). Similarly, less DMN suppression was associated with less efficient stimulus processing during attention lapses (Weissman et al., 2006). These findings support the view of a direct competition between exogenous and endogenous components for attentional and executive resources, and suggest that lower involvement of the DMN activity on a trial-by-trial basis is associated with better cognitive performance, indicating that the ability of DMN suppression is functionally important (for a review, see Anticevic et al., 2012). Therefore, it might be plausible to infer that the involvement of the DMN in functional connectivity for children with less advancement in language abilities is due to their insufficient suppression of the DMN.

Limitations

It is important to note that the interpretation of the current results should be limited to resting-state fMRI context, especially for the involvement of regions within the DMN, because the data presented here are not from a task-based fMRI experiment. Though, consistent activation of PCC was found in semantic processing, and it has been proposed that the involvement of PCC might have to do with the nature of episodic memory and PCC probably acts as an interface between the semantic retrieval and episodic encoding systems based on the fact of strong connections of PCC and hippocampus (Binder et al., 2009). Moreover, a model of involvement of regions within DMN was proposed when the task itself engages the semantic system (e.g., semantic tasks) (Binder et al., 2009), but it still requires more evidence with regarding to the role of the DMN in language processing. Therefore, in future studies, it would be necessary to identify to what extent the DMN is involved in language processing as well as the interactions between DMN and the language specific network by using language-related fMRI data. Another limitation of the present study is the relatively short acquisition time for the resting-state fMRI data. Considering the difficulties of data acquisition from typically developing young children during waking state, a total of 100 volumes resting-state fMRI data were collected, which is relatively short for intrinsic functional connectivity analysis. However, importantly, studies with comparably short acquisition of resting-state fMRI data observed stable correlation strengths with acquisition times as brief as 5 min (Van Dijk et al., 2010). Moreover, recent studies found good inter-session reliability for functional

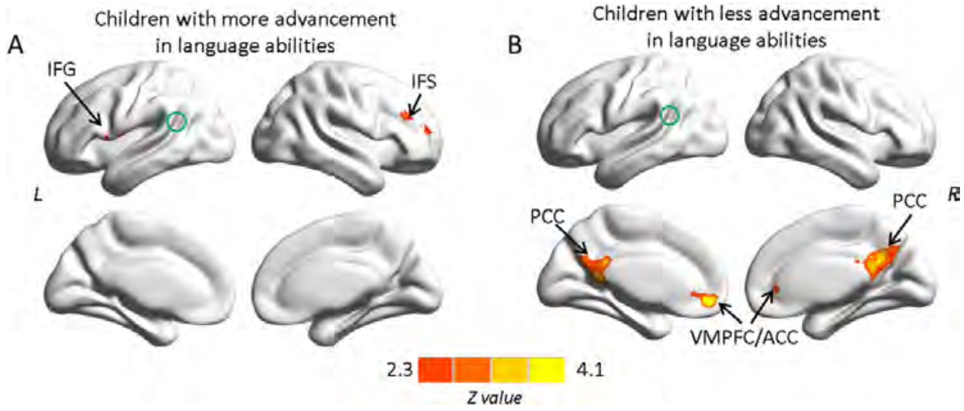

Fig. 5. Correlations between changes in functional connectivity seeded in the left posterior STG/STS cluster (green circle) and changes in language comprehension performance from age 5 to age 6 in children with greater advancement in language abilities (5A) and children with less advancement in language abilities (5B). While for the former, significant correlations to the bilateral inferior frontal cortex were found, for the latter, no such correlations to other parts of the language network were observed and rather correlations to regions within the DMN exist. Multiple comparisons were corrected at the cluster level using Gaussian random field theory ($Z > 2.3$, cluster-wise $p < .05$, GRF corrected). L, left hemisphere; R, right hemisphere. IFG, inferior frontal gyrus; IFS, inferior frontal sulcus; PCC, posterior cingulate cortex/precuneus; VMPFC/ACC, ventromedial prefrontal cortex/anterior cingulate cortex.

homogeneity analyses with scan durations as brief as 3 min (Zuo et al., 2013) and high reliability of resting-state fMRI measures available with data length of 3 min (Yan et al., 2013a). Hence, the present findings can be considered reliable and valid.

Conclusion

Exploring the development of intrinsic brain connectivity, increases in the left posterior STG/STS were identified as significant changes in the degree centrality during a one-year period in typically developing children between age 5 and age 6 years. The RSFC of left posterior STG/STS to language-relevant perisylvian regions is significantly associated with greater advancement in language abilities, whereas RSFC of left posterior STG/STS to regions within DMN is significantly correlated with less advancement in language abilities. These findings suggest that functional connectivity within the language network considerably develops from age 5 to age 6 and becomes behaviorally relevant. The present data provide evidence for alterations in functional networks with respect to language development during preschool age, and demonstrate the viability of these methods for characterizing the brain basis and ontogeny of language development in children.

Table 1
Details of RSFC–behavior correlations in two subgroups of children with greater or less advancement in sentence comprehension over the one-year period from age 5 to 6 years.

Subgroup	L/R	Region	BA	Peak MNI coordinates			Voxels	Z value
				x	y	z		
Children with greater advancement	L	IFG	44	−42	24	9	60	3.31
	R	IFS	46	51	39	30	100	3.38
Children with less advancement	L/R	PCC	7	15	−30	9	705	4.10
	L/R	VMPFC, ACC	32	−6	48	−9	148	4.01

Note: L, left hemisphere; R, right hemisphere; BA, Brodmann's area. IFG, inferior frontal gyrus; IFS, inferior frontal sulcus; PCC, posterior cingulate cortex/precuneus; VMPFC, ventromedial prefrontal cortex; ACC, anterior cingulate cortex.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.neuroimage.2015.12.008.

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Supplementary Material

Longitudinal changes in resting-state fMRI from age 5 to age 6 years covary with language development

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Degree centrality maps at alternative thresholds

Degree centrality maps were thresholded at r = 0.25, consistent with previous studies (Buckner et al., 2009; Hampson et al., 2012; Van Dijk et al., 2012). As a further test on the robustness of the binarized degree centrality results, we calculated degree centrality maps at alternative thresholds (r = 0.20; r = 0.30). This did not qualitatively affect the results as shown in Fig. S1.

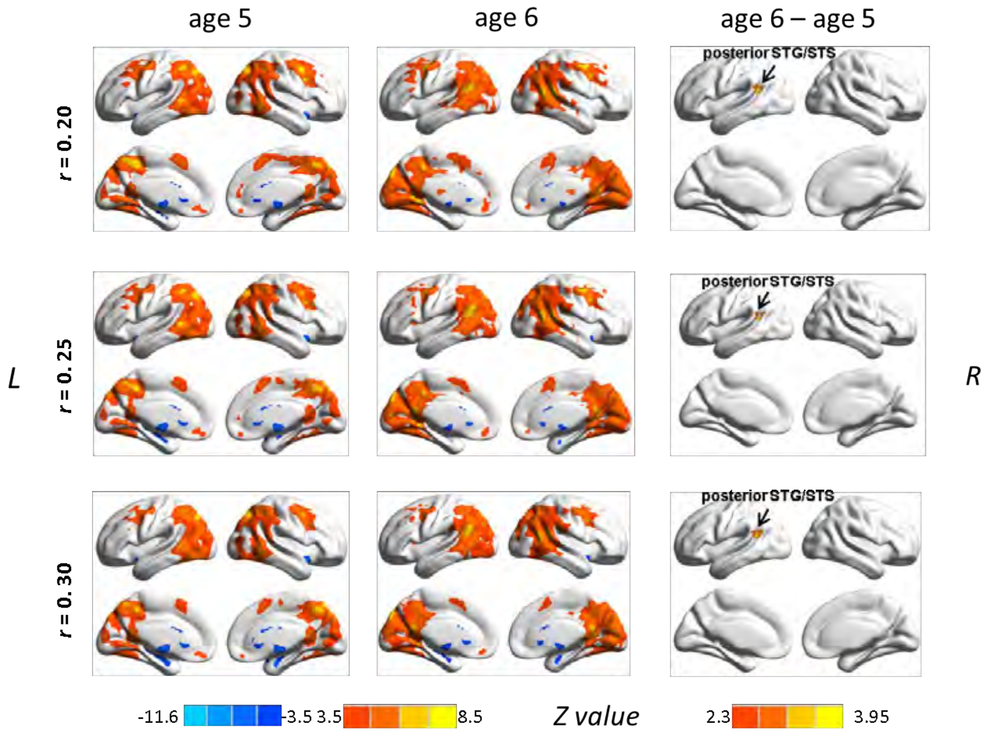

Fig. S1: Binarized degree centrality maps thresholded at r = 0.20, r = 0.25, and r = 0.30. The results are qualitatively equivalent, supporting the robustness of the findings independent of a specific threshold.

Weighted degree centrality maps

In order to confirm the robustness of the degree centrality results, also weighted versions of degree centrality maps were computed. Weighted maps confirmed the results of the binarized maps for degree centrality analysis as shown in the main results for age 5 and age 6 years (Fig. 2) as well as their contrast (Fig. 3). As shown in Fig. S2, results for binarized and weighted maps do not differ qualitatively. The location of the maximum in the resulting cluster of the direct contrast map is nearly identical, MNI coordinates for binarized maps: -45, -51, 21 (peak z: 3.95; 170 voxels); MNI coordinates for weighted maps: -42, -54, 24 (peak z: 4.16; 203 voxels).

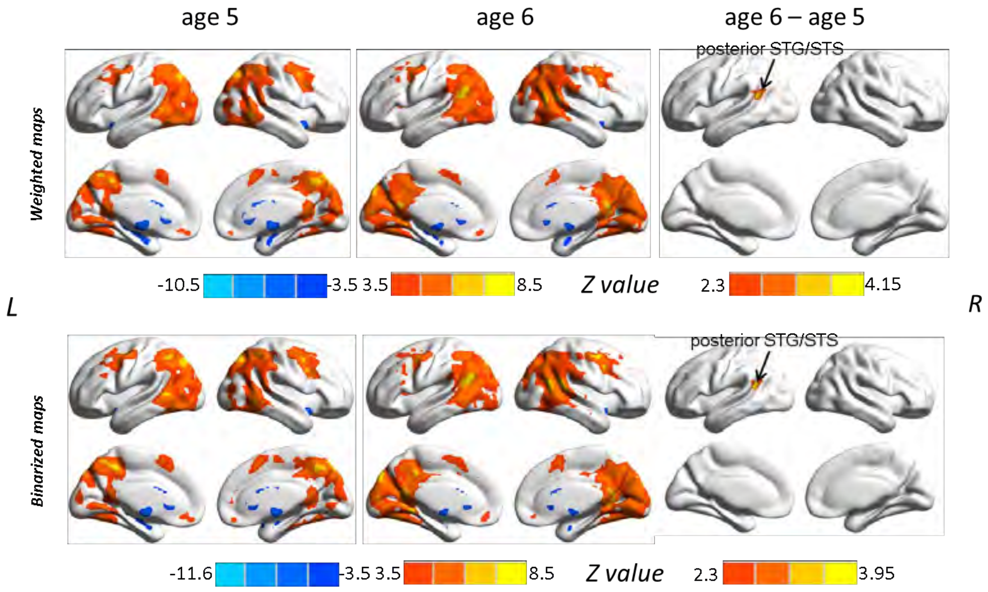

Fig. S2: Weighted (first row) and binarized (second row) maps for the degree centrality analysis. Both types of maps show qualitatively identical results. Crucially, the posterior STG/STS shows up in the direct age contrast for both types of analyzes.

3 General discussion and outlook

This thesis delineates the functional brain connectivity in typically developing children and the covariation of this connectivity in the language network with children's growing language abilities by using the rs-fMRI technique. Two studies were performed: one study detected developmental differences in interregional connectivity within language-related regions from 5-year-olds to adults and also the correlation between intrinsic functional connectivity and children's sentence comprehension performance; the other study examined longitudinal changes in functional connectivity over a one-year period and its relation to the concurrent development of language abilities in typically developing children. These two studies have different foci, but with a certain inherent connection. In this chapter, I will briefly discuss the findings of these two peer-reviewed and published studies, and provide an outlook for further research.

3.1 General discussion of the findings

In the first study (Chapter 2.1; Xiao et al., 2016a), before participating in an MRI scanning session, children at the age of 5 years were assessed in a behavioral session in order to examine their ability of sentence comprehension by using a picture-sentence matching test developed in-house and to obtain behavioral correlates for the subsequent rs-fMRI data collection. The picture-sentence matching test for behavioral topicalization (Beto) evaluates the performance in comprehending different word orders in German sentences. These sentences consisted of two syntactic conditions: simple canonical subject-initial sentences and syntactically more complex non-canonical object-initial sentences. In these sentences, the nouns were either animate (animals) or inanimate (objects), and both animate and inanimate referents were masculine nouns. Noun phrases in sentences were case marked by the nominative case (NOM, subject) or the accusative case (ACC, object). The children’s performance was above chance in both conditions of the Beto test, but showed a significant advantage of subject-initial sentences over object-initial sentences. Of note is the good performance in object-initial sentences, reflecting the ability to comprehend syntactically complex utterances in 5-year-olds. According to the Competition Model, sentence interpretation is supported by linguistic cues, among them case marking, word order, and animacy, with a language-specific weighting of these various factors (Bates & MacWhinney, 1982; Bates et al., 1984; MacWhinney, 2012). Therefore, the relatively good performance might be attributed to available animacy information of nouns across sentences in addition to the unambiguous case marking information. Even though both syntactic and semantic factors were included in these sentences, a significant main effect was only observed for the syntactic factor, which further confirmed the syntax manipulation as the main driving factor for behavioral differences in this experiment and underlined our decision to focus on the syntactic manipulation as well as its neural underpinnings.

In this study, rs-fMRI data were acquired from healthy adults and typically developing children aged 5 years. In a primary analysis, the comparison of children with adults was performed to explore the development of functional connectivity within language-related regions (i.e., bilateral IFG and posterior STS). The results showed an intrahemispheric correlation between left IFG and left posterior STS in adults and an interhemispheric correlation between left IFG and its right-hemispheric homolog in children. In a subsequent RSFC–behavior correlation analysis, left IFG was used as the seed due to its crucial role in processing complex syntax. Distinct correlation patterns were observed for the performance in two types of sentence conditions, i.e., subject-initial and object-initial sentences. Specifically, the functional connection within left IFG was related to the ability of processing subject-initial sentences, while the functional connection between left IFG and left posterior STG/STS was correlated with the competence of processing object-initial sentences that are syntactically more complex than subject-initial sentences. The strong coupling of RSFC between left IFG and left posterior STG/STS for object-initial sentences suggests that the ability to process syntactically complex sentences is positively associated with selective RSFC between these regions. This finding is consistent with previous task-related fMRI studies (Kinno et al., 2008; Knoll et al., 2012; Skeide et al., 2015), which reported enhanced selective activations in both left IFG and left posterior STG/STS when processing syntactically complex sentences. Therefore, it can be inferred that the correlation between frontal and temporal language-relevant regions in the left perisylvian cortex is selectively modulated by the ability to process syntactically complex utterances. In conclusion, children at the age of 5 years are already able to make use of long-range connectivity between left BA 44 and left posterior STG/STS to process syntactically complex sentences, although this connectivity is still immature at this age.

In the second study (Chapter 2.2; Xiao et al., 2016b), children aged 5 years were selected as the initial sample considering that the structural and functional development of the brain and language functions in children at this age have been consistently shown in full progress (Gogtay et al., 2004; Knoll et al., 2012; Skeide et al., 2014). Thus, it is reasonable to expect significant changes in both brain and behavioral performance in an interval of one year, i.e., between 5 and 6 years. Moreover, German children enter elementary school by the age of 7 years, and their language abilities might be affected by different schooling, which would inevitably be a potential confounding factor and not easy to disentangle from the natural development. Therefore, only a one-year follow-up was implemented in this study.

Prior to MRI scanning, all children performed the standardized German test of sentence comprehension (Test zum Satzverstehen von Kindern (TSVK); Siegmüller et al., 2011), by which their sentence comprehension performance at age 5 and age 6 was assessed. The behavioral results showed above chance performance in sentence comprehension (TSVK) at both measurement time points and a significant improvement over a one-year period. Longitudinal rs-fMRI data were obtained from the same cohort of children at both measurement time points in order to investigate changes of functional brain networks during brain maturation and their relation to concurrent development in language performance. A data-driven approach, i.e., degree centrality, was used to explore the development of intrinsic functional connectivity from age 5 to age 6, and the age-related positive change was observed in the posterior STG/STS. Focusing on this region, a seed-based functional connectivity analysis was performed to explore the changes of the functional network and their association with the concurrent language development. The whole group of children was divided into two subgroups by the median of changes in language performance from age 5 to age 6, and the changes in functional connectivity and changes in language performance were entered into a model of RSFC–behavior correlation. The results demonstrated that children with greater advancement in language abilities showed correlations in language-relevant regions (i.e., bilateral IFC), while children with less advancement in language abilities presented connectivity with regions in the DMN. There are two main points to be discussed with respect to these findings. One is the increased degree centrality in the left posterior STG/STS over a one-year period, which cannot be concluded directly from resting-state functional brain data alone. Although we cannot exclude that this change is potentially related to general developmental changes in brain maturation and development, we suggest that this finding is associated with the advancement in language development based on two reasons. First, the left posterior STG/STS is known for its central role in the language network, which has been repeatedly shown in a number of task-based fMRI studies in adults (Friederici, 2011; Friederici et al., 2009; Hickok & Poeppel, 2007; Vigneau et al., 2006) as well as in children (Berl et al., 2010; Brauer et al., 2008; Knoll et al., 2012; Skeide et al., 2015). Second, the correlation of this region's functional connectivity with behavioral measures of language development provides further evidence for a language-related assumption. Given the available data as examined in this study, changes in language development are a suggestive candidate. The other point to be discussed is the frontal-to-temporal connection in children with greater advancement in language comprehension. As discussed in the first study, enhanced activations in both left IFG and left posterior STG/STS have been consistently observed when processing syntactically complex sentences. We thus suggest that this long-range connection between bilateral IFC (including left IFG and right inferior frontal sulcus) and left posterior STG/STS is relevant to the progress in the language abilities. This progress may be due not only to purely syntactic processes, but also due to memory-related processes and their respective brain regions as demonstrated by a recent fMRI study in 5 to 8 years old children (Fengler et al., 2016). In children the activation in the posterior STG during processing complex sentences was predicted by the children's increase in verbal working memory (Fengler et al., 2016). Therefore, strong functional connectivity between IFC and posterior STG/STS in the left hemisphere could be helpful for syntactic processing in a narrow sense but also in a more general sense for verbal working memory related processes. Taken together, the findings in this study indicate that the development of intrinsic functional connectivity in preschool children over the course of one year is detectable by using a data-driven approach, and more importantly, it is related to the concurrent language development.

3.2 The outlook for future research

The present thesis provides primary data to describe the relationship between the development of intrinsic functional brain connectivity within the language network and the concurrent improvement in sentence comprehension in typically developing children. However, in order to better understand the language-related organization of the developing brain, several concerns should be taken into consideration in future research.

First, it is suggested to evaluate the developmental changes in structural connectivity and their relation to the advancement of language abilities during the course of typical development in children. Research has found that functional connectivity between two core language processing regions and structural maturation connecting these regions predict children's performance in parsing syntactically complex sentences (Skeide et al., 2015), which suggests a potential relation between structural maturation and language development. So far, the longitudinal changes in functional connectivity have been detected (Xiao et al., 2016b), and one would hypothesize that structural maturation should also be observable over the same one-year period. Evidence from structural connectivity, together with functional development, could possibly define the neural basis of language development and facilitate a better comprehension of the brain basis underlying the ontogeny of language.

Secondly, more empirical evidence needs to be gained from language-related fMRI experiments in order to achieve a comprehensive understanding of the language-related brain organization. Although rs-fMRI can investigate language-related brain systems in a relatively straightforward manner, the explanation for these findings has to be constrained to a resting-state context. Moreover, comparable language-related fMRI data would allow identifying the role of brain regions involved in the intrinsic language network. For example, the precuneus is regarded as a core region of the DMN, but it has also been found in semantic processing (Binder et al., 2009). In the second study (Chapter 2.2; Xiao et al., 2016b), functional connectivity between left posterior STG/STS and the DMN regions, such as the precuneus and anterior cingulate cortex, was observed in children with less advancement in language abilities. However, without fMRI data from language experiments, it is difficult to determine whether the involvement of these regions is very general for cognitive processing or whether it is rather language specific. Therefore, the combination of rs-fMRI and task-based fMRI data is suggested to better understand the brain organization of the language network, which might also be able to present a more comprehensive picture of the language function in the developing brain.

Lastly, a further advancement from the present results is to perform resting-state studies in pediatric patients with atypical language development. The application of rs-fMRI makes it feasible to acquire data from both typical and atypical pediatric populations, and multiple approaches for rs-fMRI data analysis are viable to detect abnormal brain functions (for a review, see M. H. Lee et al., 2013). The comparison of the brain organization in clinical pediatric populations with that in typically developing children could broaden our knowledge of the language-related functional organization of the brain. Moreover, language-related neuroplasticity in typically developing children possibly provides a basis for clinical diagnoses for aberrant language development.

3.3 Conclusion

In this thesis, the rs-fMRI technique was employed to investigate the functional brain connectivity and its relation to language processing in typically developing children. The first study reported children’s performance in comprehending sentences with different word orders and its correlation with intrinsic functional connectivity within the language network. Behaviorally, 5-year-olds are able to understand relatively complex sentences. Although children at this age are still in the process of developing their ability to parse complex syntax, they can make use of semantic information in sentences to comprehend complex syntactic information as shown in a neurocognitive model of language development (Skeide & Friederici, 2016). The ability to process syntactically complex sentences in children is related to the functional connection between left IFG and left posterior STG/STS in the resting brain, suggesting this connection serving as a predictor of processing complex sentences in young children. The second study reported the developmental changes in functional connectivity over a one-year period and their relevance to the concurrent language development. This study further confirmed the importance of the frontal-to-temporal connection in the left perisylvian regions, which was found to be related to greater advancement in children’s language abilities. The coupling of RSFC between left IFG and left posterior STG/STS observed in these two studies corroborates and enriches the neurocognitive model of language development from the perspective of rs-fMRI studies. According to this model, the selective connectivity between IFG and posterior STG in the left hemisphere is associated with enhanced ability to process complex syntax information in children (Skeide & Friederici, 2016); however, the findings in this thesis reveal that this connectivity is also related to complex sentence processing in 5-year-old children and greater advancement in language development. In summary, this thesis presented first studies describing the relationship between the intrinsic brain activity and language processing in typically developing children. These findings provide new insights into the intrinsic language network and its relation to the language processing and development as the brain matures.

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Summary

Introduction

The capacity to acquire and process syntactic information with complex structures is unique in human, although non-human primates can also learn and deal with simple structures (Fitch & Hauser, 2004). In young children, despite the fact that they have developed the ability to process sentence-level semantic and syntactic information as young as 3 years of age, they still need extra cues (e.g., semantic information and animacy) to comprehend syntactically complex sentences until age 9 (Skeide & Friederici, 2016). The cue that is crucial for sentence comprehension is not reliably accessible in the early stage of language learning because of the competitions among different cues, such as competitions among animacy, case-marking, word order, and subject-verb agreement in German. The winning cue with the relatively strongest strength is dominant in sentence comprehension, which is also an important determinant of the ability to process sentences at different stages. Take German for example, children at the age of 4.5 years using word order as the main cue strategy cannot differ object-initial and subject-initial sentences, and children at 6 years are able to use case-marking cues to better process object-initial sentences than younger children (Schipke et al., 2012). In general, the case-marking cue becomes dominant for sentence interpretation in German children until the age of 6 years, and before this age, word order and animacy information come into play for sentence comprehension (Dittmar et al., 2008; Knoll et al., 2012; Schipke et al., 2012).

In adults, it has been found that the underpinnings of sentence processing can be characterized by ventral and dorsal pathways (Friederici, 2012a; Hickok & Poeppel, 2004, 2007; Rauschecker & Scott, 2009; Rauschecker & Tian, 2000) and their underlying white matter pathways (Friederici et al., 2006a; Saur et al., 2008; Skeide et al., 2015). The dorsal pathway connecting left posterior superior temporal gyrus and sulcus (STG/STS) to left inferior frontal gyrus (IFG, i.e., BA 44) has been demonstrated to be specifically related to syntactically complex sentence processing, which is still underdeveloped at the age of seven years (Brauer et al., 2011; Brauer et al., 2013).

Resting-state fMRI (rs-fMRI) has been proved to be a useful tool to examine low-frequency (<0.01 Hz) fluctuations in the brain. The intrinsic activity in the resting brain can identify distinct connectivity patterns that are similar to functional systems from task-based fMRI studies (Cole et al., 2014; Smith et al., 2009). As a valid and relatively simple technique, rs-fMRI makes it feasible to acquire data from vulnerable populations such as patients and young children who are not able to perform complicated tasks in the MRI scanner. It also enables us to study various functional systems in the brain simultaneously. Considering these merits, in the present thesis, rs-fMRI was employed to investigate language-related functional connections in the developing brain and their relation to sentence comprehension performance. Moreover, the relationship between changes in intrinsic functional connectivity over a one-year period and concurrent language development was also explored.

Results & Discussion

The first study (Chapter 2.1; Xiao et al., 2016a) explored the extent to which children's behavioral performance in processing syntactic complexity as tested outside the scanner is related to functional connectivity of language-relevant brain regions in the resting brain. In a primary analysis, amplitude of low-frequency fluctuations was used to examine the functional correlations between language-relevant brain regions (i.e., bilateral IFG and posterior STS) in both 5-year-olds and adults. The results showed a strong intrahemispheric correlation between

IFG and posterior STS in the left hemisphere for adults and a strong interhemispheric correlation between left IFG and its right-hemispheric homolog for children. This implied an immature functional connectivity within language-related regions in children. Prior to scanning, all children additionally performed a picture-sentence matching test for behavioral topicalization (Beto) developed in-house to evaluate their performance in comprehending different word orders in German sentences (i.e., canonical subject-initial sentences and non-canonical object-initial sentences). The canonical subject-initial sentences are relatively simple, and children showed a significant advantage on them compared to the syntactically more complex non-canonical object-initial sentences. The children's performance in comprehending two types of sentences was separately correlated with their intrinsic brain activity. Specifically, resting-state functional connectivity (RSFC) maps were calculated for the whole brain by seeding in the left IFG due to its crucial relevance to processing syntactic complexity. These RSFC maps were then correlated with the behavioral performance in each sentence type across subjects. The correlational analysis demonstrated that connectivity within the left IFG is related to parsing subject-initial sentences that are syntactically simple, whereas connectivity between left IFG and left posterior STG/STS is associated with processing object-initial sentences that are syntactically more complex. These findings suggest that, in 5-year-olds, the left IFG and left posterior STG/STS are already able to cooperate and correlate with syntactic processes, although their connection is still not fully developed at this age.

The second study (Chapter 2.2; Xiao et al., 2016b) investigated the longitudinal changes in intrinsic functional brain connectivity and their relation to language development in a cohort of preschool children at age 5 and a one-year follow-up. The focus on this age (5 and 6 years old) is due to the full progress of the structural and functional development of the brain at this time

(Gogtay et al., 2004; Knoll et al., 2012; Skeide et al., 2014) and the concurrent steady increase of the performance in language functions (Guasti, 2002; Sakai, 2005; Skeide et al., 2014). The sentence comprehension performance of all children at these two measurement time points was assessed by the standardized German test of sentence comprehension (Test zum Satzverstehen von Kindern (TSVK); Siegmüller et al., 2011). The behavioral results showed above chance performance in sentence comprehension (TSVK) at both measurement time points and a significant improvement over a one-year period. Longitudinal rs-fMRI data were acquired from the same cohort of children at two measurement time points. Degree centrality, a data-driven approach, was employed to detect the development of intrinsic functional connectivity from age 5 to age 6. Increases in connectivity with age were found in the left posterior STG/STS. In a secondary functional connectivity analysis, this region was used as a seed to explore the changes of the functional network and their behavioral relevance. The whole group of children was divided into two subgroups by the median of changes in language performance, and RSFC–behavior correlation was obtained for each of the two subgroups. For children with greater advancement in language performance, correlations were observed in language-related regions (i.e., inferior frontal cortex (IFC), including left IFG and right inferior frontal sulcus), suggesting that the long-range connection between left posterior STG/STS and IFC is related to the progress in the language abilities. Instead, children with less advancement in language performance showed correlations in regions within the default mode network (DMN). The findings in this study suggest that functional connectivity within the language network develops considerably from age 5 to age 6 and becomes behaviorally relevant; they provide primary evidence for language-related neuroplasticity in preschool children, which may have implications for further investigations of normal and aberrant language development.

To sum up, the present thesis seeks to explore the intrinsic functional neural basis underlying language development in preschool children. The main focus of these two studies is the correlation between the functional brain connectivity and off-line language performance. Distinct correlation patterns are observed not only in 5-year-olds dealing with different sentence complexity, but also for the different developmental rate in the language domain over a one-year period. Moreover, studies in this thesis demonstrate the viability of the approaches for rs-fMRI data analysis despite the limited data length. These findings provide new insights into the brain basis of language processing as well as the development of language abilities in typically developing children.

For future research, firstly, it is suggested to detect the developmental changes in structural connectivity and its relation to language performance. Evidence from the maturation of structural connectivity, along with functional development, could possibly define the neural basis of language development and therefore allow for a better comprehension of the brain basis underlying the ontogeny of language. Secondly, the combination of rs-fMRI and language-related fMRI data is necessary to better understand the functional brain organizations of the language network. In some cases, rs-fMRI data alone are not sufficient to identify brain regions involved in language processing, such as the DMN regions, and thus task-based fMRI experiments might be helpful to determine the specific functions of these regions. Finally, rs-fMRI studies in pediatric patients with atypical language development could be considered as a further advancement from the present results. Current findings from typically developing children provide a basis for normal language development and its comparison with abnormal development in children would shed light on clinical diagnoses for aberrant language development.

Zusammenfassung

Einleitung

Der Erwerb der Fähigkeit, syntaktische Informationen in komplexen Satzstrukturen zu verarbeiten, ist eine speziell menschliche, wohingegen nicht-menschlichen Primaten lediglich nur einfachen Strukturen erlernen können (Fitch & Hauser, 2004). Kleinen Kinder erlernen schnell die Grundlagen ihrer Muttersprache, dennoch haben sie bis ins Schulalter hinein noch Schwierigkeiten mit der Verarbeitung syntaktisch komplexer Sätze (Skeide & Friederici, 2016). Die Nutzung von Hinweisreize, die helfen, Satzkonstruktionen eindeutig zu verstehen, wird von Kindern im frühen Stadium des Sprachenlernens zusätzlich für das Satzverständnis genutzt. Dieses Wissen ist noch nicht stabil etabliert und erfordert eine Abwägung zwischen verschiedenen Hinweisreizen, wie etwa Belebtheit, Kasusmarkierung, Wortfolge und Subjekt-Verb-Kongruenz. Diese Hinweisreize weisen je nach Sprache und Sprachentwicklungsalter unterschiedliche Verfügbarkeiten und Reliablitäten auf. Der Hinweisreiz mit der relativ stärksten Validität ist im Sprachverständnis dominant. Im Deutschen zeigen Kinder im Alter von 4,5 Jahren unter Verwendung der Wortfolge als dominantem Hinweisreiz eine Verarbeitungsstrategie, die nicht zwischen subjektinitialen- und objektinitialen Sätzen unterscheiden kann. Kinder im Alter von 6 Jahren sind bereits in der Lage, Kasusmarkierung für das Satzverständnis zu nutzen und damit objektinitiale Sätze besser zu verarbeiten als jüngere Kinder (Schipke et al., 2012). Im Allgemeinen etabliert sich der Hinweisreiz der Kasusmarkierung für die Satzinterpretation bei deutschen Kinder im Vorschulalter bis zum Alter von etwa 6 Jahren. Bei jüngeren Kindern kommen Wortfolge- und

Belebtheitsinformationen für das Sprachverständnis stärker zum Tragen (Dittmar et al., 2008; Knoll et al., 2012; Schipke et al., 2012).

In den letzten zwei Jahrzehnten haben funktionellen Magnetresonanztomographie (fMRT) Studien die sich entwickelnden Fähigkeit der Sprachverbeitung bei Kindern in Bezug zur Hirnreifung gesetzt. In Arbeiten zum ausgereiften Sprachverarbeitungssystem bei Erwachsen hat sich gezeigt, dass die Sprachverarbeitung unter Einbeziehung eines Hirnnetzwerkes bestehend aus vor allem einem ventralen und einem dorsalen Verarbeitungsweg der vornehmliche linkshemisphärischen perisylvischen Hirnregion erfolgt, und die relevanten Hirnregionen (Friederici, 2012a; Hickok & Poeppel, 2004, 2007; Rauschecker & Scott, 2009; Rauschecker & Tian, 2000) sowie ihre zugrundeliegenden Nervenfaserverbindungen sind umfänglich beschrieben worden (Friederici et al., 2006a; Saur et al., 2008; Skeide et al., 2015). Für das sich entwickelnde Sprachverarbeitungsnetzwerk bei Kindern hat sich gezeigt, dass der dorsalen Pfad, welcher den posterioren Gyrus et Sulcus temporalis superior (STG/STS) mit dem Gyrus frontalis inferior (IFG, i.e., BA 44) verbindet und bei der Verarbeitung insbesondere syntaktisch komplexerer Sätze eine wichtige Rolle spielt, im Alter von sieben Jahren noch immer unterentwickelt ist (Brauer et al., 2011; Brauer et al., 2013).

Funktionelle MRT im Ruhezustand (rs-fMRT) hat sich als ein geeignetes Instrument erwiesen, niederfrequente (<0.01 Hz) Schwankungen der Hirnaktivität zu untersuchen. Die intrinsische Aktivität des Gehirns im Ruhezustand kann Muster funktioneller neuronaler Netzwerke identifizieren ähnlich denen von Funktionssystemen, die sich bei fMRT Studien unter Aufgabenstellung zeigen (Cole et al., 2014; Smith et al., 2009). Als valide und relativ einfach anzuwendende Technik ermöglicht rs-fMRT beispielsweise, Daten von sonst nur schwer zugänglichen Probandenpopulationen wie etwa Patienten oder kleinen Kindern zu erheben, die nicht in der Lage sind, komplizierte Aufgaben im MRT-Scanner durchführen. Darüber hinaus können verschiedene funktionelle Systeme im Gehirn gleichzeitig untersucht werden. Unter Berücksichtigung dieser Möglichkeiten wurde rs-fMRT in der vorliegenden Arbeit eingesetzt, um die funktionelle Organisation des Sprachnetzwerks in der Entwicklung des Gehirns zu erforschen.

Ergebnisse & Diskussion

Der Schwerpunkt der ersten Studie (Kapitel 2.1; Xiao et al., 2016a) lag auf der hirnfunktionellen Grundlage der Verarbeitung syntaktischer Komplexität bei 5-jährigen Kindern. Dazu wurden Verhaltensdaten erhoben und in Bezug zu rs-fMRT Daten der sprachrelevanten Hirnregionen gesetzt. Die Ergebnisse zeigten eine intrahemispherische Korrelation der LFF-Amplituden zwischen IFG und posteriorem STS in der linken Hemisphäre für Erwachsene, während für Kinder eine vornehmlich interhemisphärische Korrelation zwischen dem linken IFG und seinem rechtshemisphärischen Homolog auffallend war. Dies ist gleichzusetzen mit einer noch unreifen funktionellen Konnektivität bei Kindern. Die Konnektivität ließ sich zudem in Bezug setzen zur Leistung der Kinder in einem Satzverständnistest für unterschiedlich komplexe Satzstrukturen (kanonische subjektinitiale Sätze und nichtkanonische objektinitiale Sätze). Die Kinder zeigten für relativ einfache kanonische Sätze signifikant bessere Leistungen in der Satzverarbeitung im Vergleich zu syntaktisch komplexeren nicht-kanonischen Sätzen. Dabei ist es wichtig festzuhalten, dass die Leistung für die Verarbeitung dieser Sätze mit der intrinsischen Hirnaktivität im rs-fMRT korreliert. Im einzelnen wurden die funktionelle Konnektivität (RSFC) des linken IFG im Ruhezustand berechnet, da es sich hierbei um die entscheidende Region handelt, die relevant ist für die Verarbeitung syntaktischer Komplexität. Die Korrelationsanalyse zeigte, dass die Verarbeitungsleistung für kanonische Satzkonstruktionen mit der Konnektivität innerhalb des linken IFG zusammenhängt, während die Konnektivität zwischen linkem IFG und linkem posteriorem STG/STS mit der Verarbeitungsleistung für syntaktisch komplexere nichtkanonische objektinitiale Sätze zusammenhängt. Das wichtigste Ergebnis dieser Studie ist, dass das linke frontotemporalen Konnektivitätsnetzwerk bereits in funktioneller Verbindung mit der Verarbeitung komplexer Syntax bei 5-jährigen zu sehen ist.

Die zweite Studie (Kapitel 2.2; Xiao et al., 2016b) untersuchte die Entwicklungsveränderung der intrinsische funktionellen Konnektivität im Gehirn und ihre Beziehung zur Sprachentwicklung bei Kindern im Vorschulalter von 5 Jahren sowie einem Jahr später. Dieses Alter (5 bis 6 Jahre) ist aufgrund der großen Entwicklungsschritte in der strukturellen und funktionellen Hirnentwicklung in dieser Zeit von besonderem Interesse (Gogtay et al., 2004; Knoll et al., 2012; Skeide et al., 2014) sowie aufgrund der stetigen Zunahme der Verarbeitungsleistung für Sprachfunktionen zur gleichen Zeit (Guasti, 2002; Sakai, 2005; Skeide et al., 2014). Das Satzverständnis der Kinder wurde zu beiden Messzeitpunkten mit einem standardisierten deutschen Satzverständnistest untersucht (Test zum Satzverstehen von Kindern (TSVK); Siegmüller et al., 2011). Auch rs-fMRT Daten wurden zu beiden Testzeitpunkten erhoben. Als Konnektivitätsmaß diente *degree centrality*, ein datengetriebener Ansatz zur Untersuchung funktioneller Konnektivität. Veränderungen der intrinsischen Konnektivität im Alter von 5 bis 6 Jahren konnte im linken posterioren STG beobachtet werden, woraufhin diese Region als *seed* für eine RSFC-Analyse verwendet wurde, um die Änderungen der funktionellen Netzwerke sowie deren Verhaltensrelevanz zu erkunden. Der Schwerpunkt der Studie lag auf der Erforschung der Korrelation zwischen den Veränderungen der funktionellen Konnektivität und den Veränderungen in der Sprachperformanz. Dazu wurde die Gesamtgruppe der Kinder mittels *median split* in zwei Untergruppen der Veränderungen in der Sprachleistung aufgeteilt. Für

Kinder mit größerem Fortschritt in der Sprachleistung zeigten sich Korrelationen in sprachrelevanten Bereichen (d.h., inferiorem Frontalkortex (IFC), einschließlich des links IFG und rechten Sulcus frontalis inferior), was darauf hindeutet, dass die Verbindung zwischen dem links posterioren STG/STS und dem IFC mit dem Entwicklungfortschritt in der Sprachfähigkeiten eng zusammenhängt. Stattdessen zeigten Kinder mit weniger Fortschritt in der Sprachperformanz Korrelationen zu *default mode network* Regionen. Diese Ergebnisse legen nahe, dass die funktionelle Konnektivität innerhalb des Sprachnetzwerks sich deutlich im Alter von 5 zu 6 Jahren entwickelt und verhaltensrelevant ist. Dies indiziert primäre Anhaltspunkte für die sprachbezogene Neuroplastizität bei Vorschulkindern, die Auswirkungen auf den weiteren Forschritt der typischen wie auch atypischen Sprachentwicklung haben kann.

Insgesamt adressiert die vorliegende Dissertation die intrinsische funktionelle neuronale Basis, welche der Sprachentwicklung bei Kindern im Vorschulalter zugrundeliegt. Der Schwerpunkt der beiden Studien ist die Korrelation zwischen der hirnfunktionellen Konnektivität und der offline gemessenen Sprachverstehensleistung. Klar unterscheidbare Korrelationsmuster sind nicht nur bei 5jährigen für unterschiedlich komplexe Satzkonstruktionenzu beobachten, sondern auch für verschieden ausgeprägte Entwicklungsfortschritte in der Sprache innerhalb eines einjährigen Zeitraums für das Alter von 5 bis 6 Jahren. Außerdem zeigen die Studien in dieser Arbeit die Bedeutung der Ansätze von rs-fMRT Datenanalysen. Die Erkenntnisse, die in dieser Dissertation gewonnen werden konnten, liefern neue Einblicke in die neuronale Basis der Sprachverarbeitung sowie die Entwicklung der sprachlichen Fähigkeiten.

Für die zukünftige Forschung wird zum einen vorgeschlagen, im nächsten Schritt zusätzlich die entwicklungsbedingten Veränderungen der strukturellen Konnektivität sowie ihre Beziehung zur Sprachleistung zu erfassen. Forschung bei Kindern haben bereits die die hauptsächlich relevanten Sprachverarbeitungsbereiche (das heißt, des linken IFG und des linken posterioren STG) verbindenden Nervenfasern als wichtige Prädiktoren für die Entwicklung der Sprachverarbeitungsfähigkeiten für syntaktische Komplexität identifiziert (Skeide et al., 2015), so dass die Entwicklung der strukturellen Konnektivität in einem Ein-Jahres-Intervall die Möglichkeit böte, die Veränderungen der Hirnstruktur im Zusammenhang mit der gleichzeitigen Veränderung der sprachlichen Fähigkeiten zu untersuchen. Zweitens ist die Kombination von rs-fMRT und sprachbezogenen Daten auf aufgabenbezogene fMRT notwendig, um ein besseres Verständnis der Hirnfunktionsorganisation des Sprachnetzwerk zu erlangen. In bestimmten Fällen sind rs-fMRT Daten allein nicht ausreichend, um alle innerhalb des Standardnetzwerks der Sprachverarbeitung beteiligten Hirnregionen zu identifizieren. Drittens können Untersuchungen mit fMRT-Studien im Ruheszustand bei pädiatrischen Patienten mit atypischer Sprachentwicklung als Weiterentwicklung aus den vorliegenden Ergebnissen genutzt werden. Aktuelle Erkenntnisse mit typisch entwickelten Kindern bieten eine Grundlage für die Untersuchung der Sprachentwicklung bei Kindern mit atypischer Entwicklung als Vergleich und könnten möglicherweise mehr Licht auf klinischen Diagnosen für atypische Sprachentwicklung werfen.

Appendices

Curriculum Vitae

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Publications

Xiao, Y., Brauer, J., Lauckner, M., Zhai, H., Jia, F., Margulies, D., & Friederici, A.D (2016). Development of the intrinsic language network in preschool children from age 3 to 5 years. *PLoS ONE* 11 (11): e0165802.

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Xiao, Y., Zhai, H., & Xu, X. (2012). Effects of age of acquisition and word frequency on the processing bias of the middle/inferior frontal gyrus. *International Journal of Advances in Psychology 1*(2), 26–36.

Author contribution statement:

Title: Development of a selective left-hemispheric fronto-temporal network for processing syntactic complexity in language

Journal: Neuropsychologia

Authors: Yaqiong Xiao , Angela D. Friederici, Daniel S. Margulies, Jens Brauer

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Part Name (First author): Xiao, Y.
- analysis of the data
- writing of the publication

Part Name (Author 2): Friederici, A.D.
- experiment design
- writing of the publication

Part Name (Author 3): Margulies, D.S.
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Author contribution statement:

Title: Longitudinal changes in resting-state fMRI from age 5 to age 6 covary with language development

Journal: Neuroimage

Authors: Yaqiong Xiao , Angela D. Friederici, Daniel S. Margulies, Jens Brauer

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Part Name (First author): Xiao, Y.

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Erklärung über die eigenständige Abfassung der Arbeit

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Verbinformationen im Satzverstehen

20 Katja Werheid
Implizites Sequenzlernen bei Morbus Parkinson

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Is it Memory or Illusion? Electrophysiological Characteristics of True and False Recognition

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Verbales Arbeitsgedächtnis und die Verarbeitung ambiger Wörter in Wort- und Satzkontexten

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36 Claudia Friedrich
Prosody and spoken word recognition: Behavioral and ERP correlates

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Zentralnervöse Verarbeitung akustischer Informationen
Signalidentifikation, Signallateralisation und zeitgebundene Informationsverarbeitung bei Patienten mit erworbenen Hirnschädigungen

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Neuronal correlates of selective attention: An investigation of electrophysiological brain responses in the EEG and MEG

43 Gert Wollny
Analysis of Changes in Temporal Series of Medical Images

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Errors, Conflicts, and the Brain Current Opinions on Performance Monitoring

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Sprachverstehen mit Cochlea-Implantat: EKP-Studien mit postlingual ertaubten erwachsenen CI-Trägern

45 Kirsten G. Volz
Brain correlates of uncertain decisions: Types and degrees of uncertainty

46 Hagen Huttner
Magnetresonanztomographische Untersuchungen über die anatomische Variabilität des Frontallappens des menschlichen Großhirns

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58 Jutta L. Mueller
Mechanisms of auditory sentence comprehension in first and second language: An electrophysiological miniature grammar study

59 Franziska Biedermann
Auditorische Diskriminationsleistungen nach unilateralen Läsionen im Di- und Telenzephalon

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The Processing of Lexical Semantic and Syntactic Information in Spoken Sentences: Neuroimaging and Behavioral Studies of Native and Non-Native Speakers

61 Kerstin Leuckefeld
The Development of Argument Processing Mechanisms in German. An Electrophysiological Investigation with School-Aged Children and Adults

62 Axel Christian Kühn
Bestimmung der Lateralisierung von Sprachprozessen unter besondere Berücksichtigung des temporalen Cortex, gemessen mit fMRT

63 Ann Pannekamp
Prosodische Informationsverarbeitung bei normalsprachlichem und deviantem Satzmaterial: Untersuchungen mit ereigniskorrelierten Hirnpotentialen

64 Jan Derrfuß
Functional specialization in the lateral frontal cortex: The role of the inferior frontal junction in cognitive control

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The cognitive representation of tasks – Exploring the role of response modalities using the task-switching paradigm

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The role of the basal ganglia in auditory language processing: Evidence from ERP lesion studies and functional neuroimaging

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Behavioral and neural correlates of endogenous control processes in task switching

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The Functional Neuroanatomy of Text Comprehension

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Aufgabeninhibition als Mechanismus der Konfliktreduktion zwischen Aufgabenrepräsentationen

76 Juliane Hofmann
Phonological, Morphological, and Semantic Aspects of Grammatical Gender Processing in German

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Attaching Relative Clauses in German – The Role of Implicit and Explicit Prosody in Sentence Processing

78 Uta Wolfensteller
Habituelle und arbiträre sensomotorische Verknüpfungen im lateralen prämotorischen Kortex des Menschen

79 Päivi Sivonen
Event-related brain activation in speech perception: From sensory to cognitive processes

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Music phrase structure perception: the neural basis, the effects of acculturation and musical training

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Neural Correlates of Working Memory for Verbal and Tonal Stimuli in Nonmusicians and Musicians With and Without Absolute Pitch

82 Korinna Eckstein
Interaktion von Syntax und Prosodie beim Sprachverstehen: Untersuchungen anhand ereigniskorrelierter Hirnpotentiale

83 Florian Th. Siebörger
Funktionelle Neuroanatomie des Textverstehens: Kohärenzbildung bei Witzen und anderen ungewöhnlichen Texten

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Aktivität im Gamma-Frequenzbereich des EEG: Einfluss demographischer Faktoren und kognitiver Korrelate

85 Jörg Bahlmann
Neural correlates of the processing of linear and hierarchical artificial grammar rules: Electrophysiological and neuroimaging studies

86 Jan Zwickel
Specific Interference Effects Between Temporally Overlapping Action and Perception

87 Markus Ullsperger
Functional Neuroanatomy of Performance Monitoring: fMRI, ERP, and Patient Studies

88 Susanne Dietrich
Vom Brüllen zum Wort – MRT-Studien zur kognitiven Verarbeitung emotionaler Vokalisationen

89 Maren Schmidt-Kassow
What's Beat got to do with ist? The Influence of Meter on Syntactic Processing: ERP Evidence from Healthy and Patient populations

90 Monika Lück
Die Verarbeitung morphologisch komplexer Wörter bei Kindern im Schulalter: Neurophysiologische Korrelate der Entwicklung

91 Diana P. Szameitat
Perzeption und akustische Eigenschaften von Emotionen in menschlichem Lachen

92 Beate Sabisch
Mechanisms of auditory sentence comprehension in children with specific language impairment and children with developmental dyslexia: A neurophysiological investigation

93 Regine Oberecker
Grammatikverarbeitung im Kindesalter: EKP-Studien zum auditorischen Satzverstehen

94 Şükrü Barış Demiral
Incremental Argument Interpretation in Turkish Sentence Comprehension

95 Henning Holle
The Comprehension of Co-Speech Iconic Gestures: Behavioral, Electrophysiological and Neuroimaging Studies

96 Marcel Braß
Das inferior frontale Kreuzungsareal und seine Rolle bei der kognitiven Kontrolle unseres Verhaltens

97 Anna S. Hasting
Syntax in a blink: Early and automatic processing of syntactic rules as revealed by event-related brain potentials

98 Sebastian Jentschke
Neural Correlates of Processing Syntax in Music and Language – Influences of Development, Musical Training and Language Impairment

99 Amelie Mahlstedt
The Acquisition of Case marking Information as a Cue to Argument Interpretation in German
An Electrophysiological Investigation with Pre-school Children

100 Nikolaus Steinbeis
Investigating the meaning of music using EEG and fMRI

101 Tilmann A. Klein
Learning from errors: Genetic evidence for a central role of dopamine in human performance monitoring

102 Franziska Maria Korb
Die funktionelle Spezialisierung des lateralen präfrontalen Cortex: Untersuchungen mittels funktioneller Magnetresonanztomographie

103 Sonja Fleischhauer
Neuronale Verarbeitung emotionaler Prosodie und Syntax: die Rolle des verbalen Arbeitsgedächtnisses

104 Friederike Sophie Haupt
The component mapping problem: An investigation of grammatical function reanalysis in differing experimental contexts using eventrelated brain potentials

105 Jens Brauer
Functional development and structural maturation in the brain's neural network underlying language comprehension

106 Philipp Kanske
Exploring executive attention in emotion: ERP and fMRI evidence

107 Julia Grieser Painter
Music, meaning, and a semantic space for musical sounds

108 Daniela Sammler
The Neuroanatomical Overlap of Syntax Processing in Music and Language - Evidence from Lesion and Intracranial ERP Studies

109 Norbert Zmyj
Selective Imitation in One-Year-Olds: How a Model's Characteristics Influence Imitation

110 Thomas Fritz
Emotion investigated with music of variable valence – neurophysiology and cultural influence

111 Stefanie Regel
The comprehension of figurative language: Electrophysiological evidence on the processing of irony

112 Miriam Beisert
Transformation Rules in Tool Use

113 Veronika Krieghoff
Neural correlates of Intentional Actions

114 Andreja Bubić
Violation of expectations in sequence processing

115 Claudia Männel
Prosodic processing during language acquisition: Electrophysiological studies on intonational phrase processing

116 Konstanze Albrecht
Brain correlates of cognitive processes underlying intertemporal choice for self and other

117 Katrin Sakreida
Nicht-motorische Funktionen des prämotorischen Kortex: Patientenstudien und funktionelle Bildgebung

118 Susann Wolff
The interplay of free word order and pro-drop in incremental sentence processing: Neurophysiological evidence from Japanese

119 Tim Raettig
The Cortical Infrastructure of Language Processing: Evidence from Functional and Anatomical Neuroimaging

120 Maria Golde
Premotor cortex contributions to abstract and action-related relational processing

121 Daniel S. Margulies
Resting-State Functional Connectivity fMRI: A new approach for assessing functional neuroanatomy in humans with applications to neuroanatomical, developmental and clinical questions

122 Franziska Süß
The interplay between attention and syntactic processes in the adult and developing brain: ERP evidences

123 Stefan Bode
From stimuli to motor responses: Decoding rules and decision mechanisms in the human brain

124 Christiane Diefenbach
Interactions between sentence comprehension and concurrent action: The role of movement effects and timing

125 Moritz M. Daum
Mechanismen der frühkindlichen Entwicklung des Handlungsverständnisses

126 Jürgen Dukart
Contribution of FDG-PET and MRI to improve Understanding, Detection and Differentiation of Dementia

127 Kamal Kumar Choudhary
Incremental Argument Interpretation in a Split Ergative Language: Neurophysiological Evidence from Hindi

128 Peggy Sparenberg
Filling the Gap: Temporal and Motor Aspects of the Mental Simulation of Occluded Actions

129 Luming Wang
The Influence of Animacy and Context on Word Order Processing: Neurophysiological Evidence from Mandarin Chinese

130 Barbara Ettrich
Beeinträchtigung frontomedianer Funktionen bei Schädel-Hirn-Trauma

131 Sandra Dietrich
Coordination of Unimanual Continuous Movements with External Events

132 R. Muralikrishnan
An Electrophysiological Investigation Of Tamil Dative-Subject Constructions

133 Christian Obermeier
Exploring the significance of task, timing and background noise on gesture-speech integration

134 Björn Herrmann
Grammar and perception: Dissociation of early auditory processes in the brain

135 Eugenia Solano-Castiella
In vivo anatomical segmentation of the human amygdala and parcellation of emotional processing

136 Marco Taubert
Plastizität im sensomotorischen System – Lerninduzierte Veränderungen in der Struktur und Funktion des menschlichen Gehirns

137 Patricia Garrido Vásquez
Emotion Processing in Parkinson's Disease: The Role of Motor Symptom Asymmetry

138 Michael Schwartze
Adaptation to temporal structure

139 Christine S. Schipke
Processing Mechanisms of Argument Structure and Case-marking in Child Development: Neural Correlates and Behavioral Evidence

140 Sarah Jessen
Emotion Perception in the Multisensory Brain

141 Jane Neumann
Beyond activation detection: Advancing computational techniques for the analysis of functional MRI data

142 Franziska Knolle
Knowing what's next: The role of the cerebellum in generating predictions

143 Michael Skeide
Syntax and semantics networks in the developing brain

144 Sarah M. E. Gierhan
Brain networks for language
Anatomy and functional roles of neural pathways supporting language comprehension and repetition

145 Lars Meyer
The Working Memory of Argument-Verb Dependencies
Spatiotemporal Brain Dynamics during Sentence Processing

146 Benjamin Stahl
Treatment of Non-Fluent Aphasia through
Melody, Rhythm and Formulaic Language

147 Kathrin Rothermich
The rhythm's gonna get you: ERP and fMRI evidence on the interaction of metric and semantic processing

148 Julia Merrill
Song and Speech Perception – Evidence from fMRI, Lesion Studies and Musical Disorder

149 Klaus-Martin Krönke
Learning by Doing?
Gesture-Based Word-Learning and its Neural Correlates in Healthy Volunteers and Patients with Residual Aphasia

150 Lisa Joana Knoll
When the hedgehog kisses the frog
A functional and structural investigation of syntactic processing in the developing brain

151 Nadine Diersch
Action prediction in the aging mind

152 Thomas Dolk
A Referential Coding Account for the Social Simon Effect

153 Mareike Bacha-Trams
Neurotransmitter receptor distribution in Broca's area and the posterior superior temporal gyrus

154 Andrea Michaela Walter
The role of goal representations in action control

155 Anne Keitel
Action perception in development: The role of experience

156 Iris Nikola Knierim
Rules don't come easy: Investigating feedback-based learning of phonotactic rules in language.

157 Jan Schreiber
Plausibility Tracking: A method to evaluate anatomical connectivity and microstructural properties along fiber pathways

158 Katja Macher
Die Beteiligung des Cerebellums am verbalen Arbeitsgedächtnis

159 Julia Erb
The neural dynamics of perceptual adaptation to degraded speech

160 Philipp Kanske
Neural bases of emotional processing in affective disorders

161 David Moreno-Dominguez
Whole-brain cortical parcellation: A hierarchical method based on dMRI tractography

162 Maria Christine van der Steen
Temporal adaptation and anticipation mechanisms in sensorimotor synchronization

163 Antje Strauß
Neural oscillatory dynamics of spoken word recognition

164 Jonas Obleser
The brain dynamics of comprehending degraded speech

165 Corinna E. Bonhage
Memory and Prediction in Sentence Processing

S 2 Tania Singer, Bethany E. Kok, Boris Bornemann, Matthias Bolz, and Christina A. Bochow
The Resource Project
Background, Design, Samples, and Measurements

166 Anna Wilsch
Neural oscillations in auditory working memory

167 Dominique Goltz
Sustained Spatial Attention in Touch: Underlying Brain Areas and Their Interaction

168 Juliane Dinse
A Model-Based Cortical Parcellation Scheme for High-Resolution 7 Tesla MRI Data

169 Gesa Schaadt
Visual, Auditory, and Visual-Auditory Speech Processing in School Children with Writing Difficulties

170 Laura Verga
Learning together or learning alone: Investigating the role of social interaction in second language word learning

171 Eva Maria Quinque
Brain, mood and cognition in hypothyroidism

172 Malte Wöstmann
Neural dynamics of selective attention to speech in noise

173 Charles-Étienne Benoit
Music-based gait rehabilitation in Parkinson's disease

174 Anja Fengler
How the Brain Attunes to Sentence Processing Relating Behavior, Structure, and Function

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Breaking Down Complexity: The Neural Basis of the Syntactic Merge Mechanism in the Human Brain

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2nd Edition The Resource Project
Background, Design, Samples, and Measurements

176 Manja Attig
Breaking Down Complexity: The Neural Basis of the Syntactic Merge Mechanism in the Human Brain

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Out of control behaviors?
Investigating mechanisms of behavioral control in alcohol addition, binge eating disorder, and associated risc factors

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The processing of complex syntax in early childhood

179 Smadar Ovadia-Caro
Plasticity following stroke: the recovery of functional networks as measured by resting-state functional connectivity

180 Indra Kraft
Predicting developmental dyslexia at a preliterate age by combining behavioral assessment with structural MRI

181 Sabine Frenzel
How actors become attractors
A neurocognitive investigation of linguistic actorhood

182 Anja Dietrich
Food craving regulation in the brain: the role of weight status and associated personality aspects

183 Haakon G. Engen
On the Endogenous Generation of Emotion

184 Seung-Goo Kim
Myeloarchitecture and Intrinsic Functional Connectivity of Auditory Cortex in Musicians with Absolute Pitch