Identifying Individual Differences in the Neural Correlates of Language Processing Using fMRI

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How to cite:

WEBER, SARAH (2017) Identifying Individual Differences in the Neural Correlates of Language Processing Using fMRI. Doctoral thesis, Durham University.

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Thesis submitted for the degree of Doctor of Philosophy

Department of Psychology
Durham University
July 2017

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The empirical work presented in this thesis is currently under review or in preparation for submission to peer-reviewed journals:

Weber, S., Hausmann, M., Kane, P., & Weis, S. (in preparation). Nerual Neural Correlates of Semantic and Syntactic Processing During Sentence Comprehension.

Weber, S., Hausmann, M., Kane, P., & Weis, S. (in preparation). Revisiting the Ambiguous Relationship Between Language Ability and Brain Activity.

Weber, S., Weis, S., Kane, P., & Hausmann, M. (under review). Brain Lateralization Across Different Language Processes and Its Relationship with Verbal Ability.

Acknowledgements

My special thanks go to my supervisors, Dr Susanne Weis and Dr Markus Hausmann, for their constant support, time, energy and advice. Thank you for always having an open ear for my ideas and concerns, for giving me a lot of freedom as well as guidance, and for your optimism and encouragement when I needed it.

I want to thank my friends and fellow Ph.D. students from Durham University for providing a sympathetic ear and lots of encouragement especially in the write-up phase, and for much-needed distractions during coffee mornings and Thursday dinners.

I would also like to thank my friends at the University of York. I was so lucky to have had your continuing support, reassurance and advice throughout my Ph.D. and I am grateful for all the fun times on National Trust outings, brunches, bake-offs and Pub nights. In particular, a huge thank you goes to my great friend Mark Hymers – I could not have done this Ph.D. without you! Thank you for your endless patience, compassion and encouragement, and for being on my side in countless fights with Matlab, Python and Bash.

Last but not least, I want to thank my entire family, especially my Mama, my sister Jana, and my Oma, for their loving support, for passionately sharing my excitement as well as frustrations along the way, for cheering me on and always believing in me.

Identifying Individual Differences in the Neural Correlates of Language Processing Using fMRI

Sarah Weber

Mapping language functions in the brain is of profound theoretical and clinical interest. The aim of the current Ph.D. project was to develop an fMRI paradigm to assesses different language processes (i.e., phonological, semantic, sentence processing) and modalities (listening, reading, repetition) in a stimulus-driven manner, keeping non-linguistic task demands to a minimum. Cortical activations and functional connectivity patterns were largely in line with previous research, validating the suitability of the paradigm for localizing different language processes. The first empirical chapter of the thesis investigated sentence comprehension in listening and reading, which elicited largely overlapping activations for the two modalities and for semantic and syntactic integration in the left anterior temporal lobe (ATL). Functional connectivity of the left ATL with other parts of the cortical language network differed between the modalities and processes. The second empirical chapter explored individual differences in brain activity in relation to verbal ability. Results supported the notion of more extended as well as stronger activations during language processing in individuals with higher verbal ability, possibly reflecting enhanced processing. The third empirical chapter further investigated individual differences in brain activity, focusing on lateralization in activity as a fundamental principle of how language processing is functionally organized in the brain. Degrees of left-lateralization differed significantly between language processes and were positively related to behaviorally assessed language lateralization. Furthermore, the results provided new evidence supporting a positive relationship between left-lateralization and verbal ability. The thesis concludes with a discussion of the significance of the results with regard to general principles of brain functioning and outlines potential clinical implications.

Chapter 1

General Introduction

The localization of language functions in the brain has been a matter of great interest for more than a hundred years (Broca, 1861; Lichtheim, 1885; Wernicke, 1874). Since the first investigations, extensive knowledge about the neural bases of language processing has been accumulated, particularly since the emergence of neuroimaging techniques. However, despite great advances, there are still many unanswered questions and contradictory results concerning the localization of language processing in the brain. Finding consensus between different neuroimaging studies has been complicated by several factors. First, language processing is a multidimensional concept, comprising a wide range of subcomponents and processing modalities. Second, neuroimaging studies on language processing typically investigate language processing in a specific task context that require a variety of cognitive functions to be performed in addition to (and interacting with) the linguistic component of the task. Both of these issues make it difficult to compare different studies and to reliably localize language processing in the brain. Third, even within a single study, individuals' neural responses to the stimuli and the task differ slightly with regard to the exact location and strength. These differences can arise from situational factors, such as attention or motivation, but also from more stable inter-individual differences, such as verbal ability.

1.1 Localization of language functions in clinical contexts

Historically, the localization of language in the brain has raised great interest in clinical contexts. Specifically, localizing different language functions (and in fact other cognitive functions) in the brain is an essential part of preoperative assessments in different neurological patient groups, such as brain tumor patients (Giussani, Roux, Ojemann, Sganzerla, Pirillo, & Pagano, 2010). While aiming at removing as much affected tissue as necessary during surgery, it is crucial to spare tissue that controls critical cognitive functions, such as those related to language processing. Currently, electrocortical stimulation mapping (ESM) is seen as the “gold standard” for localizing language functions prior to surgery (Giussani et al., 2010). With this technique, patients perform language tasks while a small electrical current is applied to different parts of the brain, disrupting neural activity in this area. If the area is critically involved in language processing, stimulation results in speech arrest or errors. ESM is typically performed immediately before surgery and has been shown to reliably localize cortical language areas, minimizing the risk of postoperative impairments (Haglund, Berger, Shamseldin, Lettich, & Ojemann, 1994). However, ESM also has distinct disadvantages, including stress on the patient, any risks inherent to invasive procedures, the lack of longer-term presurgical planning possibilities, and the restriction of investigations to brain areas that are exposed during surgery (Bookheimer, 2007; McDermott, Watson, & Ojemann, 2005; Roux, Boulanouar, Lotterie, Mejdoubi, LeSage, & Berry, 2003; Tieleman, Deblaere, van Roost, van Damme, & Achten, 2009; Vlieger, Majoie, Leenstra, & den Heeten, 2004). The search for a non-invasive alternative to ESM has led clinicians and researchers to explore the usefulness of functional magnetic resonance imaging (fMRI) for preoperative language assessments. Comparing localization results acquired with the two techniques has revealed great variance in the degree of agreement, depending on the tasks used, comparison methods, and patient groups (Giussani et al., 2010).

One of the problems in fMRI - ESM comparisons is that the two techniques employ different measures of neural activity. fMRI measures relative differences in blood flow, indicating which areas of the brain are engaged to a greater extent during performance of one task as opposed to another. Therefore, fMRI activations reveal brain areas that are involved in performing a certain task, but they do not give any information about the areas’ essentiality to perform the task. That is, damage to or resection of this area would not necessarily affect task performance. ESM on the other hand indicates brain areas that are absolutely crucial for performing the task in question (Garrett, Pouratian, & Liau, 2012; Giussani et al., 2010; Vlieger et al., 2004). Furthermore, preoperative assessments with ESM and fMRI usually employ different language tasks. For ESM, object naming is the standard task of choice (Bookheimer, 2007; Garrett et al., 2012; for examples see Roux et al. 2003; Rutten, Ramsey, van Rijen, Noordmans, & van Veelen, 2002). For preoperative fMRI, on the other hand, a great variety of paradigms has been used in different studies. The importance of a suitable language paradigm for the effectiveness of preoperative fMRI has long been acknowledged (McDermott et al., 2005; Roux et al., 2003) and some authors have postulated that any preoperative language assessment should comprise different language processes, such as sublexical as well as lexical processing (Garrett et al., 2012). Indeed, it has been shown that a combination of different tasks enhances the predictive value of fMRI assessments, as indicated by ESM concordance (FitzGerald et al., 1997; Roux et al., 2003).

1.2 Localization of language functions in healthy subjects

The role of fMRI paradigms in the localization of language functions in the brain has been recognized in healthy participants as well. Some authors have criticized extreme variability of cortical activations reported in the language literature (Fedorenko & Kanwisher, 2009; Lindenberg, Fangerau, & Seitz, 2007). Discussing results from meta-analyses and reviews, the authors asserted that there is little agreement between fMRI studies with respect to brain areas involved in different language functions. However, other researchers have explained this variability by pointing out important differences between single localization studies (Friederici, 2011; Grodzinsky, 2010). These authors have concluded that a fairly clear localization of different language functions across fMRI studies can be obtained, as long as differences in tasks, type of stimuli, and control conditions are taken into account. Indeed, direct comparisons of language paradigms that use the same stimuli but in the context of different tasks, have repeatedly shown significant task effects (e.g., Davis, Zhuang, Wright, & Tyler, 2014; Yang & Zevin, 2014). Specifically, comparing active tasks, such as linguistic decision tasks, with passive listening or reading of the same stimuli, typically results in additional or stronger activations, particularly in frontal brain regions (e.g., Noesselt, Shah, & Jäncke, 2003; Plante, Creusere, & Sabin, 2002; Wright, Randall, Marslen-Wilson, & Tyler, 2011). Thus, frontal activations in such active tasks might not primarily reflect linguistic processing, which would be present in both, active tasks and passive listening/reading. Instead, frontal activations in active task paradigms may predominantly be driven by non-linguistic, domain-general cognitive demands (e.g., working memory, decision making) (e.g., Fiebach, Schlesewsky, Lohman, Von Cramon, & Friederici, 2005; Grodzinsky & Friederici, 2006), which are absent or reduced in passive listening and reading paradigms compared to active tasks.

Of course, the large variety in language paradigms is not only a result of specific task instructions, but also a reflection of the multidimensionality of language processing. Natural language processing comprises a multitude of different language functions, such as phonology, semantics, and sentence processing, and can take place in different modalities, such as listening, speaking, reading, and writing. Comparisons of language processing in different modalities have shown considerable concurrence of results, apart from obvious differences in sensory brain areas, such as occipital areas for reading when compared to listening (Carpentier et al., 2001; Constable et al., 2004; Jobard, Vigneau, Mazoyer, & Tzourio-Mazoyer, 2007). The overlapping activations for different language functions across modalities have been interpreted in the light of “supramodal” or “amodal” language processing systems that act relatively independently of perceptual or motor systems (Jobard et al., 2007; Lindenberg & Scheef, 2007).

In contrast to modality comparisons, comparisons of different language processes typically show effects in a variety of brain areas in the fronto-temporal language network. This can be demonstrated with, for example, directed attention paradigms, which present the same stimuli and the same task across conditions (e.g., same-different judgements, error detection tasks), but selectively direct attention to, for example, phonological, semantic or syntactic features of the stimuli (e.g., Gitelman, Nobre, Sonty, Parrish, & Mesulam, 2005; Heim, Eickhoff, & Amunts, 2008; McDermott, Petersen, Watson, & Ojemann, 2003; Rogalsky & Hickok, 2009). Alternatively, passive language processing paradigms keep domain-general cognitive demands to a minimum, and manipulate the type of linguistic processing in a bottom-up manner by presenting different stimuli (e.g., stimuli that elicit semantic processing and stimuli that do not allow for semantic processing, such as words versus pseudowords) (e.g., Hagoort, Indefrey, Brown, Herzog, Steinmetz, & Seitz, 1999; Humphries, Binder, Medler, & Liebenthal, 2006; Mechelli, Gorno-Tempini, & Price, 2003). Both of these paradigms typically result in differential activations for different language processes, despite considerable overlap, especially when contrasted with a low-level baseline such as rest.

1.3 The dual stream model of language processing

Several researchers have summarized findings from neuroimaging data, often in combination with patient data, to develop models that describe different subcomponents of language processing and their neural basis. A widely-accepted model of speech processing is the dual stream model developed by Hickok and Poeppel (2004, 2007). The model proposes two processing streams in the brain that are involved in language processing. A ventral pathway for sound-to-meaning mapping is described to be responsible for identifying the semantic content of speech, leading to speech comprehension. A dorsal pathway, on the other hand, is responsible for sound-to-articulation mapping and plays an important role in the interface between the phonological information of speech and the respective motor representations. The latter processes are crucial in speech production, for example in repetition tasks, but also in speech perception, particularly in situations where the focus is on sublexical rather than lexical aspects of speech (e.g. in phoneme discrimination tasks).

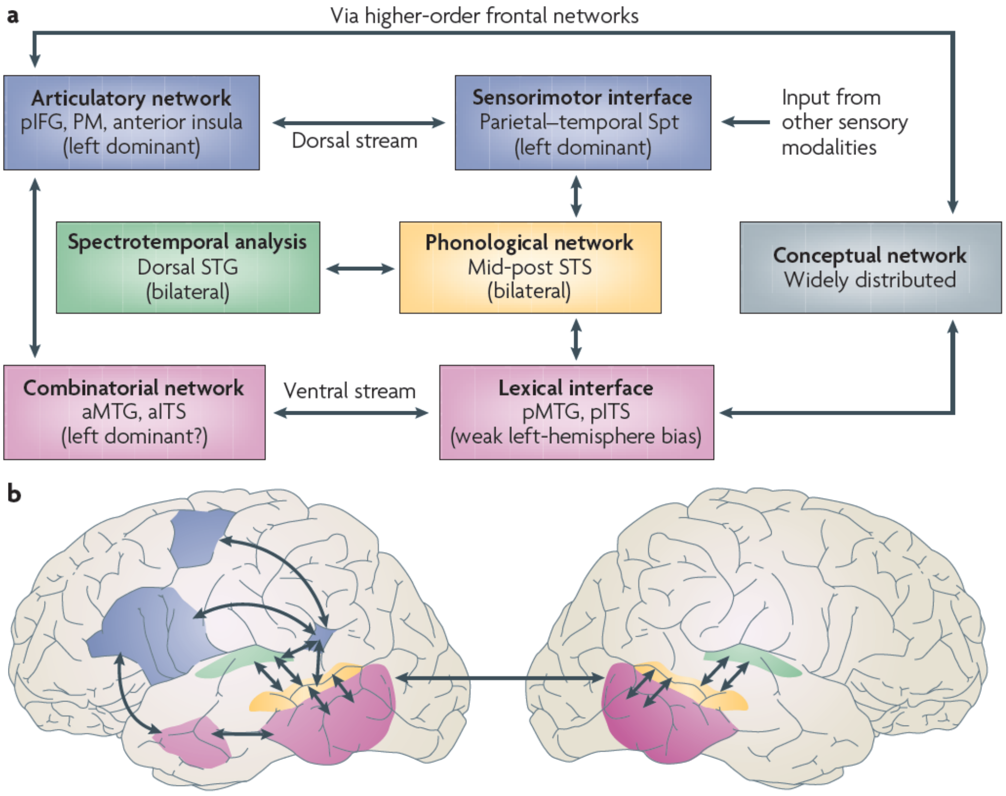

Figure 1: Dual stream model for speech processing (from Hickok & Poeppel, 2007, p. 395)

Sound-to-meaning-mapping and sound-to-articulation-mapping each comprise several levels of processing, taking place in different parts of the fronto-temporo-parietal language network. These brain areas are thought to exchange information generated at different stages of speech perception and production, although these stages are not necessarily organized in a serial manner. The initial stages of auditory perception are shared between the ventral and the dorsal stream, starting with a spectrotemporal analysis of speech stimuli in the auditory cortex. The speech signal is then forwarded to the phonological network, comprising the middle and posterior superior temporal sulcus. Here, sound-based representations of speech on the level of phonemes are generated, resulting in sublexical representations of speech (e.g., in the form of syllables). These representations are further processed in the ventral or the dorsal stream, depending on task requirements and situational demands (i.e., focus on semantic processing or phonological processing).

For semantic processing of speech stimuli (i.e., sound-to-meaning mapping), phonological representations are used to access higher-level conceptual representations within the ventral stream, running along the temporal lobe. A lexical interface in the posterior temporal lobe combines phonological information with lexical representations that are distributed across different areas of the cortex. Subsequently, a combinatorial network in the anterior temporal lobe (ATL) is engaged to integrate conceptual information into a wider context, for example during sentence comprehension.

For sound-to-articulation mapping on the other hand, the dorsal stream is engaged, consisting of parietal and frontal regions. A sensorimotor interface, located in the Spt (Sylvian-parietal-temporal) area, maintains phonological information in working memory and links it to established motor representations of the speech sound. The Spt area closely interacts with the inferior frontal gyrus and premotor cortex during preparatory stages of articulation and during phonologically demanding speech perception (e.g., conscious segmentation or recoding of speech).

1.4 Brain lateralization in language processing

The dual stream model (Hickok & Poeppel, 2007) diverges from the traditional focus on the left hemisphere for language processing (Broca, 1861, Wernicke, 1874). While the dorsal stream is described to be strongly left-lateralized, the ventral stream is considered to be organized more bilaterally, with varying degrees of left-lateralization for different language processes. During the first stages of speech processing, parallel ventral pathways in the left and right hemisphere are thought to serve different functions in lower-level auditory perception. Specifically, the right auditory cortex is hypothesized to integrate speech sounds over a long timescale (~150-300 ms), corresponding to information on the syllable level, such as word stress and tonal information. In contrast, analysis of speech sounds on a short timescale (~20-50 ms) is thought to take place bilaterally. Analyses on short timescales include information on the level of single speech segments, such as rapid acoustic changes (e.g., the difference between “pets” and “pest”). Segmental and suprasegmental analyses are proposed to take place in parallel streams and are subsequently integrated in order to serve as input for semantic processing.

For phonological processing in the superior temporal sulcus (STS), the dual stream model suggests bilateral but asymmetric involvement of the STS, without specifying the exact differences between the left and the right hemisphere (Hickok & Poeppel, 2004; 2007). However, the left STS has repeatedly been shown to be involved in processing phonetic and phonological information (e.g., Rimol, Specht, Weis, Savoy, & Hugdahl, 2005; Turkeltaub & Coslett, 2010), whereas the right STS appears to be sensitive to characteristics of the human voice and emotional prosody in speech (Specht, 2014).

For subsequent steps of lexical-semantic processing in posterior temporal cortex, the dual stream model suggests a general left hemisphere advantage but proposes capacities in the right hemisphere as well. In contrast, for high-level combinatorial computations in the ATL, for example during sentence comprehension, the model proposes a strong left-hemisphere dominance.

Recent reviews of neuroimaging studies investigating different components of language processing, confirmed the lateralization pattern proposed by the dual stream model (Hickok & Poeppel, 2007), introducing a “lateralization gradient” within the ventral stream (Specht, 2013, 2014). Lower-level auditory processing was shown to elicit bilateral activations with differential sensitivities of the left and the right hemisphere, as described by Hickok and Poeppel. Higher-level language processes, from lexical to sentence processing, were shown to result in increasingly stronger left-lateralization of brain activity.

1.5 Structural and functional connectivity within the cortical language network

In comparison to activations associated with different language processes, connectivity between the brain areas involved has received less attention in the literature. Saur and colleagues have tested the predictions of the dual stream model (Hickok & Poeppel, 2007), with regard to brain areas involved as well as structural and functional connectivity between these areas (Saur et al., 2008; Saur et al., 2010). Networks within the ventral and the dorsal processing streams were investigated with two tasks that were hypothesized to engage the sound-to-meaning pathway and the sound-to-articulation pathway, respectively. Sound-to-meaning mapping was investigated with sentence comprehension (contrasting sentence listening to pseudosentence listening, i.e., strings of pseudowords that contain syntactic but no semantic information). Sound-to-articulation mapping was investigated with pseudoword repetition (contrasted with word repetition). Pseudoword repetition requires increased phonological-articulatory processing, caused by the lack of an existing articulatory-motor template in long-term memory for novel pseudowords compared to a direct access of motor representations for existing words (Hickok, 2009; Hickok & Poeppel, 2007).

As expected, sentence comprehension primarily engaged parts of the ventral stream along the temporal lobe, and additional (inferior) frontal regions, ascribed to cognitive control functions, for example when accessing grammatical rules. Pseudoword repetition activated parts of the dorsal stream, namely the left superior temporal gyrus and left frontal areas. In line with predictions of the dual stream model (Hickok & Poeppel, 2007), activations within the ventral stream were bilateral but stronger in the left hemisphere, while activations in the dorsal stream were restricted to the left hemisphere. Peaks of these activations (all located in the left-hemisphere) were used as seed regions for Diffusion Tensor Imaging (DTI), revealing structural connections within the comprehension and the repetition network. For seed regions derived from sentence comprehension peaks, analyses confirmed a ventral pathway, connecting temporal and frontal brain regions, running through the extreme capsule with contributions from the middle and inferior longitudinal fasciculi. Fiber tracking from pseudoword repetition seeds, revealed connections of inferior frontal and premotor areas with superior temporal areas through the superior longitudinal fasciculus and the arcuate fasciculus, thus confirming a dorsal pathway. In contrast, the frontal operculum was connected with temporal regions not via the dorsal stream but via the ventral pathway (i.e., extreme capsule). Saur et al. (2008) interpreted this connection to be a route for monitoring processes that are crucial when repeating novel phoneme combinations.

Saur et al. (2010) combined DTI data with results from directed partial correlation analyses of fMRI time series data. This method allowed for the investigation of functional connectivity during speech processing while exploring fiber tracts that were most likely to mediate these interactions. As in Saur et al. (2008), the ventral stream was investigated with semantic processing, contrasting sentence listening with pseudosentence listening. Functional connectivity for sentence comprehension was most prominent between the posterior middle temporal gyrus and frontal/premotor areas, mediated through the extreme capsule. The direction of this connectivity was hypothesized to go from posterior temporal regions, where semantic concepts are stored, to frontal regions, where concepts are selected and integrated. In accordance with the dual stream model (Hickok & Poeppel, 2007), these connections were found bilaterally, with stronger connections in the left hemisphere.

The dorsal stream was investigated with a contrast measuring phonological processing, namely pseudosentence listening contrasted with listening to temporally reversed pseudosentences (in which phonetic information is disrupted). Functional connectivity was most prominent between the left posterior superior temporal gyrus (STG) and left frontal/premotor areas, mediated through the arcuate fasciculus. This interaction was interpreted as motor simulations of incoming speech sounds aiding in effortful phonological processing. Additional connectivity of the left posterior STG with frontal/premotor areas was found to be realized through a ventral pathway (i.e., extreme capsule), which Saur et al. (2010) interpreted as a control mechanism for the dorsal sensory-motor loop.

Other investigations of language processing pathways have also focused on dorsal and ventral fiber tracts. For example, Friederici (2011, 2012) has developed a sentence comprehension model, describing fronto-temporal connections involved in semantic and syntactic processing (see Figure 2). In contrast to the dual stream model, Friederici's model describes *two* ventral and *two* dorsal streams, involved in different subcomponents of sentence comprehension. As in the dual stream model (Hickok & Poeppel 2007), speech analysis is hypothesized to start in the auditory cortex which forwards the signal to the anterior and posterior STG. From the temporal lobe, two ventral pathways project to the different parts of the frontal lobe. The anterior STG is connected to the frontal operculum and ultimately BA 44 via the uncinate fascicle. More posterior parts of the temporal lobe are connected to BA 45 and BA 47 via the extreme capsule. The former stream supports the processing of higher-order syntax and grammatical relations whereas the latter serves semantic associations between words within a sentence.

In addition to this stimulus-driven bottom-up processing of speech, Friederici's model also describes mechanisms of top-down control that are executed in parallel. These processes are hypothesized to be realized through a dorsal pathway connecting frontal areas, especially BA 44, with parietal and temporal regions where semantic and syntactic integration takes place. The input from frontal areas aids these integrative processes by offering predictions with regard to remaining incoming sentence elements based on syntactic rules and templates used for phrase structure building.

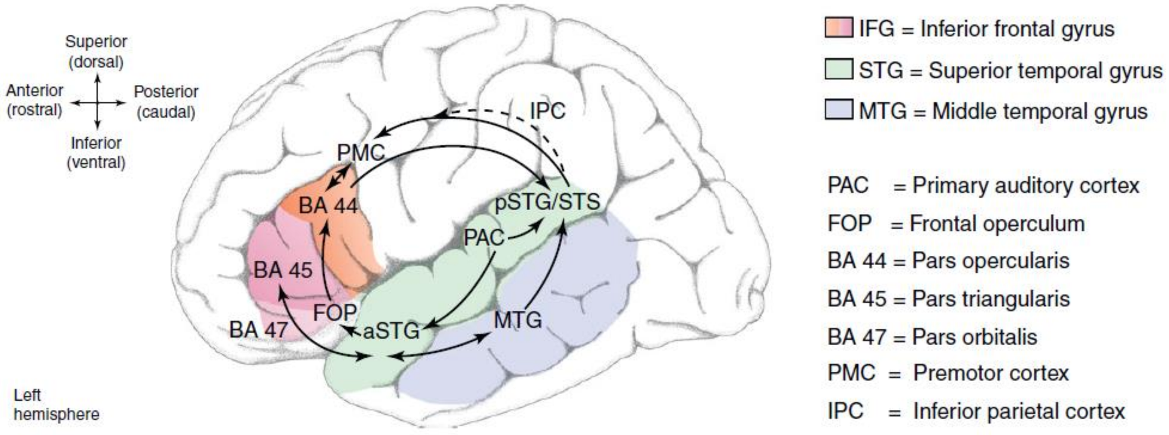

Figure 2: Cortical language circuit (from Friederici, 2012, p. 263)

Thus, Friederici (2012) proposed a language network with two ventral streams, one for semantic processing, previously described as sound-to-meaning mapping (Hickok & Poeppel, 2007), and one for syntactic processing. With respect to dorsal pathways, the model acknowledges the sound-to-motor mapping stream connecting temporal areas and premotor areas. In addition, Friederici postulated a second dorsal stream between temporal cortex and Broca's area for complex syntactic processing. Hence, according to the model, syntactic processing involves ventral as well as dorsal connections. During sentence comprehension, these two structurally as well as functionally distinguishable streams closely interact to integrate the different types of information and enable contextual processing. The necessity of interactions between the different streams has previously been described (Weiller, Bormann, Saur, Musso, & Rijntjes, 2011), particularly for situations of natural language processing (Saur et al. 2008).

1.6 Verbal ability and language-related activity and connectivity

The vast majority of neuroimaging studies on language processing, such as the ones discussed above, involve group analyses, which average language-related activity across participants. Therefore, findings are usually a good indication of the approximate locations in the brain that are involved in certain language processes for the majority of individuals. However, there is of course individual variation in the neural responses to language stimuli and tasks, which are not only determined by circumstantial factors (e.g., motivation, alertness) but also by more stable differences between subjects. One of the factors that seems to be linked to neural responses to language tasks, is verbal ability. Brain activations have repeatedly been shown to vary with a range of verbal ability measures. However, despite the clear indication of a relationship between verbal ability and brain activity, the direction of this relationship is still unclear. Some studies have found positive correlations (e.g., Szenkovits, Peelle, Norris, & Davis, 2012), others have found negative correlations (e.g., Prat, Mason, & Just, 2012), and many have found a mixture of positive and negative relationships (e.g., Prat, Keller, & Just, 2007; Van Ettinger-Veenstra, Ragnehed, McAllister, Lundberg, & Engström, 2012). A variety of explanations has been offered for positive as well as negative correlations. Most prominently, increased activity with higher verbal ability has been interpreted as adaptive recruitment of additional neural resources during language processing or deeper processing of language stimuli (e.g., Prat & Just, 2010; Van Ettinger-Veenstra, McAllister, Lundberg, Karlsson, and Engström, 2016). On the other hand, decreased activity with higher verbal ability has been explained with neural efficiency, that is individuals with higher ability requiring fewer neural resources to adequately perform language tasks (e.g., Prat, Mason, & Just, 2011; 2012).

Apart from contradictory findings regarding the direction of a relationship between verbal ability and brain activity, it is also unclear where in the brain activity varies with ability. Correlations have been found in a variety of cortical areas in the left (Van Ettinger-Veenstra et al., 2016; Welcome & Joanisse, 2012) and in the right hemisphere (Van Ettinger-Veenstra et al., 2012; Prat et al., 2011; 2012), thus, areas that have traditionally been associated with language processing, as well as their right-hemisphere homologues. Occasionally, verbal ability has also shown to be related to activity in brain areas that have traditionally been associated with cognitive control functions rather than linguistic processes (Prat et al., 2011; 2012). The large variation in results might partially be attributable to differences in the fMRI language paradigms and measurements of verbal ability used in the different studies. For example, one could hypothesize that paradigms with high domain-general cognitive demands (e.g., selection and inhibition processes in word decision tasks) or verbal ability measures that heavily rely on non-linguistic processes (e.g., verbal working memory), show greater correlations in brain areas of the cognitive control network. Given the wide range of tasks and ability measures used in the current literature, it is difficult to draw any conclusions about the exact nature of the relationship. Even less is known about the relationship between verbal ability and functional connectivity between different brain areas during language processing. Some studies have found increased connectivity with higher verbal ability but evidence is sparse (Prat et al., 2007).

Verbal ability has not only been linked to the strength of activations in different brain areas as described above, but also to asymmetries in brain activity (e.g., Everts et al., 2009; Mellet et al., 2014). Language processing has repeatedly been shown to engage the left hemisphere more than the right hemisphere in the vast majority of subjects (Rasmussen & Milner, 1977; Knecht et al., 2000), leading researchers to discuss potential benefits of a strong left-lateralization for language processing, for example with regard to processing efficiency or performance (e.g., Hirnstein, Hausmann, Güntürkün, 2008). While there is increasing evidence for a positive relationship between verbal ability and left-lateralization in brain activity, the strength of this relationship varies greatly between studies, and some fail to find any significant correlation (Knecht et al., 2001; Powell, Kemp, & García-Finaña, 2012). Variation in results regarding the strength of a potential relationship might partly stem from differences between studies with respect to the methods used to calculate degrees of lateralization and with regard to the way that language processing was assessed, with the majority of studies operationalizing language lateralization with only one specific language task, despite indications that different language processes might be differentially lateralized (Buchinger, Flöel, Lohmann, Deppe, Henningsen, & Knecht, 2000; Hund-Georgiandis, Lex, & Von Cramon, 2001; Stroobant, Buijs, & Vingerhoets, 2009). Systematic investigations of brain lateralization across different language functions might shed some light on patterns of language lateralization and clarify relationships with verbal ability.

1.7 The current thesis

The first aim of the current Ph.D. project was the development of an fMRI paradigm that allowed for the localization of different language functions in the brain in a task-independent manner. This was achieved by choosing a bottom-up, stimulus-driven approach which employed different language stimuli that triggered differential linguistic processes. In order to investigate language processing in different modalities, stimuli were presented in a passive listening task, a silent reading task, and a repetition task. Non-linguistic, domain-general cognitive demands (e.g., working memory, decision making, executive control) were kept at a minimum. This approach allowed for the localization of language processes in a context that was more similar to natural language processing in everyday communication settings than paradigms that require the active manipulation in task-driven language processing contexts. Thus, activations derived from the current paradigm should reflect linguistic processes to a greater degree than domain-general cognitive processes. Three well-accepted subcomponents of language processing were chosen as the focus of the paradigm, namely phonological, semantic, and sentence processing (Hickok & Poeppel, 2007). These processes were investigated by manipulating the absence/presence of specific linguistic characteristics in the language stimuli in the different conditions. First, phonological processing was assessed by comparing stimuli with phonological information (i.e., pseudowords) with perceptual control stimuli containing lower-level auditory/visual/ motor information but no phonological information. Second, semantic processing was assessed by comparing stimuli with phonological and lexical-semantic information (i.e., words) with stimuli containing only phonological information (i.e., pseudowords). Third, sentence processing was assessed by comparing stimuli with phonological, lexical-semantic, and syntactic and sentence-level semantic information (i.e., sentences) with stimuli containing only phonological and lexical-semantic information (i.e., words). Furthermore, sentences were contrasted with scrambled sentences and pseudosentences to assess processing of syntactic structure and sentence-level semantics, respectively.

The second aim of the Ph.D. project was the investigation of individual differences in the neural correlates of language processing and relationships with verbal ability. The question of how differences in ability are reflected in brain activity (and in lateralization of activity) has been of great interest to scientists across various cognitive domains (Neumann, Lotze, & Eickhoff, 2016). However, potential links between ability and brain activity might not be specific to any given cognitive domain but rather follow the same principle across domains (e.g., increased neural efficiency with higher ability; increased lateralization with higher ability). Therefore, studying the relationship between verbal ability and language-related brain activity might shed some light on the general principles of functional brain organization for higher cognitive domains.

The first empirical chapter of the current thesis (Chapter 2) will investigate the neural basis of sentence processing across modalities (i.e., listening and reading), with a particular focus on semantic and syntactic integration processes. Despite extensive research on sentence processing, the neural correlates of semantic and syntactic integration are still not fully understood. This is partly caused by a focus on semantic/syntactic complexity, typically comparing complex sentences with less complex sentences. This approach is problematic for two reasons. First, complexity (especially syntactic complexity) is often manipulated by increasing domain-general demands, such as working memory, rather than linguistic demands (Fiebach et al., 2005). Second, using easy sentences as a control condition subtracts all basic sentence processing components that are present in easy and complex sentences (Hagoort & Indefrey, 2014; Rodd, Vitello, Woollams, & Adank, 2015). In contrast, the paradigm of the current study investigated semantic and syntactic processes during sentence comprehension in a task-independent manner, assessing basic cognitive processes required in everyday-language processing. As part of this investigations, cortical activations as well as functional connectivity associated with sentence processing will be explored.

The second empirical chapter (Chapter 3) will focus on individual differences in brain activity, studying links between language-related activity and verbal ability. Specifically, we aimed to test whether inconsistencies in previous studies can partly be explained by their focus on different language processes, modalities and verbal ability measurements in the different studies. Therefore, we investigated sentence comprehension in listening and reading, and phonological processing in repetition, as well as two different measures of verbal ability (i.e., verbal IQ and verbal fluency).

The third empirical chapter (Chapter 4) investigated the relationship between verbal ability and lateralization of brain activity during language processing. As a basis for this investigation, patterns of brain lateralization were studied across different language processes and different modalities. The majority of previous studies restricted their investigation of language lateralization to one particular subcomponent (e.g., semantic processing), typically in the context of one particular task (e.g., synonym judgement). This approach ignores the multitude of processes and modalities involved in natural language processing and neglects the possibility that different language processes and modalities might be differentially lateralized (Buchinger et al., 2000; Hund-Georgiandis et al., 2001; Stroobant et al., 2009). This can, in turn, affect relationships between language lateralization and verbal ability. Chapter 4 also discusses the relationship between language lateralization as assessed with fMRI and well-established behavioral paradigms (i.e., a dichotic listening paradigm and a visual half-field task).

Altogether, the results of the current thesis will allow for a systematic investigation and comparison of different language processes and modalities in a relatively task-independent manner, and will shed some light on individual differences in the neural correlates of language processing in relation to verbal ability.

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Chapter 2

Neural Correlates of Semantic and Syntactic Processing During Sentence Comprehension

2.1 Abstract

Sentence comprehension has repeatedly been shown to activate the left anterior temporal lobe (ATL), but the role of posterior temporal and frontal brain regions has been under debate. Furthermore, the degree to which semantic and syntactic processes during sentence comprehension are topographically separable, is not clear. In addition, functional connectivity of different brain areas during sentence comprehension, and during semantic and syntactic processing specifically, are less well understood than associated activations. The current study investigated activations and functional connectivity during semantic and syntactic processing during sentence comprehension in listening and reading, using a passive listening and a silent reading paradigm. Functional MRI data were acquired while twenty-two healthy adult participants were presented with words, sentences, pseudosentences and scrambled sentences. As expected, sentence comprehension activated the left ATL in listening and reading. This area of activation was shared by semantic and syntactic processes. However, functional connectivity of the left ATL with left temporal, parietal and bilateral frontal regions varied for the two modalities, and for semantic and syntactic processing. The results suggest that the left ATL functions supramodally and integrates semantic as well as syntactic information, but shows differential interactions with other brain areas, depending on the processing modality and the language process involved.

2.2 Introduction

Sentence comprehension relies on the semantic and syntactic integration of single words into a meaningful entity. Despite the complexity of the cognitive processes involved, sentence comprehension normally requires relatively little conscious effort and takes place more or less automatically in everyday language processing. Studying sentence comprehension therefore offers a possibility to investigate the complex cognitive processes inherent in language processing, while using stimuli and task situations that are relatively close to natural language processing.

Functional neuroimaging studies on language processing have shown that sentence comprehension can engage a wide range of brain areas, with activations being most prominent in left-hemispheric frontal and temporal regions (Price, 2010; Price 2012; Specht, 2014; Vigneau et al., 2006). Accordingly, well-established models of language processing have ascribed a dominant role in particular to the left temporal lobe in sentence comprehension. For example, the dual stream model of language processing (Hickok & Poeppel, 2007) proposes a “combinatorial network” in the left anterior temporal lobe (ATL) that is involved in the semantic and syntactic integration of single words into a coherent sentence. The combinatorial network is hypothesized to receive input from a “lexical interface”, which is located in the posterior temporal lobe and is engaged in processing word-level meaning. The model also proposes functional interactions between the left ATL and the left inferior frontal gyrus (IFG). While Hickok and Poeppel do not specify a potential role of the left IFG in sentence processing, they discuss the implication of this region in working memory processes during speech comprehension.

Friederici (2012) also stresses the importance of the left temporal lobe for sentence comprehension. However, in contrast to the dual stream model (Hickok & Poeppel, 2007), Friederici’s model of sentence processing has suggested the posterior rather than the anterior part of the left temporal lobe as an area of semantic and syntactic integration. The ATL, on the other hand, is thought to be involved in initial, lower-level syntactic processes, in which word category information is used to make local connections between words (e.g., determiner-noun phrases). In order to process more complex syntax (e.g., sentences with embedded clauses that require reordering of words), the left ATL is hypothesized to interact with the left posterior IFG. For semantic processing during sentence comprehension (e.g., assignment of thematic roles – who does what?), Friederici has suggested an involvement of anterior as well as posterior parts of the left temporal lobe and the left angular gyrus.

Thus, the dual stream model (Hickok & Poeppel, 2007) as well as Friederici's sentence comprehension model (2012) both propose a brain area that is dedicated to semantic and syntactic integration of words during sentence comprehension. However, the location of this integration area differs between the two models, with the left *anterior* temporal lobe proposed in the dual stream model, and the left *posterior* temporal lobe proposed in Friederici's model. Furthermore, Friederici ascribes to this integration area a final stage of sentence comprehension in which semantic and syntactic information interact with each other and with broader contextual information (e.g., world knowledge), after being processed separately and in distinct brain areas in previous processing steps. In contrast, the dual stream model describes the combinatorial network in the left ATL as an area of both, semantic as well as syntactic integration processes, without discussing potential topographical differences or interactions between the two types of information.

2.2.1 Neural correlates of semantic integration and syntactic integration

Two recent meta-analyses provide evidence for separability of semantic and syntactic processes in left frontal and temporal brain areas, despite considerable overlap of activations for the two processes. Hagoort and Indefrey (2014) analyzed fMRI and PET studies that have investigated effects of semantic or syntactic demand during sentence comprehension by contrasting sentences with high versus low semantic/syntactic demand. Effects of semantic as well as syntactic demand were found in bilateral IFG, left posterior middle temporal gyrus (pMTG), and to a lesser degree in more anterior left temporal areas and the right temporal lobe. Direct comparisons of semantic and syntactic effects showed significantly greater activity for semantic demand in the *anterior* left IFG and left pMTG, and significantly greater activity for syntactic demand in the *posterior* left IFG. Another meta-analysis (Rodd, Vitello, Woollams, & Adank, 2015) included fMRI studies on semantic and syntactic demand that used different types of language stimuli, ranging from single words, over sentences, to narratives. Results confirmed the overlap of activations for semantic and syntactic demand in the left IFG, as well as the preference of the *anterior* left IFG for semantic processing, and the *posterior* left IFG for syntactic processing. In the temporal lobe, Rodd et al., (2015) found significantly greater effects of semantic demand compared to syntactic demand in the left mid STG and left pITG. The left pMTG showed activation for syntactic processing but not semantic processing, contradicting Hagoort and Indefrey (2014) who found a preference of the pMTG for semantic rather than syntactic processing. Thus, the exact role of subregions in the left temporal lobe in semantic and syntactic processing remains unclear.

Neither of the two meta-analyses reported any effects of semantic or syntactic demand in the ATL, despite its well-established involvement in semantic and sentence processing (Hickok & Poeppel, 2007; Specht, 2014). Both meta-analyses discuss a potential underestimation of effects in this area due to artefact problems with fMRI measurements in the ATL (Visser, Jefferies, & Ralph, 2009). An alternative explanation for the lack of reliable ATL activations in the two meta-analyses is the choice of studies that were included. All of those studies investigated effects of semantic or syntactic demand by comparing more demanding stimuli to less demanding stimuli. This means that basic cognitive processing steps, which are present even in the less demanding condition, will be subtracted in comparisons of the two conditions. The authors therefore concluded that brain areas involved in, for example, basic sentence comprehension, may not be depicted in the results of the two meta-analyses (Hagoort & Indefrey, 2014; Rodd et al., 2015). The focus of the meta-analyses on effects of semantic and syntactic demand might also explain the involvement of the inferior frontal gyrus that was found, despite propositions that its role in language comprehension might be more limited than previously thought (Grodzinsky, 2000; Adank, 2012). Hagoort and Indefrey (2014) as well as Rodd et al. (2015) both discuss the possibility that IFG recruitment may reflect cognitive demand associated with processing complex stimuli in general, independent of their linguistic nature, or with cognitive demands imposed by the tasks rather than the stimuli. This view is consistent with suggestions that confounding effects of working memory load, rather than syntactic processes per se, might be responsible for left IFG activations during some sentence comprehension tasks (Grodzinsky & Friederici, 2006; Sakai, Hashimoto, & Homae, 2001; Stromswold, Caplan, Alpert, & Rauch, 1996), a suggestion that has received empirical support when manipulating syntactic complexity and working memory independently (Fiebach, Schlesewsky, Lohman, Von Cramon, & Friederici, 2005). Furthermore, even complex syntactic processing has been shown to engage the left ATL rather than the left IFG when investigated in the context of natural language processing rather than active, experimental manipulation (Brennan, Nir, Hasson, Malach, Heeger, & Pylkkänen, 2012). Other authors have ascribed left IFG activity during sentence comprehension to cognitive control functions and conflict resolution (Novick, Trueswell, & Thompson-Schill, 2005).

In contrast to investigations of semantic and syntactic demand, other studies have researched semantic and syntactic processing by manipulating the presence/absence of semantic and syntactic information in sentences (Humphries, Binder, Medler, & Liebenthal, 2006; Vandenberghe, Nobre, & Price, 2002). For example, semantically random sentences, in which all content words are replaced with randomly chosen, semantically unrelated words, allow for the syntactic combination of words but not for their integration into a larger semantic entity. Therefore, comparing normal sentences with semantically random sentences allows for the investigation of semantic integration. On the other hand, scrambled sentences, in which the position of words in a sentence is randomly reordered, allow for the semantic combination of words based on their coherence in meaning, but the syntactic structure of the sentence is disrupted. Therefore, comparing normal sentences with scrambled sentences allows for the investigation of syntactic integration. In these comparisons, syntactic integration has been associated with activations in the left ATL

(Humphries et al., 2006; Vandenberghe et al., 2002). Semantic integration, on the other hand, has been more difficult to localize. Comparing normal sentences to semantically random sentences, Humphries et al. (2006) found an effect of semantic integration in the left aMTG/pMTG, partly overlapping with the more posterior part of the activation cluster for syntactic integration. In contrast, Vandenberghe et al. (2002) did not find any significant activations for the comparison of normal sentences with semantically random sentences. Instead, the reverse contrast resulted in left pMTG activitation (i.e., greater activity for semantically random sentences versus normal sentences), which was interpreted as an effect of semantic randomness and effortful attempts to integrate semantically unrelated words.

Results of a selective attention study confirmed the role of the left ATL in semantic and syntactic processing (Rogalsky & Hickok, 2009). Participants were instructed to listen to sentences and detect either semantic or syntactic errors. As in Humphries et al. (2006), semantic processing showed an overlap with syntactic processing in the left ATL. An additional area anterior to this shared activation, was sensitive only to *semantic* attention, contradicting Humphries et al. (2006) who found an area anterior to the shared semantic-syntactic ATL activation being sensitive only to *syntactic* processing. Thus, despite overlapping activations for semantic and syntactic processes during sentence comprehension, some brain areas seem to indicate a preference for either semantic or syntactic processing. However, the exact pattern of these process-specific activations is unclear.

2.2.2 Modality effects during sentence comprehension

The role of different processing modalities in semantic and syntactic integration is currently unclear. The meta-analyses discussed above (Hagoort & Indefrey, 2014; Rodd et al., 2015) both included listening as well as reading studies. Humphries et al. (2006) and Rogalsky and Hickok (2009) employed listening paradigms, whereas Vandenberghe et al. (2002) employed a reading paradigm, potentially explaining activation differences between the studies. fMRI studies that compared auditory and visual sentence processing directly, have found overlapping activations in left temporal and left frontal areas, in addition to modality-specific activations in auditory and visual cortices (Carpentier et al., 2001; Constable et al., 2004; Jobard, Vigneau, Mazoyer, & Tzourio-Mazoyer, 2007), but also in language-related brain areas such as the left IFG (Carpentier et al., 2001; Constable et al., 2004; Lindenberg & Scheef, 2007). However, none of these studies have investigated differences between modalities with regard to semantic or syntactic integration processes specifically.

2.2.3 Functional connectivity during sentence comprehension

Neural differences between language processes or modalities are possibly not restricted to differential activations, but might also involve differences in functional connectivity between brain areas. Hickok and Poeppel (2007) have proposed interactions between different regions of the temporal lobe within a ventral processing stream that is engaged in mapping phonological representations of speech sounds to their meaning. On the other hand, a dorsal stream from posterior temporal to frontal regions is hypothesized to map phonological representations to articulatory representations. The existence of these streams has been confirmed with structural connectivity data (Saur et al., 2008). Friederici (2012) has described two ventral and two dorsal streams with distinct roles in semantic and syntactic processing. In line with Hickok and Poeppel (2007), one ventral stream connecting the temporal lobe and the aIFG via the extreme capsule fiber system, was hypothesized to support semantic processing. Syntactic processing was proposed to be supported by another ventral stream as well as a dorsal stream. The ventral stream, connecting the aSTG/temporal pole to the posterior IFG/frontal operculum via the uncinate fasciculus, has been assumed to be involved in making initial syntactic connections between words. The dorsal stream, connecting temporal areas with the pIFG, is involved in processing complex syntax. In accordance with Hickok and Poeppel (2007), Friederici (2012) also acknowledges a second dorsal stream, connecting temporal areas and the premotor cortex for phonological processing.

Interactions between different temporal regions as well as between temporal and frontal regions during language processing have been confirmed in studies conducting analyses of functional connectivity. For example, listening to narratives has been shown to result in functional connectivity of the left ATL with surrounding anterior temporal areas, mid and posterior STG, and left IFG (Warren, Crinion, Ralph, & Wise, 2009). Functional connectivity of the left ATL with the STG has been replicated for auditory sentence comprehension, but additional connectivity with the left IFG was dependent on using an active task, rather than passive listening (Yue, Zhang, Xu, Shu, & Li, 2013). Reading sentences has been found to increase functional connectivity of the left IFG and left area Spt (sylvian-parietal-temporal area) with bilateral fusiform gyrus and premotor cortex (Keller & Kell, 2016).

Studies investigating functional connectivity during semantic or syntactic processing in particular, rather than sentence processing in general, have focused on effects of semantic/syntactic demand, and found increased connectivity between left inferior frontal and left temporal regions for more demanding compared to less demanding conditions (Bahlmann, Mueller, Makuuchi, & Friederici, 2011; Den Ouden et al., 2012; Humphreys & Gennari, 2014; Just, Newmann, Keller, McEleney, & Carpenter, 2004; Papoutsi, Stamatakis, Griffiths, Marslen-Wilson, & Tyler, 2011; Snijders, Petersson, & Hagoort, 2010). In contrast, functional connectivity associated with basic semantic and syntactic integration processes is still to be explored.

The aim of the current study was to investigate neural correlates associated with sentence comprehension in listening and reading, and in particular, disentangle semantic and syntactic integration processes. fMRI data were acquired during passive listening and silent reading, allowing for the examination of sentence comprehension while minimizing the influence of additional non-linguistic cognitive demands that are part of the experimental task context. Sentence comprehension (in contrast to single word processing) in listening and reading were expected to elicit primarily overlapping activations in the left ATL

(Carpentier et al., 2001; Friederici, 2012; Hickok & Poeppel, 2007; Lindenberg & Scheef, 2007).

The current study further aimed to disentangle brain areas involved in semantic and syntactic processing (or both) during sentence comprehension. Sentence and pseudosentences processing was contrasted to identify brain areas involved in semantic processing. Comparisons of sentences and scrambled sentences were conducted to identify brain areas involved in syntactic processing. Both processes were expected to result in predominantly overlapping activation in the left ATL (Humphries et al., 2007; Rogalsky & Hickok, 2009; Vandenberghe et al., 2002).

Finally, functional connectivity was investigated for sentence comprehension in listening and reading, and for semantic and syntactic processing separately. Previous research suggests different connectivity patterns for sentence reading and listening (Keller & Kell, 2016; Yue et al., 2013). Passive listening has been shown to result in functional connectivity between the left ATL and bilateral Heschl's gyrus and STG (Yue et al., 2013), that is, brain areas associated with auditory speech processing (Hickok & Poeppel, 2007). Covert sentence reading has been found to elicit functional connectivity of the left IFG and area Spt with bilateral fusiform gyrus and premotor cortex (Keller & Kell, 2016), that is, brain areas involved in visual word recognition (Dehaene, Le Clec'H, Poline, Le Bihan, & Cohen, 2002; Turkeltaub, Eden, Jones, & Zeffiro, 2002) and phonological-articulatory recoding during reading (Carpentier et al., 2001; Friederici, 2002), respectively. We hypothesized that the left ATL, which was expected to be activated by sentence reading in the current study, would show similar functional connectivity patterns as the IFG in Keller and Kell (2016), that is, with the left fusiform gyrus and the left premotor cortex.

Functional connectivity during sematic and syntactic integration is difficult to predict, due to the lack of studies comparable to this one. Results from paradigms that manipulate semantic or syntactic demand (Bahlmann et al., 2011; Den Ouden et al., 2012; Humphreys & Gennari, 2014; Just et al., 2004; Papoutsi et al., 2011; Snijders et al., 2010) might be of limited generalizability to the current paradigm due to their focus on effortful processing of complex semantic or syntactic features and, hence, on connectivity of seed regions in the left IFG. In contrast, the current study was expected to show activations in the left ATL, associated with basic semantic and syntactic integration during natural sentence comprehension (Humphries et al., 2006; Vandenberghe et al., 2002). Semantic integration was hypothesized to increase functional connectivity of the left ATL with posterior temporal regions associated with lexical semantic processing (Hickok & Poeppel, 2007). Syntactic integration was hypothesized to increase functional connectivity of the left ATL with the left IFG, based on suggestions of interactions between these brain areas during sentence comprehension (Friederici, 2012; Hickok & Poeppel, 2007).

2.3 Methods

2.3.1 Subjects

Twenty-six right-handed native English speakers gave informed consent to take part in the study. All participants had normal or corrected-to-normal vision and normal self-reported hearing. All participants reported to have no history of any psychiatric conditions. Four participants were excluded due to head movements of more than one voxel size between volumes. Thus, the final sample consisted of twenty-two subjects (14 female, mean age 22.05 years, *SD* = 7.66). The study was approved by the Durham University Ethics Committee and conformed to the guidelines of the Declaration of Helsinki.

2.3.2 Stimuli

To investigate semantic and syntactic integration during sentence comprehension across different modalities, several types of sentence stimuli as well as modality-specific control stimuli were presented in a passive listening task, a silent reading task, and a repetition task (results not reported in this paper). All words were taken from the MRC Psycholinguistic Database (Coltheart, 1981) and pseudowords were derived from these words, using the Wuggy software (Keuleers, & Brysbaert, 2010).

For all nouns, either used in word lists in the word condition or used in sentences in the sentence condition, the mean number of letters was 6.11 (*SD* = 2.00), mean word frequency (Kucera & Francis, 1967) was 74.13 (*SD*=118.04), mean familiarity was 528.82 (*SD*=76.71), and mean concreteness was 514.31 (*SD*=101.40). Across subjects, the same stimuli were used in the three modalities, listening, reading, and repetition.

To avoid effects of potential differences between words (e.g. with regard to length or frequency), the same words were used in the word condition, the sentence condition, and the scrambled sentence condition across subjects. This was achieved by generating sentences with multiple possible ending words. One of these ending words was then presented in the sentence condition whereas the other ones were presented in the word condition. The distribution of ending words to either the word condition or the sentence condition differed between subjects (see Table 1 for examples). All sentences consisted of six or seven words and had the same grammatical structure. Scrambled sentences were generated by randomly changing the order of words in each sentence, with the restriction of not leaving any two consecutive words from the original sentences as consecutive words in the scrambled sentences. Pseudosentences were generated by replacing all content words and prepositions with pseudowords. Any word endings that are typically associated with certain syntactic categories (e.g., -tion or -ist for nouns, -s for singular verbs, -y or -ous or -ive for adjectives) were retained in the pseudowords. These word endings induced recognition of syntactic categories in pseudowords and thereby enhanced the perception of syntactic structure. In total, 1009 content words were used in the study: 533 nouns, 238 verbs, and 238 adjectives.

For the auditory control condition, pseudowords were temporally reversed, using the Audacity software. The resulting stimuli therefore required auditory processing, but lacked phonological information. For the visual control condition, strings of slashes and backslashes were created (e.g., “/ / \ /” or “\ / / / \ /”) by replacing half of the letters of the alphabet with a forward slash and the other half with a backward slash. The resulting symbol strings lacked any orthographic information but required visual processing.

Table 1
Example of stimuli used in the sentence condition and in the word condition across participants

	Participant A	Participant B
Sentence condition	The customer tries the spicy soup	The customer tries the spicy meal
	The nephew finds the hidden toy	The nephew finds the hidden box
Word condition	meal … stew …	soup … stew …
	box … sweets …	toy … sweets …
Pseudo-sentence condition	The cussager trous the spazy toup	The cussager trous the spazy mool
	The nambew fimps the hirmen moy	The nambew fimps the hirmen bof
Pseudo-word condition	mool … steg …	toup … steg …
	bof … swoots …	moy … swoots …
Scambled sentences condition	spicy customer the soup the tries	spicy customer the meal the tries
	the nephew toy the finds hidden	the nephew box the finds hidden

2.3.3 Procedure

All participants took part in two identical fMRI sessions with three runs each (listening, reading, repetition), only changing the specific stimuli that were presented. The order of the runs was counterbalanced and the order of conditions in each run was determined by one of four pseudorandomly generated lists of conditions.

Participants performed a passive listening task, a silent reading task and a repetition task. After each stimulus, participants pressed a response box button with their index finger. Participants used different hands for responding in the two sessions, counterbalancing the order of left and right hand across participants. The button press ensured that participants attended the stimuli appropriately but kept language-unrelated cognitive demands minimal and constant across modalities and conditions. In the repetition runs, participants repeated the stimulus out loud after pressing the button.

The listening runs lasted 19.2 min and consisted of four blocks per condition (i.e., a total of eight blocks per condition for the entire study): control, pseudowords, words, pseudosentences, scrambled sentences, and sentences. For control stimuli, pseudowords, and words, 14 stimuli were presented per block. For pseudosentences, scrambled sentences and sentences, 6 stimuli were presented per block. Interstimulus intervals (ISI) were jittered. The mean length of the stimuli and their ISI were as follows: 812 ms (ISI of 2991 ms) for control, 811 ms (ISI of 2999 ms) for pseudowords, 843 ms (ISI of 2997) for words, 2424 ms (ISI of 6350 ms) for pseudosentences, 3057 ms (ISI of 6349 ms) for scrambled sentences, and 2388 ms (ISI of 6342 ms) for sentences. fMRI compatible in-ear headphones were used for stimulus presentation and the listening volume was confirmed by the participant before each session. During the auditory stimulus presentation, participants were instructed to fixate a white cross presented at the center of a screen in front of them. The reading runs lasted 15.0 min, including four blocks per condition: control, pseudowords, words, pseudosentences, and sentences. For control stimuli, pseudowords, and words, 14 stimuli were presented per block (presentation time of 1000 ms). For pseudosentences, and sentences, 6 stimuli were presented per block, each (pseudo-) sentence divided into three chunks of 1400 ms (e.g., The customer – finds – the hidden toy). ISI were jittered, with the following means: 2487 ms for control, 2506 ms for pseudowords, 2517 ms for words, 5865 ms for pseudosentences, and 5877 ms for sentences. Stimuli were presented via a BOLD screen (Cambridge Research Systems) and a mirror mounted on the head coil. Stimuli were presented in white on a black background in the center of the screen. The repetition runs lasted 13.1 min, including four blocks per condition: control, pseudowords, words, and sentences. For control stimuli, pseudowords, and words, 7 stimuli were presented per block. In the sentence condition, 3 stimuli were presented per block. ISI were jittered. The mean length of the stimuli and their ISI were as follows: 840 ms (ISI of 5563 ms) for control, 811 ms (ISI of 5590 ms) for pseudowords, 843 ms (ISI of 5478) for words, and 2388ms (ISI of 12188ms) for sentences. Stimulus presentation in the repetition runs was the same as in the listening runs, except for longer ISI to allow for repetition of the stimuli by the participant. Each run also included four blocks of a low-level baseline condition (looking at a fixation cross for 37.5 s). Each condition block started with a 2-second prompt screen, providing a brief reminder of the task and condition. Stimulus presentation was run with the Psychtoolbox-3 software (MATLAB version R2014a).

Each scanning session lasted about one hour, including short breaks between the three runs and a structural scan (T1 or DTI) at the end of the session. Between the two sessions, participants were given a break of approximately one to two hours. All participants also took part in a one-hour session of behavioral testing outside the MRI scanner on a different day (results not reported in this paper).

2.3.4 fMRI data acquisition

Data were acquired at the Durham University Neuroimaging Centre (DUNIC) at James Cook University Hospital, Middlesbrough, UK, using a Siemens 3T Magnetom Trio Scanner with a 32 channel head coil. EPI imaging of the whole head was performed, using a 96 x 96 matrix with a field of view of 210 x 210 and a voxel size of 2.1875 x 2.1875 x 3 mm. 35 axial slices were collected in ascending acquisition with a 10% gap in between slices. The TR was 2.16 s, TE 30 ms and the flip angle was 90°. The total number of volumes acquired per person (across the two sessions) was 2660 (i.e., 1080 for listening runs, 844 for reading runs, and 736 for repetition runs).

Anatomical data was acquired with a T1-weighted 3D sequence comprising 192 slices (TR = 2250 ms, TE = 2.52 ms, TI = 900 ms; flip angle 9°, FOV = 25.6cm, 512x512 matrix, voxel size = 0.5x0.5 mm).

2.3.5 Data preprocessing and analysis

Data were preprocessed and analyzed using FMRIB's Software Library, version 4.1 (FSL, http://www.fmrib.ox.ac.uk/fsl). For each subject, two first-level analyses were performed, one for each of the two fMRI sessions. Motion correction was carried out using FSL's MCFLIRT and motion parameters were later included in the model as regressors of no interest. Data were high-pass filtered with the cut-off set to twice the maximum cycle length for each of the runs (Poldrack, Mumford, & Nichols, 2012), resulting in 168 s for listening runs, 140 s for reading runs and 152 s for repetition runs. The data were spatially smoothed with a full-width half-maximum kernel of 6 mm. In an event-related analysis (i.e., using timings of single stimulus onsets and durations rather than blocks), each stimulus type was modelled as an explanatory variable and convolved with a double gamma hemodynamic response function. Resting blocks were used as an implicit baseline not specified in the model.

In a second step, the results from the first-level analysis were combined for each subject in a fixed-effects analysis. In a third step, a group analysis was carried out, using FSL FLAME 1+2. Outliers were automatically de-weighted by the software.

Sentence processing was assessed by comparing listening to or reading sentences versus listening to or reading single words. Word processing and sentence processing share basic semantic processes, whereas only sentence processing involves semantic integration of words into a larger semantic entity, as well as syntactic integration of words. For separate investigations of semantic and syntactic processing, sentences were compared to pseudosentences and scrambled sentences, respectively. The contrast of sentences versus pseudosentences was computed for the listening and the reading modality. The contrast of sentences versus pseudosentences was only computed for the listening modality.

2.3.5.1 Conjunction analyses

Conjunction analyses were carried out using the publicly available easythresh_conj script by Nichols (2007). The script determines conjunctions of activation for two contrasts by combining their z images into one conjunction image. Specifically, the conjunction image is created by taking the smaller one of the two contrasts' z values for each voxel. The resulting conjunction image is then cluster-thresholded, in the current study with the FSL default values of $z = 2.3$ and $p < .05$. Clusters surviving the thresholding reflect brain areas that show a significant effect of both input contrasts.

To investigate conjunctions of sentence comprehension in listening and reading, the contrast of sentences > words in each of the two modalities were entered into a conjunction analysis. Analyses were restricted on areas of the cortical language network, using an anatomical mask covering the entire frontal and temporal lobe.

Further conjunction analyses were conducted to determine appropriate seed regions for PPI analyses (see below).

2.3.5.2 Psychophysiological Interaction analyses (PPI)

Psychophysical interaction analysis offers a way to investigate changes in functional connectivity between brain regions that are associated with changes in cognitive conditions. That is, PPI reveals brain regions where activity is more strongly related to activity in a specified seed region under one task condition compared to another. In short, PPI detects those voxels in the brain whose time courses can be explained by an interaction effect of a specific task contrast and the time series of the seed region. Importantly, the main effect of the respective contrast and the main effect of the seed region's time course (i.e., the correlation between the seed time course and the resulting voxels' time course) are not included in the interaction effect. Therefore, results do not reflect any variation in the resulting voxels' time course that can be ascribed to either the task alone (i.e., task-dependent activation) or to an inherent co-fluctuation of activity with the seed region (i.e., across the entire fMRI session, independent of task conditions). Instead, PPI results reflect cognitively modulated co-variations of activity which are interpreted as a “functional coupling” of the brain areas involved (O’Reilly, Woolrich, Behrens, Smith, & Johansen-Berg, 2012).

In this study, PPI analyses were carried out to investigate functional connectivity between brain areas during sentence comprehension in listening and reading, and during semantic and syntactic integration in particular. Specifically, for semantic integration we were interested in whether brain regions that were activated by sentence processing independent of semantic content (i.e., by sentences as well as pseudosentences) would show differential functional connectivity during processing of semantic sentences versus non-semantic sentences (i.e., sentences > pseudosentences). To that end, seed regions were determined as the maximum of the conjunction of group activations for sentences > control and pseudosentences > control. Both of these contrasts require the integration of language elements into a greater sentence entity. However, only sentence processing also involves semantic integration of the language elements. Based on the seed region, individual seeds were determined in each participant as the voxel with the maximum intensity (i.e., z value) for sentences > control and pseudosentences > control, respectively, within a 10mm-radius sphere of the group-level seed region. Time series were extracted from a 6mm-radius sphere around each of these seeds and entered into separate PPI analyses for sentences and pseudosentences, together with the respective contrasts sentences > baseline and pseudosentences > baseline. This ensured that the main effect of the respective contrast as well as contrast-independent covariation in voxel intensities (i.e., the main effect of time series) were modelled separately and did not enter into the PPI effect. The PPI effect was defined as the interaction between the main effect of the contrast and the main effect of the time series.

This procedure was carried out for sentences and pseudosentences in listening and reading separately. In a final step, a paired t-test was conducted in both modalities to compare functional connectivity during sentence processing to functional connectivity during pseudosentence processing, i.e. during semantic integration versus no semantic integration. The equivalent procedure was followed for syntactic integration, with a seed at the maximum of the conjunction of sentences > control and scrambled sentences > control (which was the same maximum as for the conjunction of sentences > control and pseudosentences > control).

2.4 Results

2.4.1 fMRI group activations

In line with our hypothesis, sentence processing, reflected by a comparison of sentences and single words, activated the left ATL in listening and reading (Figure 1). A conjunction analysis between the two modalities revealed significant overlap of activation in the left temporal pole [MNI coordinate -52 10 -18, z=4.37] and anterior [-56 -4 -14, z=4.8] and posterior [-50 -18 -10, z=3.95] STG and MTG. Furthermore, there were additional modality-specific activations (see Table 2 and 3).

Table 2
Activation details for sentence comprehension in listening

	Size (k)	Sig. (p)	Peak (x y z)	Z-value	Brain areas covered
Cluster 1	728	.009	-56 -4 -14	4.80	LH: temporal pole, aSTG, aMTG, pSTG, pMTG
Cluster 2	1371	<.001	-10 -78 10	4.02	LH: temporooccipp MTG, lat occip c, intracalcarine c
Cluster 3	6600	<.001	32 -48 56	4.43	RH: postcentral g, SMG, Precuneous c, superior parietal lobule, precuneous c, intracalcarine c, cing g

Peak locations are given in mm in MNI-152 standard space. Probabilistic locations are derived from the Harvard-Oxford Cortical Structural Atlas. Abbreviations: LH/RH=left/right hemisphere, a=anterior, p=posterior, c=cortex, g=gyrus, lat = lateral, IFG=inferior frontal gyrus, tri=triangularis, op=opercularis, SFG = superior frontal gyrus, MFG=middle frontal gyrus, cing=cingulate, SMG=supramarginal gyrus, STG = superior temporal gyrus, MTG = middle temporal gyrus, ITG, inferior temporal gyrus, occip = occipital.

Table 3
Activation details for sentence comprehension in reading

	Size (k)	Sig. (p)	Peak (x y z)	Z-value	Brain areas covered
Cluster 1	748	.012	-48 -2 44	4.83	LH: precentral g, postcentral g
Cluster 2	809	<.008	26 -6 62	4.34	RH: SFG, precentral g
Cluster 3	1475	<.001	46 2 28	4.12	RH: IFG op, MFG, precentral g, postcentral g
Cluster 4	41440	<.001	14 -74 -2	6.85	LH: IFG tri, aSTG, aMTG, pSTG, pMTG, temporo-occip MTG, angular g, SMG Bilateral: temp pole, lat occip c, lingual g, occip fusiform g, precuneous c, intracalcarine c, occip pole, superior parietal lobule, postcental g, cingulate g RH: temporooccip ITG

Peak locations are given in mm in MNI-152 standard space. Probabilistic locations are derived from the Harvard-Oxford Cortical Structural Atlas. Abbreviations: see Table 2.

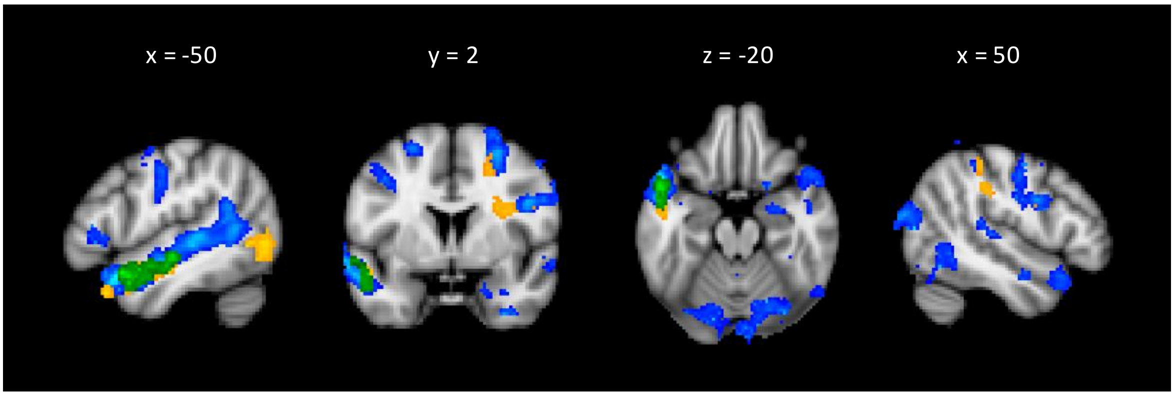

Figure 1. Group activations for sentence processing (sentences > words). Yellow = listening, blue = reading, green = conjunction of the two modalities. All results are cluster-corrected at z = 2.3, p < .05, corrected for multiple comparisons. For coronal and axial slices, the left side of the image is the left side of the brain.

Semantic and syntactic integration processes were investigated by comparing different types of sentences (Figure 2). As expected, semantic integration in listening (sentences > pseudosentences) activated the left ATL, with a cluster covering the temporal pole [-42 18

-28, z=4.25] and anterior [-54 2 -14, z=4.5] and posterior [-50 -18 -16, z=4.85] STG and MTG. Syntactic integration in listening (sentences > scrambled sentences) activated a smaller cluster that overlapped with the activation for semantic integration in the anterior [-58 2 -14, z=3.83] and posterior [-50 -10 -18, z=3.82] STG and MTG. Additional activation was found in bilateral STG and auditory cortex [62 -4 -2, z=3.81; -50 -22 12, z=3.39]. Semantic integration processes in sentence reading resulted in widespread activation in the left anterior [-54 -4 -14, z=5.04] and posterior [-50 -16 -10, z=5.32] STG and MTG, reaching into the lateral occipital cortex [-54 -72 24, z=4.69]. A smaller cluster of activation was found in the right ATL [56 16 -20, z=4.1].

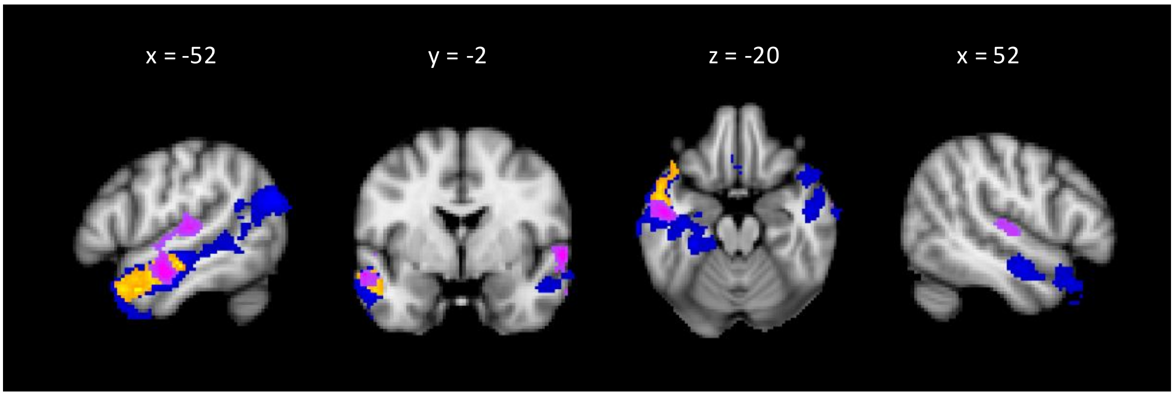

Figure 2. Groups activations for semantic integration in listening (yellow), during syntactic integration in listening (pink), and during semantic integration in reading (blue). All results are cluster-corrected at z = 2.3, p < .05, corrected for multiple comparisons.

2.4.2 Functional connectivity (PPI analyses)

The seed region for all PPI analyses was located in the left ATL (-56 12 -14). This seed region showed increased functional connectivity with the left anterior and posterior STG/MTG and planum temporale as well as with the left juxtapositional lobule and precentral gyrus during listening to sentences versus baseline (Figure 3). There was decreased connectivity of the seed region with the right frontal pole, IFG opercularis, and MFG compared to baseline (Appendix Figure A1). For pseudosentences, there was no increased connectivity of the seed region with any other brain areas compared to baseline. There was, however, decreased connectivity with the right posterior MTG and temporal pole as well as with bilateral frontal orbital cortex and anterior cingulate cortex (Appendix Figure A1). The direct comparison of functional connectivity during sentence processing versus pseudosentence processing in listening revealed significantly greater connectivity of the left ATL with the left temporal pole [-36 22 -34, z=3.76], posterior MTG [-50 -54 2, z=3.3] and juxtapositional lobule [-10 -4 58, z=4.18] as well as right superior parietal lobule [28 -56 54, z=3.4] during sentence processing (Figure 4). There was no greater connectivity of the left ATL with any other brain areas during pseudosentence processing compared to sentence processing.

For listening to scrambled sentences, there was no increased functional connectivity of the left ATL with any other brain regions compared to baseline. However, there was decreased connectivity of the left ATL with bilateral SMG/angular gyrus, precentral and postcentral gyrus, and cingulate gyrus as well as occipital areas (Appendix Figure A1). A direct comparison of sentences and scrambled sentences resulted in significantly greater functional connectivity of the left ATL with left SMG and superior parietal cortex [-22 -48 38, z=3.41] and precentral [-60 2 30, z=3.75] and postcentral [-60 -20 42, z=3.58] gyrus for sentences (Figure 4). There were no brain areas of greater functional connectivity with the left ATL for listening to scrambled sentences than sentences.

For reading sentences, there was increased functional connectivity of the left ATL with the left IFG triangularis and opercularis, central opercular cortex and precentral gyrus compared to baseline (Figure 3). There were no decreases in functional connectivity of the left ATL for reading sentences compared to baseline. For reading pseudosentences, there was no increased functional connectivity of the left ATL compared to baseline. However, there was decreased connectivity of the left ATL with the right frontal pole and frontal medial cortex for pseudosentences compared to baseline (Appendix Figure A2). Directly comparing sentences and pseudosentences resulted in increased connectivity of the left ATL with the right frontal pole [44 40 4, z=2.78], IFG opercularis [58 14 12, z=3.26], precentral [40 -16 48, z=3.28] and postcentral [38 -18 38, z=3.12] gyrus, and SMG [42 -44

38, z=3.13] during sentence reading (Figure 4). There were no brain areas of increased connectivity for reading pseudosentences compared to sentences.

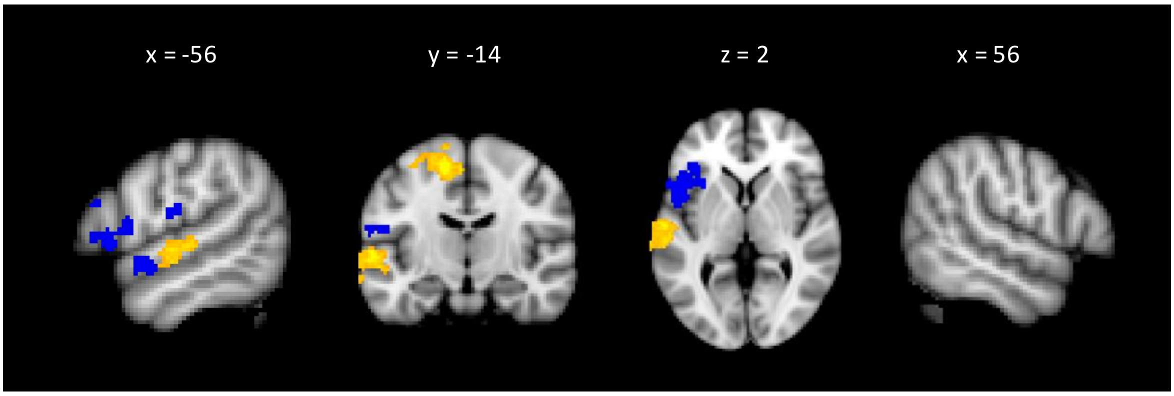

Figure 3. Functional connectivity from a seed in the left ATL during sentence processing in listening (yellow) and in reading (blue). All results are cluster-corrected at z = 2.3, p < .05, corrected for multiple comparisons.

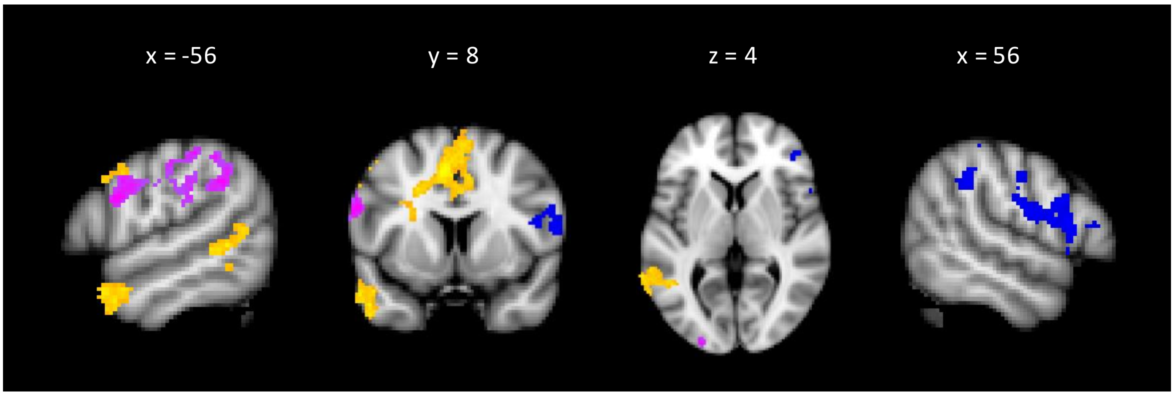

Figure 4. Functional connectivity from a seed in the left ATL during semantic integration in listening (yellow), during syntactic integration in listening (pink), and during semantic integration in reading (blue). All results are cluster-corrected at z = 2.3, p < .05, corrected for multiple comparisons.

2.5 Discussion

2.5.1 Sentence comprehension across modalities

The current study investigated the neural correlates of semantic and syntactic processing during auditory and visual sentence comprehension, focusing on patterns of cortical activations as well as functional connectivity. As expected (Hickok & Poeppel, 2007; Specht, 2014), sentence comprehension, as compared to single word processing, engaged the left temporal lobe, with particularly strong activation in the ATL. In support of a supramodal processing system for sentence comprehension (Jobard et al., 2007; Lindenberg & Scheef, 2007), activations for listening and reading overlapped considerably in the left ATL. However, in line with previous research (Carpentier et al., 2001; Homae, Yahata, & Sakai, 2003; Jobard et al., 2007), reading sentences elicited more widespread activations than listening to sentences, particularly along more posterior parts of the left STG/MTG and, to a lesser degree, in the left IFG and premotor cortex. Activation of the IFG during reading has previously been explained with phonological recoding processes of written language material (Carpentier et al., 2001; Friederici, 2002). This explanation could be extended to cover the activation in the left premotor cortex, an area strongly associated with articulatory representations (Hickok & Poeppel, 2007; Saur et al., 2008). The left IFG has also been associated with working memory processes during sentence comprehension (Fiebach et al., 2005; Grodzinsky & Friederici, 2006; Sakai et al., 2001; Stromswold et al., 1996), which might have been required during sentence reading in the current study, particularly due to the presentation of sentence parts in chunks, rather than in a continuous stream of words, as in auditory sentence comprehension.

2.5.2 Cortical activations for semantic and syntactic processing

Disentangling semantic and syntactic processes revealed overlap as well as local differences between activations for the two processes. Semantic integration activated the left ATL in listening and reading, with more extensive activations in reading. Syntactic integration, which was only studied during listening, activated a subregion in the more posterior part of the activation cluster for semantic integration. Thus, semantic and syntactic integration showed overlapping activation in the left anterior and mid STG/MTG, but semantic integration elicited additional activation in the most anterior part of the left ATL. These findings are in line with activations for attention to semantic as compared to syntactic features during sentence processing (Rogalsky & Hickok, 2009). Interestingly, this pattern of activations for semantic and syntactic processing mirrors results from a recent meta-analysis (Rodd et al., 2015). The authors found overlapping activations for semantic and syntactic complexity in the posterior part of the left IFG and additional activation for semantic complexity only in a more anterior part of the left IFG. The resemblance of activity patterns for semantic and syntactic processing between the temporal and frontal lobe supports a previously suggested parity in the topographical organization of language functions across different lobes (Ben Shalom & Hickok, 2008).

The engagement of the left ATL in semantic and syntactic integration during sentence processing is in accordance with the "combinatorial network" suggested by the dual stream model of language processing (Hickok & Poeppel, 2007). In contrast, the current results do not support a primary involvement of posterior temporal regions in integration processes during sentence comprehension (Friederici, 2012). The current results are also in line with the dual stream model with respect to the limited IFG involvement in sentence processing (Hickok & Poeppel, 2007). Friederici's model, on the other hand, proposed an engagement of the left IFG in sentence processing under specific circumstances, namely top-down regulated, strategic semantic processing and processing of complex syntax (Friederici, 2012). Particularly, sentences with syntactic structures that require reordering of words, a cognitive operation relying on (amongst other things) verbal working memory, have been found to elicit activation in the left IFG (Friederici, Fiebach, Schlesewsky, Bornkessel, & Von Cramon, 2006; Kuhnke, Meyer, Friederici, & Hartwigsen, 2017). Since the current study required natural processing of syntactically simple sentences, hence no strategic (task-induced) semantic processing, and no restructuring of syntactically complex sentences, the lack of activation in the left IFG would be expected based on Friederici's sentence comprehension model.

2.5.3 Functional connectivity during sentence comprehension

Despite great resemblances between listening and reading with regard to cortical activations for sentence comprehension, functional connectivity differed between the two modalities. Specifically, the left ATL showed overlapping activations for listening and reading, but differential connections to other brain areas for the two modalities. As expected (Warren et al., 2009; Yue et al., 2013), auditory sentence comprehension resulted in functional connectivity of the left ATL with left auditory cortex and pSTG, an area involved in phonological processing of speech (Hickok & Poeppel, 2007; Rimol, Specht, Weis, Savoy, & Hugdahl, 2005), which is also sensitive to the intelligibility of speech (Adank, 2012). The interaction between auditory-phonological areas and the left ATL might be realized through a ventral processing stream which maps the sound of speech to its meaning, as suggested by the dual stream model of language processing (Hickok & Poeppel, 2007).

When reading sentences, the left ATL showed functional connectivity with the left aSTG, an area associated with sentence processing (Vigneau et al., 2006) and semantic processing of language stimuli (Visser, Jefferies, Embleton, & Ralph, 2012; Visser & Ralph, 2011). Furthermore, the left ATL was functionally connected with the left IFG/operculum and premotor cortex. Connections between anterior temporal and inferior frontal brain regions have been proposed by different models of language processing. Friederici's sentence processing model (2012) suggests connections via two ventral streams, one from the ATL to anterior IFG for task-dependent strategic semantic processing, and one from the ATL to posterior IFG for complex syntax. Given the bottom-up, stimulus-driven processing of syntactically simple sentences required in the current study, it seems unlikely that the functional connectivity between the left ATL and left IFG reflects either top-down semantic processing or processing of complex syntax, but might rather reflect the involvement of verbal working memory processes, as suggested by the dual stream model of language processing (Hickok & Poeppel, 2007). Working memory processes might be required during reading, particularly due to the presentation of sentence parts in separate chunks, but to a much lesser degree in listening, where the sentence is delivered as a continuous stream of speech and unfolds over a shorter period of time. Contrary to our hypothesis, reading sentences did not elicit significant changes in the functional connectivity of the left ATL with the fusiform gyrus, an area strongly associated with reading (Dehaene et al., 2002; Price, Moore, & Frackowiak, 1996; Turkeltaub et al., 2002). Functional connectivity with the fusiform gyrus during sentence reading has previously been shown (Keller & Kell, 2016), but with a seed region in the left IFG, rather than the ATL as in the current study, and only in a “preparatory time window” defined as the three seconds before stimulus presentation, rather than during reading, possibly explaining the divergence in results.

The current study further explored functional connectivity specifically for semantic and syntactic processing during sentence comprehension. Semantic processing during auditory sentence comprehension elicited increased connectivity between the left ATL and the left pMTG. Posterior temporal regions are involved in lexical knowledge and processing of single-word semantics (Fiebach, Friederici, Müller, & Von Cramon, 2002; Xu, Kemeny, Park, Frattali, & Braun, 2005). Furthermore, the dual stream model of language processing proposes that information is transferred from the left posterior temporal lobe to the left ATL via a ventral processing stream during sentence comprehension (Hickok & Poeppel, 2007). A recent investigation of functional connectivity confirmed interactions between the two brain regions for semantic integration processes during sentence comprehension (Hartwigsen et al., 2017). The study found positive functional connectivity between the left anterior and posterior temporal lobe during rest, and negative connectivity when participants listened to sentences with unexpected ending words. Considering the involvement of the left posterior temporal lobe in storage and retrieval of lexical information, the authors interpreted the negative connectivity of the left ATL with the left pSTG/MTG as an inhibitory connection, necessary to suppress the expected, dominant sentence ending.

In the current study, the left ATL did not only show functional connectivity with the left pMTG but also with the left temporal pole. The left temporal pole has been shown to be involved in processing wider-context semantic processing, such as text comprehension (Ferstl, Neumann, Bogler, & Von Cramon, 2008). In line with this, previous research has found functional connectivity between the left ATL and left temporal pole during story listening (Warren et al., 2009). The connectivity between the left ATL and temporal pole found in the current study during sentence comprehension, might therefore reflect interpretation of sentences within a wider semantic context.

For reading, semantic processing during sentence comprehension elicited increased functional connectivity of the left ATL with right-hemisphere frontal brain areas, including the right IFG. This increased connectivity for sentence reading as compared to reading pseudosentences stemmed from both, increased connectivity for sentences (compared to baseline) and decreased connectivity for pseudosentences (compared to baseline). Interhemispheric connections during language processing are neither discussed in the dual stream model (Hickok & Poeppel, 2007) nor in Friederici's sentence processing model (Friederici, 2012). However, previous studies provide evidence for increased interhemispheric connectivity of frontal as well as temporal regions during semantic processing (Keller & Kell, 2016; Warren et al., 2009). Within the left hemisphere, frontal and temporal regions have been shown to interact during sentence processing (Den Ouden et al., 2012; Papoutsi et al., 2011) and during semantic processing in particular (Humphreys & Gennari, 2014). Given that not only the left but also the right IFG has been shown to be involved in semantic and sentence processing (Jung-Beeman, 2005; Vigneau et al., 2011), increased connectivity between the left ATL and right frontal lobe during sentence comprehension, as found in the current study, might reflect semantic processing. In contrast, pseudosentence processing does not allow for semantic processing, deeming functional connectivity of the left ATL with the right IFG unnecessary and explaining a decrease in connectivity.

Functional connectivity analyses for syntactic integration in auditory sentence comprehension revealed increased connectivity of the left ATL with the left parietal lobe and pre- and postcentral gyrus, predominantly stemming from a decreased connectivity during processing of scrambled sentences compared to baseline. The finding of decreased connectivity was unexpected given that left parietal regions have previously been considered to be part of the language network (Price, 2010, Vigneau et al., 2006). However, the left parietal lobe has also repeatedly been included in a brain network that shows decreases in activity when participants perform cognitive tasks, regardless of their specific nature and demands, compared to a resting baseline (Binder, Frost, Hammeke, Bellgowan, Rao, & Cox, 1999; Mazoyer et al., 2001; McKiernan, Kaufman, Kucera-Thompson, & Binder, 2003; Shulman et al., 1997). This decrease has been suggested to reflect a reallocation of neural resources from general attention areas (such as the parietal lobes) to task-specific cortical areas (McKiernan et al., 2003). The decrease in functional connectivity between the left ATL and left parietal lobe found here, might reflect such a “deactivation” of the resting state network. However, it should be noted that this pattern of negative connectivity did not emerge for other conditions that were compared to the resting baseline in our functional connectivity analyses. Since task-induced deactivation of the resting state network has been shown to be greater when cognitive tasks become more difficult (McKiernan et al., 2003), it cannot be ruled out that the scrambled sentence condition simply imposed higher cognitive demands than other conditions for which potential interactions with the resting state network might then be weaker and, hence, not significant. However, this explanation remains speculative and further research is required to explore the role of temporal-parietal connectivity during syntactic processing.

2.5.4 Potential limitations of the current study

The current study assessed semantic integration by comparing sentence processing to processing of pseudosentences. It should be noted that while this contrast measures semantic processing during sentence comprehension specifically, it does not only include processes of semantic integration, but could also capture semantic processes on the single-word level. Other studies have investigated semantic integration during sentence comprehension using semantically random sentences, in which all content words have been replaced with other, randomly selected content words (Humphries et al., 2006; Vandenberghe et al., 2002). However, when comparing those semantically random sentences with normal sentences, both directions of the contrast can be, and have been, interpreted as semantic integration. On the one hand, it has been argued that sentences versus random sentences measure semantic integration because combining words semantically is possible in sentences but not in random sentences (Humphries et al., 2006). On the other hand, it has been argued that random sentences versus sentences measure semantic integration because combining words semantically is more demanding for random sentences, hence eliciting increased semantic integration efforts (Vandenberghe et al., 2002). In contrast, pseudosentences do not allow for any semantic integration, which is why they were chosen as a contrast for sentences in the current study. Previous comparisons have shown that contrasting sentences with pseudosentences resulted in almost identical neural activations as contrasting sentences with semantically random sentences (Humphries et al., 2006).

In conclusion, the results of the current study provide support for the dual stream model of language processing (Hickok & Poeppel, 2007). Sentence comprehension engaged the left ATL, with mostly overlapping activations for semantic and syntactic integration, as predicted for the model's “combinatorial network”. This sentence processing area seems to be supramodal, with mostly overlapping activations during listening and reading. However, functional connectivity of the left ATL with temporal, frontal, and parietal regions differed between the two modalities, and between semantic and syntactic integration. The limited involvement of the left IFG in sentence comprehension is in line with results from previous studies using passive language processing paradigms, but diverges from investigations of sentence comprehension under active task conditions and from studies manipulating semantic or syntactic demand rather than the presence/absence of semantic or syntactic processing per se. This discrepancy between studies suggests that activations in the left IFG during sentence processing might party be driven by domain-general task demands, such as working memory, rather than linguistic factors, emphasizing the value of more natural, passive language paradigms.

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2.7 Appendix

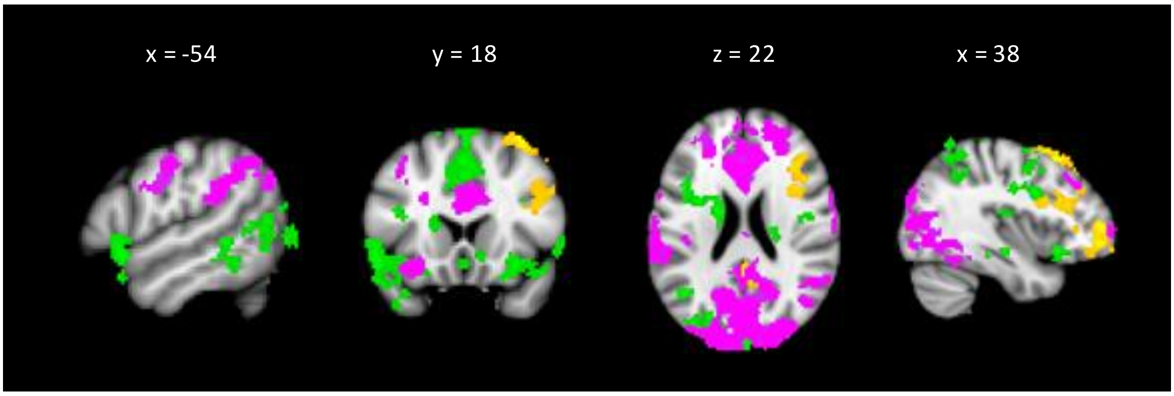

Figure A1. Decreased functional connectivity of the left ATL during listening. Results show decreased connectivity compared to baseline for sentences (yellow), for pseudosentences (green), and for scrambled sentences (pink). All results are cluster-corrected at z = 2.3, p < .05, corrected for multiple comparisons.

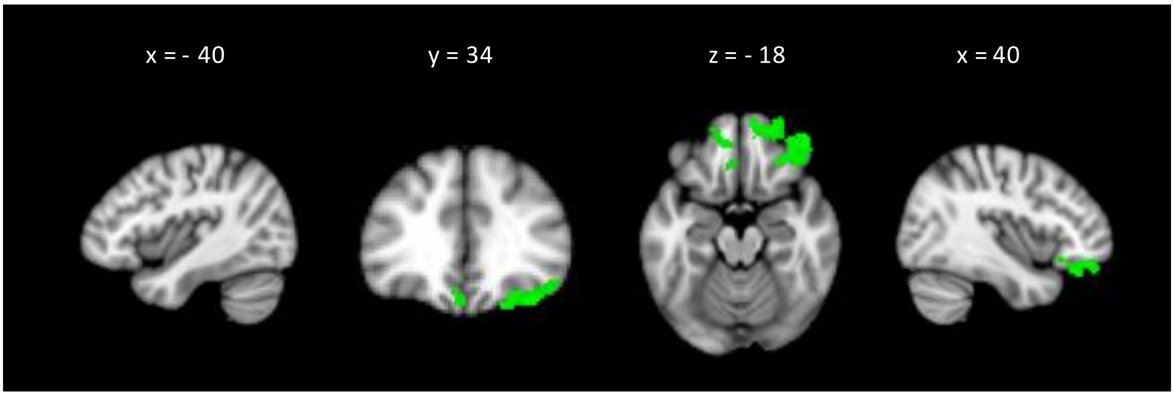

Figure A2. Decreased functional connectivity of the left ATL during pseudosentences reading (compared to baseline). All results are cluster-corrected at z = 2.3, p < .05, corrected for multiple comparisons.

Chapter 3

Revisiting the Ambiguous Relationship Between Language Ability and Brain Activity

3.1 Abstract

Neuroimaging studies on the relationship between language ability and brain activity have found contradictory evidence: On the one hand, *increased* activity with higher language ability has been interpreted as deeper or more adaptive language processing. On the other hand, *decreased* activity with higher language ability has been interpreted as more efficient language processing. In contrast to previous studies, we investigated the relationship between language ability and neural activity across different language processes and modalities in a task-independent manner. In an fMRI study, twenty-two healthy adults performed a sentence listening task, a sentence reading task and a phonological production task. Outside of the scanner, language ability was assessed with the verbal scale of the Wechsler Abbreviated Scale of Intelligence (WASI-II) and a verbal fluency task. As expected, sentence comprehension activated the left anterior temporal lobe. Phonological processing activated the left inferior frontal and precentral gyrus. Higher language ability was associated with increased activity in the left temporal lobe during auditory sentence processing and with increased activity in the left frontal lobe during phonological processing. Increased activity was reflected in higher intensity and greater extent of activations. Less consistent evidence was found for decreased activity associated with higher language ability. The results indicate a differential recruitment of brain areas in individuals with higher versus lower language ability, predominantly supporting the hypothesis of deeper language processing in individuals with higher language ability. The consistency of results across language processes, modalities, and brain regions suggests a general positive link between cognitive ability and brain activity.

3.2 Introduction

The neuroimaging literature offers a large number of studies investigating the neural correlates of language processing for the purpose of localizing its different components in the brain. These studies have reached some consensus about the brain areas involved in processes such as phonology, semantics, and syntax (Hickok & Poeppel, 2007; Price, 2010; Vigneau et al., 2006). In contrast, the number of neuroimaging studies focusing on the role of individual differences, such as participants' language ability, in the neural correlates of language processing, is rather small.

Language ability is a multidimensional concept that covers a wide range of linguistic processes. It has previously been operationalized as, for example, verbal working memory span, vocabulary size, or high-level language abilities such as metaphor processing and inference generation (Prat & Just, 2010; Van Ettinger-Veenstra, Ragnehed, McAllister, Lundberg, & Engström, 2012). In neuroimaging studies, these abilities have been found to be associated with increases as well as decreases of activity in different areas of the brain. These brain areas can be categorized into (1) left-hemisphere primary language areas (2) right-hemisphere homologues of these areas and (3) areas associated with cognitive control. Importantly, the direction of correlations between ability and activity in these areas differs between studies and a range of interpretations has been offered.

3.2.1 Language ability and neural activity in left-hemisphere language areas

The relevance of left-hemispheric frontal and temporal brain regions for language processing has been well established in neuroimaging studies and theoretical models (Hickok & Poeppel, 2007; Vigneau et al. 2006). However, there have been studies to suggest that the exact patterns of activations in these areas might vary with language ability. For example, a recent study found a link between a measure of high-level language ability (the Bedömning av Subtila Språksvårigheter (BeSS) – Assessment of subtle language disabilities) and activity in the left angular gyrus during a sentence reading task (Van Ettinger-Veenstra, McAllister, Lundberg, Karlsson, & Engström, 2016). Higher ability scores were associated with increased activity in this brain region. The authors interpreted the results as an indication of deeper semantic processing of the sentence contents in subjects with relatively higher language ability. Prat, Mason, and Just (2011) also found positive correlations between ability and activity, using vocabulary size as a measure of language ability. They investigated the processing of causal inferences during reading by comparing activations for semantically related passages to incoherent passages. Subjects with larger vocabulary showed increased activation in the left inferior frontal gyrus (IFG) and the left temporal lobe. The authors concluded that subjects with relatively higher language ability might be more sensitive to the semantic relations between sentences than subjects with lower language ability.

In contrast, Welcome and Joanisse (2012) found a negative correlation between performance in a visual word recognition task outside the MRI scanner and activity in the left middle temporal gyrus (MTG) during an fMRI paradigm in which participants read words and made decisions on their spelling, sound, or meaning. It was hypothesized that, in less skilled participants, word reading is less automated and therefore requires more effort and more neural engagement. Prat and colleagues have repeatedly found negative relationships between language abilities and activity in different brain regions, some of which were left-hemisphere language areas (Prat et al., 2011; Prat, Mason, & Just, 2012). They interpreted their finding in the light of neural efficiency (Maxwell, Fenwick, Fenton, & Dollimore, 1974; Haier, Siegel, Tang, Abel, & Buchsbaum, 1992). According to this concept, subjects with higher language ability show reduced brain activity when performing language tasks, as compared to subjects with lower language ability. This is thought to reflect the reduced effort that higher-ability individuals need to invest in order to perform a language task, consequently saving neural resources compared to individuals with lower language ability. The neural efficiency concept has not only been applied to explain activity differences in left-hemisphere language areas but also right-hemisphere regions and areas associated with cognitive control (e.g., Prat, Keller, & Just, 2007).

3.2.2 Language ability and neural activity in right-hemisphere homologues

Despite the well-established dominance of the left hemisphere in language processing, there is also evidence of areas in the right hemisphere being activated during language tasks, although usually to a lesser extend (Vigneau et al., 2011). There has been research to suggest that the degree of right-hemisphere involvement in language processing might vary with language ability. For example, Van Ettinger-Veenstra et al. (2012) investigated the relationship between brain activity in a sentence completion task and the performance on two behavioral measures of language ability, a reading comprehension test and the BeSS test. Both of those measures correlated positively with activations in the right IFG and the right MTG. The authors concluded that the demands imposed by difficult language tasks are "positively modulated in the right hemisphere" and that higher-ability individuals use those brain regions to better cope with these demands. On the other hand, Prat and colleagues (2011, 2012) found a negative relationship between participants' vocabulary size and activity in the right IFG during two reading paradigms. They explained the increased recruitment of right-hemisphere regions in lower-ability subjects with the dynamic spillover hypothesis. This hypothesis proposes that the right hemisphere is capable of processing language, but not as efficiently and as precisely as the left hemisphere. Therefore, the right hemisphere is only used as a reserve when task demands are high and part of the processing "spills over" into right-hemisphere homologues of the already occupied typical left-hemisphere areas. Since individuals with lower language ability experience higher demands during language processing than higher-ability individuals, their left-hemisphere capacities are thought to be exhausted more quickly. Thus, individuals with lower language ability resort to right-hemisphere areas to a greater degree, resulting in negative correlations between ability and activity in the right hemisphere. However, the direction of causality for these correlations is impossible to determine. While the spill-over hypothesis suggests inferior language ability as a cause for right-hemisphere activity, it is equally possible that an increased involvement of the right hemisphere, which is inferior in its language processing ability to the dominant left hemisphere, leads to worse performance on language tasks. Thus, an additional recruitment of right-hemisphere areas by lower-ability subjects would not be a remedy to processing difficulties, but rather the cause of their inferior performance.

3.2.3 Language ability and neural activity in the cognitive control network

The cognitive control network has been defined as a set of brain areas involved in domain-general cognitive processes such as attention, working memory, planning and inhibition. The network is thought to comprise (pre-)frontal brain regions, the anterior cingulate cortex, and parietal cortex (Cole & Schneider, 2007; Niendam, Laird, Ray, Dean, Glahn, & Carter, 2012; Breukelaar et al., 2016). Positive as well as negative relationships between language ability and activity in these brain areas have been found in the past. Prat and Just (2011) found that participants with a greater reading span, a measure of verbal working memory, showed increased activity in prefrontal cortex, cingulum, striatum, hippocampus, and precuneus when reading syntactically complex versus easy sentences. The authors concluded that higher-ability subjects showed neural adaptability because they were able to activate additional resources when faced with increasing demands. However, in a later study, Prat et al. (2012) found the opposite, i.e., a negative correlation between ability and activity. When participants integrated semantically relevant context information while reading sentences, those with a smaller reading span showed increased activation in the anterior cingulate cortex as opposed to those with a greater reading span. The same was true for participants with smaller vocabulary size who also presented increased neural activity compared to participants with larger vocabulary in middle frontal regions, precuneus and striatum. Prat et al. (2012) argued that the greater involvement of these brain areas by subjects with relatively lower language ability reflected the increased demands they faced.

In summary, neural activity during language processing has been shown to vary with individuals' language ability in typical language areas in the left cerebral hemisphere, areas in the right hemisphere, and areas associated with other cognitive functions, such as cognitive control. However, the direction of the relationship between ability and activity is unclear and contradicting interpretations have been offered to explain the diverse results. For example, the engagement of areas in the right hemisphere and the cognitive control network has been suggested as a reaction to increased task demands. However, this explanation has been employed as an interpretation for both, positive (Van Ettinger-Veenstra et al., 2012; Prat & Just, 2010) and negative (Prat et al., 2011; 2012) correlations between ability and activity. While increased activation is regarded as a sign of neural adaptability when found in subjects with higher language ability, in subjects with lower language ability it is described as a coping mechanism that is necessary to compensate for their inferior ability.

It is also worth mentioning that inconsistencies between findings do not only arise between, but even within studies (e.g., Buchweitz, Mason, Tomitch, & Just, 2009; Prat et al., 2011; Van Ettinger-Veenstra et al., 2012). In the majority of studies reported above, any measure of language ability often showed a mixture of positive and negative correlations with a given fMRI language task, or no correlation at all. Furthermore, the same measure of language ability was often associated with activity changes in a wide range of areas distributed across the whole brain. Thus, while there is convincing evidence for a relationship between language ability and neural activity during language processing, the nature of this relationship seems to be strongly dependent on the specific ability measures and fMRI tasks used in different studies, making it difficult to extract a clear pattern.

3.2.4 Language-specific effects versus domain-general cognitive demands

Most of the studies investigating the relationship between language ability and brain activity have investigated activity derived from sentence reading paradigms. However, the specific task that participants had to perform while reading, varied between paradigms and involved, for example, answering questions about sentence meaning (e.g., Buchweitz et al., 2009; Van Ettinger-Veenstra et al., 2016), integrating information from working memory (e.g., Prat & Just, 2010; Prat et al., 2012), or completing sentences (e.g., Van Ettinger-Veenstra et al., 2016). It is difficult to determine how these task requirements contribute to the activations that have been found in the studies. This is particularly true for activations in the right-hemisphere and the cognitive control network that are not typically involved in language processing per se. It is possible that, when comparing subjects with relatively higher versus lower language ability, differences in activations do not solely stem from differences in language-specific activations but rather from differences in activations associated with general cognitive demands imposed by the particular task. Furthermore, language paradigms that are high in cognitive demand might result in behavioral differences between higher-ability and lower-ability individuals. Differences in activations might then reflect differences in processing, such as cognitive engagement or performance levels, rather than differences in ability (Prat, 2011).

Tasks that are low in domain-general, non-linguistic cognitive demand, however, might give more insight into the relationship between language ability and language-specific neural activity. For example, Virtue, Parrish, and Jung-Beeman (2008) used a passive story listening paradigm to study the neural correlates of inference generation. While participants were asked to answer comprehension questions at the end of the fMRI runs, there was no additional task interfering with basic language processing while listening to the stories. On the group level, inference generation activated the bilateral inferior frontal gyri and bilateral temporal gyri. Neural responses in the right superior temporal gyrus were positively correlated with performance on a reading span task assessing verbal working memory, suggesting enhanced processing and inference generation in individuals with higher language ability. Another example for the use of fMRI paradigms with low general cognitive demand comes from the field of intelligence research. Passively watching videos with an audio narrative was found to elicit brain activity that was positively correlated with intelligence (Haier, White, & Alkire, 2003). Thus, these two studies suggest positive relationships between ability and activity for paradigms that are low in domain-general cognitive demand and rely on bottom-up stimulus processing.

In the study reported here, task demands were kept at a minimum, aiming to assess language processing without any additional, non-linguistic cognitive processes such as decision making or memorizing. Neural responses to sentence processing (in listening and reading) and phonological processing (in repetition) were correlated with performance on two measures of language ability, the Verbal Comprehension Index (VCI) as defined by the verbal subscale of the Wechsler Abbreviated Scale of Intelligence (WASI-II), and verbal fluency. The VCI (known as verbal IQ in the WASI-I) is a well-established measure of language ability that has been validated in a large sample of subjects spanning different age groups (Wechsler, 2011). The verbal fluency task is a well-established paradigm that has frequently been used to assess individuals' semantic and phonological fluency (e.g., Birn et al., 2010; Costafreda, Fu, Lee, Everitt, Brammer, & David, 2006). Performance on verbal fluency tasks relies on linguistic aspects of language processing, such as vocabulary knowledge, as well as on aspects of executive functioning, such as cognitive inhibition (Shao, Janse, Visser, & Meyer, 2014; Stolwyk, Bannirchelvam, Kraan, & Simpson, 2015), but has been shown to be predominantly a measure of language ability (Whiteside et al., 2016). Therefore, it offers a complementary way of assessing language ability in the current study, along with the traditional, more linguistic verbal IQ.

Given the language-specific processing demands of our fMRI paradigm, we expected correlations between language ability and neural responses to sentence processing and phonological processing in language-related brain areas. Specifically, we expected BOLD responses in left-hemisphere temporal regions during sentence processing and BOLD responses in left frontal regions during phonological processing to vary with the VCI and verbal ability.

While there have been contradictory findings regarding the direction of potential relationships, we expected positive correlations based on similarities of our fMRI paradigm with the ones employed by Virtue et al. (2008) and Haier et al. (2003). Both of these studies used paradigms that were stimulus-driven and low in cognitive effort. Likewise, our fMRI paradigm investigated language processing in the absence of any additional, non-linguistic task demands. While our pseudoword repetition task is arguably more engaging and effortful than our listening and reading task, it is still low in domain-general cognitive demand and requires effort that is stimulus-driven (and therefore linguistic) rather than task-driven. In that way, it shows more similarities with the studies of Virtue et al. and Haier et al. than with previous studies that involved cognitive demand in the form of decision making or working memory processes and found negative relationships between language ability and brain activity (e.g., Welcome & Joanisse, 2012; Prat et al., 2012).

3.3. Methods

3.3.1 Subjects

Twenty-six right-handed native English speakers were recruited through the Durham University participant pool and gave informed consent to take part in the study. They had normal or corrected-to-normal vision and normal self-reported hearing. All participants reported no history of any psychiatric conditions. After motion correction, four participants had to be excluded due to movements greater than one voxel size between volumes, leaving a sample of twenty-two subjects (14 female, mean age 22.05, *SD* = 7.66). Participants completed the Edinburgh Handedness Inventory (Oldfield, 1971), revealing a mean handedness index of 83.13 (*SD* = 20.18). The study was approved by the Durham University Ethics Committee and conformed to the guidelines of the Declaration of Helsinki.

3.3.2 Stimuli

Different types of language stimuli as well as modality-specific control stimuli were used to tap into different language processes. The language stimuli included words, sentences, scrambled sentences (reported elsewhere), pseudowords, and pseudosentences (reported elsewhere). All words (used in word conditions and sentence conditions) were taken from the MRC Psycholinguistic Database (Coltheart, 1981). Pseudowords were generated based on those words, using the Wuggy software (Keuleers, & Brysbaert, 2010).

The word condition consisted of lists of nouns only, in order to avoid the possibility of grammatically combining words. For all nouns, used in the word and sentence conditions, the mean number of letters was 6.11 (*SD* = 2.00), mean word frequency (Kucera & Francis, 1967) was 74.13 (*SD*=118.04), the mean familiarity was 528.82 (*SD*=76.71), and the mean concreteness was 514.31 (*SD*=101.40). Across subjects, the same stimuli were used in the three modalities, listening, reading, and repetition.

The sentences consisted of six to seven words and all sentences had the same grammatical structure. The majority of sentences had several possible ending words. One of those words was presented as the last word in a sentence. The other ones were presented in the word condition (see Table 1 for examples). This way, the same nouns were used in the word lists and in the sentences and scrambled sentences across participants. Across conditions, a total of 1009 content words was used, 533 of which were nouns, 238 of which were verbs, and 238 of which were adjectives.

Auditory control stimuli were created in Audacity by temporally reversing the pseudowords used in the pseudoword condition. Visual control stimuli were generated from words in the word condition by replacing half of the letters of the alphabet with / and the other half with \. This resulted in length-matched stimuli in the form of, for example "/ / \ /" or "\ / / / \ /".

Table 1
Example of stimuli used in the sentence condition and in the word condition across participants

	Participant A	Participant B
Sentence condition	The customer tries the spicy <u>soup</u> The nephew finds the hidden <u>toy</u>	The customer tries the spicy <u>meal</u> The nephew finds the hidden <u>box</u>
Word condition	meal … stew … box … sweets …	soup … stew … toy … sweets …

3.3.3 Procedure

3.3.3.1 Behavioral testing

In addition to the fMRI sessions, all participants performed further language tasks outside the scanner, typically on the day before their scanning session. *Verbal Comprehension Index*. The verbal subscale of the Wechsler Abbreviated Scale of Intelligence (WASI-II) was administered, consisting of a Vocabulary test and a Similarity test (Wechsler, 2011). In the Vocabulary test, participants were given words of different degrees of difficulty, ranging from “SHIRT” to “PAVID”, and were asked to describe what they mean. In the Similarity test, participants were given two words (e.g., “GREEN” and “BLUE” or “MEMORY” and “PRACTICE”) and were asked to describe in what way they are alike. Answers were noted down and scored according to the WASI-II manual. Scores were converted into the Verbal Comprehension Index using the normative data provided by the WASI-II.

Verbal Fluency. Participants performed a verbal fluency task, consisting of a semantic part (e.g., Basho et al., 2007; Birn et al., 2010; De Carli et al., 2007) and a phonological part (known as the Controlled Word Association Test, COWAT (e.g., Loonstra et al., 2001; Rodriguez-Aranda & Martinussen, 2006)). In the semantic part, participants were given two minutes to name as many words as they could, belonging to a certain category (i.e., animals, fruits, jobs). In the phonological part, participants were given two minutes to name as many words as they could, starting with a certain letter (i.e., F, A, S). The number of words generated per category and letter was used as a measure of semantic and phonological fluency, respectively.

3.3.3.2 fMRI

The fMRI data were acquired over two sessions with three identical runs each (listening, reading, repetition), only changing the specific stimuli that were presented. The order of runs was counterbalanced and the order of conditions in each run was determined by one of four pseudorandomly generated lists of conditions.

Stimuli were presented in a passive listening task, a silent reading task and a repetition task. For each stimulus, participants were asked to press a button with their index finger when they had finished listening to or reading the stimulus. This task ensured that participants stayed alert and processed the stimuli appropriately while keeping language-unrelated cognitive demands minimal and constant across the different modalities and stimulus types. In the repetition blocks, the button press was followed by the participant repeating the stimulus out loud. Participants used different hands for responding in the two sessions, counterbalancing the order of left and right hand across participants.

The listening runs lasted 19.2 min, including four blocks per condition (i.e., eight blocks per condition across the two sessions): control, pseudowords, words, pseudosentences, scrambled sentences, and sentences. For control stimuli, pseudowords, and words, 14 stimuli were presented per block. For pseudosentences, scrambled sentences and sentences, 6 stimuli were presented per block. Interstimulus intervals (ISI) were jittered. The mean length of the stimuli and their ISI were as follows: 812 ms (ISI of 2991 ms) for control, 811 ms (ISI of 2999 ms) for pseudowords, 843 ms (ISI of 2997) for words, 2424 ms (ISI of 6350 ms) for pseudosentences, 3057 ms (ISI of 6349 ms) for scrambled sentences, and 2388 ms (ISI of 6342 ms) for sentences. Stimuli were presented through fMRI compatible in-ear headphones at a comfortable, audible listening volume verified by the participant. During the auditory stimulus presentation, participants were instructed to fixate a white cross presented at the center of a screen in front of them. The reading runs lasted 15.0 min, including four blocks per condition: control, pseudowords, words, pseudosentences, and sentences. For control stimuli, pseudowords, and words, 14 stimuli were presented per block (presentation time of 1000 ms). For pseudosentences, and sentences, 6 stimuli were presented per block, each (pseudo-)sentence divided into three chunks of 1400 ms (e.g., The customer – finds – the hidden toy). ISI were jittered, with the following means: 2487 ms for control, 2506 ms for pseudowords, 2517 ms for words, 5865 ms for pseudosentences, and 5877 ms for sentences. A BOLD screen was used for stimulus presentation (Cambridge Research Systems). Participants viewed the screen by a mirror mounted on the head coil. Stimuli were presented in white font in the center of a black screen. The repetition runs lasted 13.1 min, including four blocks per condition: control, pseudowords, words, and sentences. For control stimuli, pseudowords, and words, 7 stimuli were presented per block. In the sentence condition, 3 stimuli were presented per block. ISI were jittered. The mean length of the stimuli and their ISI were as follows: 840 ms (ISI of 5563 ms) for control, 811 ms (ISI of 5590 ms) for pseudowords, 843 ms (ISI of 5478) for words, and 2388ms (ISI of 12188ms) for sentences. Stimulus presentation in the repetition runs was the same as in the listening runs, except for longer ISI to allow for repetition of the stimuli by the participant.

All stimuli were presented with the Psychtoolbox-3 software, run under MATLAB version R2014a. Each block was preceded by a prompt screen which was presented for 2 sec, indicating the condition. A low-level baseline condition (looking at a fixation cross) was included with four blocks of 37.5 s per run.

Between the two sessions, participants had a break of approximately one to two hours. Each session lasted about one hour, including short breaks between the three runs and a structural scan (T1 or DTI) at the end of the session.

3.3.4 fMRI data acquisition

Data were acquired on a Siemens 3T Magnetom Trio Scanner in the James Cook University Hospital, Middlesbrough, UK, using a 32 channel head coil. EPI imaging of the whole head was performed, using a 96 x 96 matrix with a field of view of 210 x 210 and a voxel size of 2.1875 x 2.1875 x 3 mm. 35 axial slices were collected in ascending acquisition with a 10% gap in between slices. The TR was 2.16 s, TE 30 ms and the flip angle was 90°. The total number of volumes acquired per person (across the two sessions) was 2660: 1080 for listening runs, 844 for reading runs, and 736 for repetition runs.

Anatomical data was acquired with a T1-weighted 3D sequence comprising 192 slices (TR = 2250 ms, TE = 2.52 ms, TI = 900 ms; flip angle 9°, FOV = 25.6cm, 512x512 matrix, voxel size = 0.5x0.5 mm).

3.3.5 Data preprocessing and analysis

Data were preprocessed and analyzed using FMRIB's Software Library, version 4.1 (FSL, http://www.fmrib.ox.ac.uk/fsl). For each subject, two first-level analyses were performed, one for each of the two fMRI sessions. Motion correction was carried out using FSL's MCFLIRT and motion parameters were later included in the model as regressors of no interest. Data were high-pass filtered with the cut-off set to twice the maximum cycle length for each of the runs (Poldrack, Mumford, & Nichols, 2012), resulting in 168 s for listening runs, 140 s for reading runs and 152 s for repetition runs. The data were spatially smoothed with a full-width half-maximum kernel of 6 mm. In an event-related analysis (i.e., using timings of single stimulus onsets and durations rather than blocks), each stimulus type was modelled as an explanatory variable and convolved with a double gamma hemodynamic response function. Resting blocks were used as an implicit baseline not specified in the model.

Three contrasts were chosen to reflect the different language processes that we aimed to study: listening to sentences > control for auditory sentence comprehension; reading sentences > control for visual sentence comprehension; repeating pseudowords > repeating words for phonological processing. Due to their regular use, words have a stored sensory and motor representation and their production is therefore phonologically less demanding than the production of pseudowords (Hickok, 2009; Hickok & Poeppel, 2007; Saur et al., 2008).

For each participant, first-level results were combined in a second-level fixed effects analysis. The results of the second-level analysis were fed into a between-subjects analysis using FSL's FLAME 1+2. Outliers were automatically de-weighted by the software. All results were corrected for multiple comparisons using a cluster-threshold method ($z > 2.3$, $p < .05$).

In the group-level analysis, the behavioral data collected outside the scanner were included as covariates. Both, VCI scores and verbal fluency scores were entered as explanatory variables and orthogonalized with regard to the main effect of stimulus type (i.e., demeaned). Hence, results reflect activations that vary with the performance on the VCI or the verbal fluency task. Positive contrasts show positive correlations between language ability and the BOLD signal change (i.e., more positive signal change for participants with higher language ability), whereas the reverse contrasts show negative correlations. Correlations were quantified by performing a Pearson correlation analysis on the ability scores and the beta weights in the respective areas of correlation. These were extracted using FSL FEATquery.

3.4 Results

3.4.1 Behavioral results

Verbal Comprehension Index. Verbal ability as measured by the verbal scale of the WASI-II was high in the present sample. The mean VCI, comprised of participants' scores on the Vocabulary test and the Similarity test, was *M* = 120.14 (*SD* = 14.80).

Verbal Fluency. In a first step, the average number of words generated per semantic category and per letter was scored separately. Both tasks showed good reliability (Cronbach's alpha of .80 for category fluency and .87 for letter fluency). In the semantic task, participants generated a mean of 27.08 words within two minutes (*SD* = 4.74). Performance in the phonological task was slightly worse with 22.15 words (*SD* = 6.27). The mean overall verbal fluency was *M* = 24.61 (*SD* = 5.04). Performances on the two subparts were significantly correlated, *r*(20) = .67, *p* = .001, two-tailed.

The VCI and verbal fluency showed a significant positive correlation, *r*(20) = .460, *p* = .031, two-tailed.

3.4.2 fMRI group activations

To investigate activation patterns of sentence comprehension in listening and reading, the sentence condition was compared to the control condition in both modalities separately (reversed pseudospeech and symbol strings, respectively). For the listening task, this comparison revealed three significant clusters (Table 2), including one in the left temporal pole [-52 6 -22, z=5.01], extending into the posterior part of the superior and middle temporal gyrus [-52 -2 -20, z=4.94]. In the reading modality, the contrast resulted in more widespread activations, including the areas found in the listening modality. Additionally, activation was found in right temporal areas [54 18 -16, z=4.21] and left frontal regions [-54 14 22, z=4.57] (Table 3).

To investigate phonological processing, repetition of pseudowords was contrasted with repetition of words. This resulted in pronounced activations in the left inferior frontal gyrus [-48 12 14, z=4.95], pars opercularis, extending into pars triangularis, superior frontal gyrus [-4 22 50, z=4.81], precentral gyrus [-48 4 36, z=4.80] and bilateral insula [36 22 -2, z=4.51], also covering the superior temporal gyrus [-64 -2 -6, z=3.70]. Further activations were found in the paracingulate and medial superior frontal gyrus [-4 22 50, z=4.81], and in the right insular cortex [36 22 -2, z=4.51] and inferior frontal gyrus, pars opercularis [46 20 8, z=3.93] (Table 4). Activations for all three modalities are displayed in Figure 1.

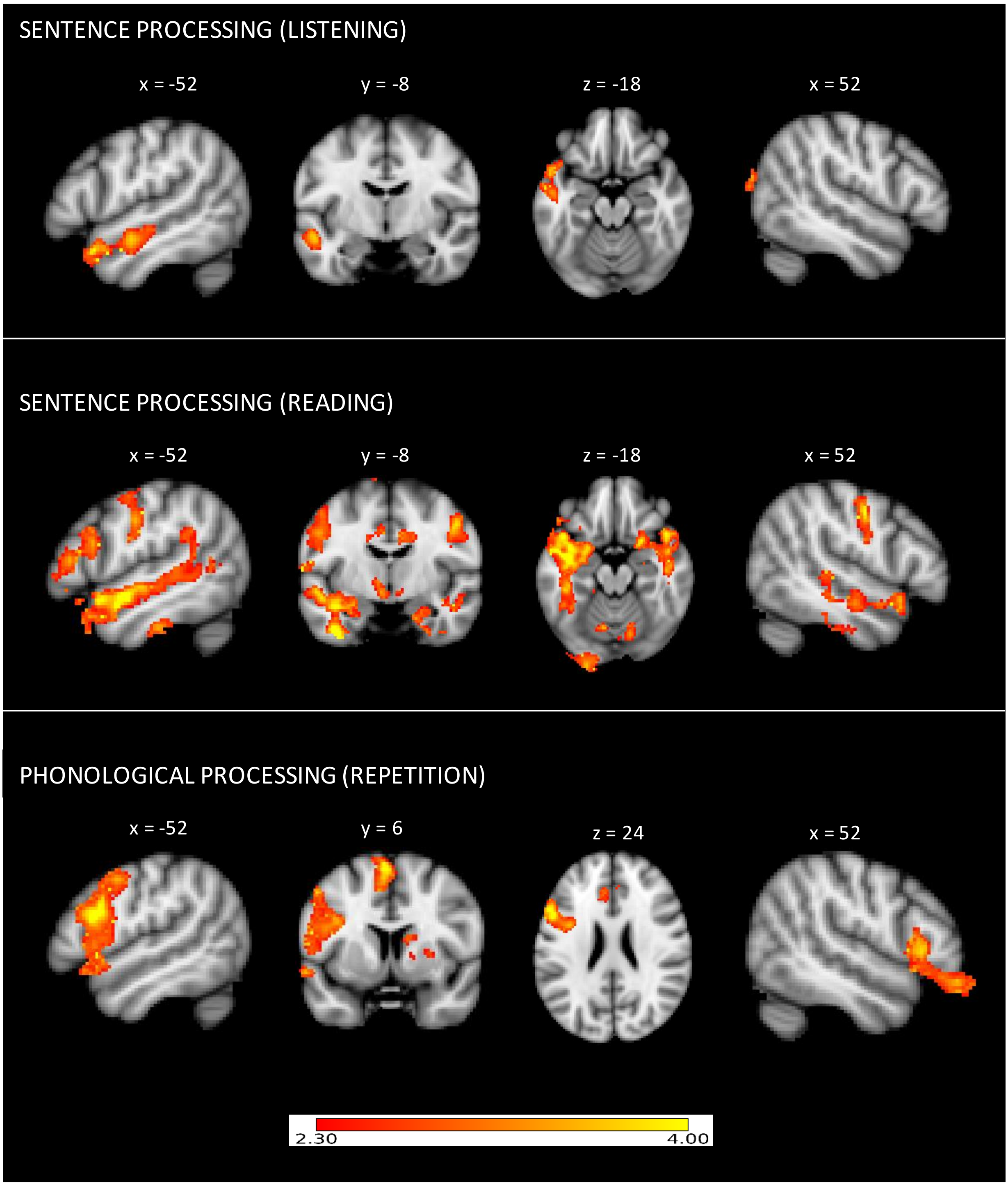

Figure 1. Group activations for the different language processes. All results are cluster-corrected at $z = 2.3$, $p < .05$. For coronal and axial slices, the left side of the image is the left side of the brain.

Table 2

Activation details for sentence comprehension in listening

	Size (k)	Sig. (p)	Peak (x y z)	Z-value	Brain areas covered
Cluster 1	586	.026	-52 6 -22	5.01	LH: temporal pole, aSTG, aMTG, pSTG, pMTG
Cluster 2	600	.023	46 -88 20	3.83	RH: lat occip c, occip pole
Cluster 3	1415	<.001	18 -40 50	3.89	RH: Precuneous c, superior parietal lobule, postcentral g, cing g

Peak locations are given in mm in MNI-152 standard space. Probabilistic locations are derived from the Harvard-Oxford Cortical Structural Atlas. Abbreviations: LH/RH=left/right hemisphere, a=anterior, p=posterior, c=cortex, g=gyrus, lat = lateral, IFG=inferior frontal gyrus, tri=triangularis, op=opercularis, SFG = superior frontal gyrus, MFG=middle frontal gyrus, cing=cingulate, SMG=supramarginal gyrus, STG = superior temporal gyrus, MTG = middle temporal gyrus, ITG, inferior temporal gyrus, occip = occipital.

Table 3

Activation details for sentence comprehension in reading

	Size (k)	Sig. (p)	Peak (x y z)	Z-value	Brain areas covered
Cluster 1	679	.024	-52 -14 40	4.14	LH: postcentral g, precentral g
Cluster 2	728	.016	38 -12 38	5.06	RH: postcentral g, precentral g, central opercular c
Cluster 3	2281	<.001	56 -30 0	4.53	RH: pSTG, pMTG, pITG, aSTG, planum polare, insular c, parahippocampal g, temporal pole, frontal orbital c
Cluster 4	5290	<.001	8 -44 62	4.93	Bilateral: precuneous c, post-central g, superior parietal lobule, precentral g, p cing g
Cluster 5	21381	<.001	-10 -92 0	6.46	Bilateral: occip pole, cuneal c, intracalcarine c, supracalcarine c, lingual g, occip fusisorm g,

					LH: p parahippocampal g, insular c, frontal orbital c, temporal pole, planum polare, aSTG, pSTG, pMTG, planum temporale, pITG, temporal fusiform c, MTG temporooccip, ITG temporooccip, parietal operculum c, SMG, angular g

Peak locations are given in mm in MNI-152 standard space. Probabilistic locations are derived from the Harvard-Oxford Cortical Structural Atlas. Abbreviations: see Table 2.

Table 4

Activation details for phonological processing (repetition)

	Size (k)	Sig. (p)	Peak (x y z)	Z-value	Brain areas covered
Cluster 1	2124	<.001	36 22 -2	4.51	RH: Insular c, frontal orbital c, IFG tri, IFG op, frontal operculum c, frontal pole
Cluster 2	2269	<.001	-4 22 50	4.81	Bilateral: SFG, juxtapositional lobule c, paracing g, cing c
Cluster 3	2995	<.001	-48 12 14	4.95	LH: IFG op, IFG tri, frontal operculum c, temporal pole, precentral g, MFG

Peak locations are given in mm in MNI-152 standard space. Probabilistic locations are derived from the Harvard-Oxford Cortical Structural Atlas. Abbreviations: see Table 2.

3.4.3 Behavioral covariates

Covariate analyses revealed significant relationships between brain activity and the two measures of language ability. For auditory sentence comprehension, activity in the left temporal gyrus varied with the VCI as well as verbal fluency. For the VCI, the covariate effect was located in a cluster covering the left temporal pole [-44 16 -32, z=4.20], anterior and posterior STG [-50 -4 -12, z=4.78], MTG [-56 -4 -14, z=4.28], ITG [-54 -12 -30, z=3.94], reaching into supramarginal gyrus and gyrus angularis [-62 -50 16, z=4.76]. A higher VCI was associated with a more positive BOLD signal in these regions. A similar pattern was found for verbal fluency scores. Positive correlations were located in a cluster covering the left temporal pole [-48 8 -28, z=4.35], anterior and posterior STG [-56 -4 -8, z=4.24], MTG [-58 0 -16, z=4.08], ITG -48 -20 -30, z=3.42], reaching into the temporal fusiform cortex [-42 -16 -30, z=4.52]. There was considerable overlap between areas of correlation for the two language ability measures and they both partly overlapped with the mean group activation for the original sentence comprehension contrast (Figure 2; appendix A1 for a table with all peaks).

Furthermore, a negative correlation was found for verbal fluency in auditory and frontal areas in the right hemisphere. As can be seen in appendix figure B1, these negative correlations arise from a negative BOLD signal change across participants which is larger in subjects with higher ability than in those with lower ability. Thus, auditory and frontal brain areas show a reduction in BOLD signal during sentence procseeing compared to the control condition (listening to reversed pseudo-speech). Since the data were modelled with the resting condition as an implicit baseline, this BOLD reduction can either stem from an increased BOLD signal for the control condition compared to rest, suggesting that right hemisphere auditory and frontal areas are involved in processing reversed pseudo-speech. On the other hand, the BOLD reduction for sentences versus control could reflect a decreased BOLD signal for the sentence condition compared to rest. Such a decrease could be interpreted as a down-regulation of activity in these areas during sentence processing specifically, for example due to an advantage of minimal contribution of the non-dominant right hemisphere to language processing. Alternatively, these areas (particularly the medial frontal pole) could be interpreted as belonging to a set of brain regions known as the default mode network which is more active during rest and unconstrained cognitive processing compared to externally driven processing for a variety of tasks (Raichle, MacLeod, Snyder, Powers, Gusnard, & Shulman, 2001; Raichle, 2015). Investigating baseline activity in the areas of negative correlation described above, revealed that the frontal pole [42 42 2, z=4.09] did indeed show a decrease in activity during sentence processing compared to rest. In contrast, the areas of negative correlation that were located in the right auditory cortex [70 -28 6, z=4.52], showed an increase in activity during the control condition relative to baseline.

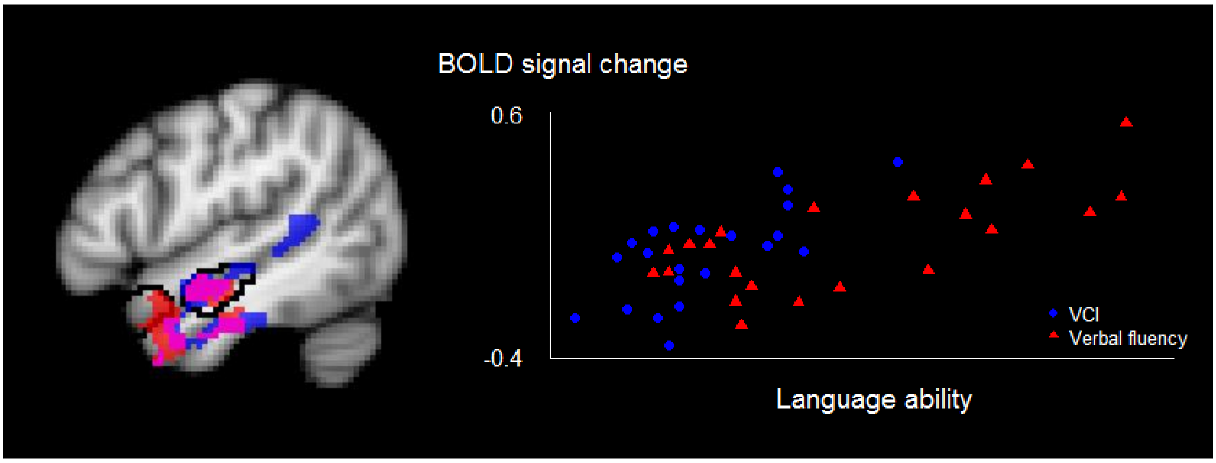

Figure 2. Correlations between language ability and BOLD responses to auditory sentence processing. Left: overlay of correlations between BOLD and the VCI (blue) and between BOLD and verbal fluency (red), areas of correlation between BOLD and both, VCI and verbal fluency, are shown in purple. The group activation for phonological processing is indicated by the black outline. All results are cluster-thresholded with z = 2.3, p < .05, corrected for multiple comparisons. Right: correlations between the VCI (blue) and verbal fluency (red) on the one hand and BOLD responses to sentence processing in the respective areas of correlation on the other hand. For VCI r(20) =.70, p < .001, for verbal fluency r(20) = .71, p < .001.

Relating brain activity for sentence comprehension in reading to the VCI revealed no significant correlations. Activation did, however, vary with participants' verbal fluency. Contrary to our hypothesis, higher performance was not associated with any increases in activity. Instead, it was associated with reduced activity in bilateral middle frontal gyrus [36 16 42, z=5.31] and frontal pole [44 58 -8, z=5.80], and bilateral occipital regions [-54 -74 20, z=4.74] reaching into the angular gyrus [-46 -58 44, z=4.23] (see Appendix table A2).

For phonological processing, activity in the left inferior frontal gyrus, pars opercularis [-54 10 18, z=3.63] and precentral gyrus [-50 2 20, z=4.96] was positively correlated with the VCI as well as verbal fluency, extending into the postcentral gyrus [-60 -18 24, z=4.30] for the latter (Figure 3). Negative correlations were found between the VCI and activity in the left middle frontal gyrus [-42 30 36, z=3.99], bilateral posterior cingulate cortex [-2 -42 30, z=4.10], precuneus and lateral occipital [48 -70 40, z=4.78] reaching into the angular gyrus [48 -56 28, z=3.40]. Verbal fluency showed negative correlations with activity in the left anterior and posterior MTG [-54 -2 -22, z=4.19] (see Appendix table A3).

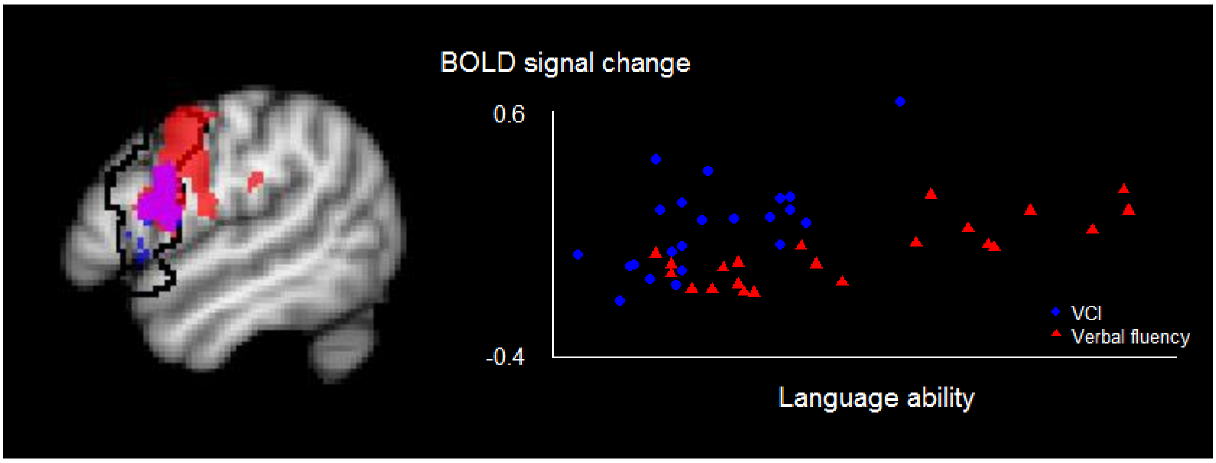

Figure 3. Correlations between language ability and BOLD responses to phonological processing. Left: overlay of correlations between BOLD and the VCI (blue) and between BOLD and verbal fluency (red), areas of correlation between BOLD and both, VCI and verbal fluency, are shown in purple. The group activation for phonological processing is indicated by the black outline All results are cluster-thresholded with z = 2.3, p < .05, corrected for multiple comparisons. Right: correlations between the VCI (blue) and verbal fluency (red) on the one hand and BOLD responses to phonological processing in the respective areas of correlation on the other hand. For VCI r =.64, p = .001, for verbal fluency r = .81, p < .001.

While these correlations reveal information about the scaling of the BOLD signal change with language ability scores, they do not provide any insight into the absolute values of the BOLD signal changes across participants. Critically, a positive correlation could emerge from three different scenarios. First, it could stem from a positive BOLD response to a particular contrast in all subjects which is larger (i.e., more positive) in subjects with higher ability than in those with lower ability. In this case, the brain area displaying the correlation would be involved in the cognitive process in question in all participants but more strongly so in higher-ability participants. Second, a positive correlation could stem from a negative BOLD signal change in all participants which is larger (i.e., more negative) in participants with lower ability than those with higher ability. Finally, a positive correlation could stem from differences in BOLD responses between participants that scale around zero. In this case, participants with lower ability would show a decrease in BOLD signal for a certain contrast while subjects with higher ability would show an increase.

The distinction between these scenarios is important for the interpretation of correlations between ability and activity. The first and second scenario would indicate that all participants activate or “deactivate” the same brain areas during a given cognitive process, only to different degrees. On the other hand, the third scenario would indicate that subjects with higher ability engage brain areas that are not engaged by subjects with lower ability.

To investigate these possible scenarios, the distributions of BOLD responses in the sample were explored in more detail. We were particularly interested in the positive correlations that were found between the VCI and verbal fluency on the one hand and activations during auditory sentence comprehension and phonological processing on the other hand. For these correlations, a partial overlap of cortical areas associated with the main effect of the respective contrast and cortical areas associated with the covariate effect was found. Thus, these areas are significantly activated by the respective contrast on the group level and this activation correlates with the VCI and verbal fluency. We hypothesize that, in these brain areas, a positive BOLD response is present in the whole sample but larger signal changes in subjects with higher VCI and verbal fluency than in subjects with lower VCI and verbal fluency.

On the other hand, for brain areas that show a covariate effect but no main effect, we expect a positive signal change in participants with higher VCI and verbal fluency but not in participants with lower VCI and verbal fluency. We thus investigated BOLD responses separately in these two types of brain areas for all possible combinations of the VCI and verbal fluency on the one hand and auditory sentence comprehension and phonological processing on the other hand. This resulted in eight different ROIs (i.e., areas of correlation between the VCI and auditory sentence comprehension that overlapped with the group activation for auditory sentence comprehension; areas of correlation between the VCI and auditory sentence comprehension that did *not* overlap with the group activation for auditory sentence comprehension; areas of correlation between the VCI and phonological processing that overlapped with the group activation for phonological processing, areas of correlation between the VCI and phonological processing that did *not* overlap with the group activation for phonological processing; areas of correlation between verbal fluency and auditory sentence comprehension that overlapped with the group activation for auditory sentence comprehension; etc.). For each of these ROIs, we extracted each participant's individual percentage of BOLD signal change in response to auditory sentence comprehension and phonological processing, respectively.

In order to compare subjects with relatively higher and lower language ability directly, a median split on the scores of both language ability measures was performed. Thus, we compared a higher VCI group (n = 11, 5 male) with a lower VCI group (n = 11, 3 male) and a higher verbal fluency group (n = 11, 4 male) with a lower verbal fluency group (n = 11, 4 male). For the VCI, three subjects fell exactly onto the median score. Hence, the median split was performed on the raw WASI score (Vocabulary and Similarities subtests combined) instead. The results of the median split group comparisons reflected the positive correlations between the ability measures and neural activity in the ROIs: the higher VCI group had more positive BOLD signal changes than the lower VCI group in each ROI. Likewise, the higher verbal fluency group had more positive BOLD signal changes than the lower verbal fluency group in each ROI.

Subsequently, the two types of ROIs were investigated separately, that is the regions that showed a main effect of the contrast in addition to a covariate effect and the regions that only showed a covariate effect. Analyses revealed the expected pattern. In those brain areas where correlations overlapped with group activations, the mean BOLD signal change for auditory sentence comprehension and phonological processing was positive in the higher as well as the lower ability groups (see Figure 4a and 5a). On the other hand, in those brain areas that showed correlations but no group activation, the higher language ability groups showed a positive signal change for both contrasts whereas the lower ability groups showed a small negative signal change (see Figure 4b and 5b).

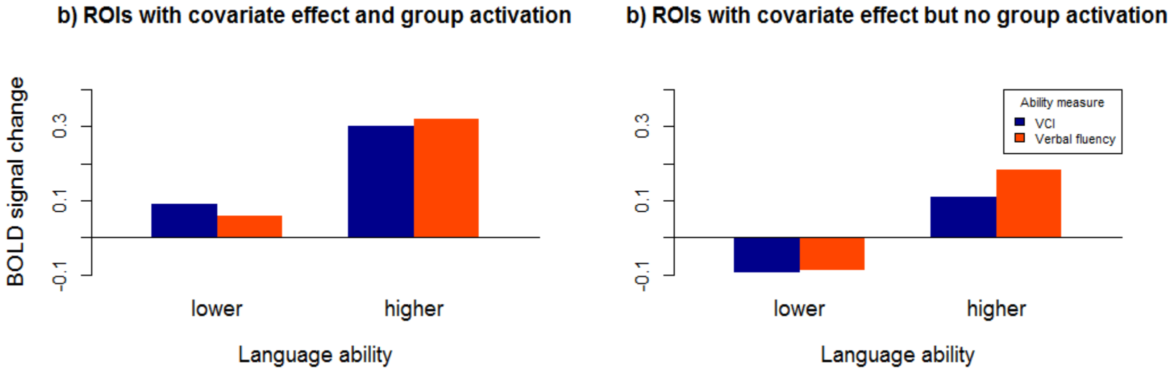

Figure 4. BOLD responses to auditory sentence comprehension, displayed separately for the two median split groups per language ability measure.

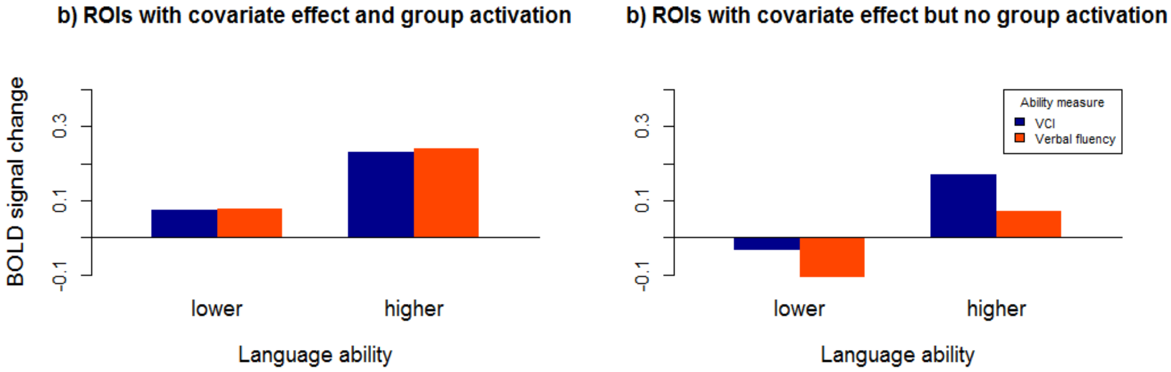

Figure 5. BOLD responses to phonological processing, displayed separately for the two median split groups per language ability measure.

Furthermore, BOLD signal changes across participants were explored in brain areas that showed a negative covariate effect of the VCI or verbal fluency. Since those areas were more distributed across different regions of the brain than the areas of positive covariate effects, we investigated them separately, based on their anatomical location. Thus, every set of negative correlations that was found between the VCI or verbal fluency and BOLD responses to one of our three contrasts, was split into several ROIs.

For the negative correlation between verbal fluency scores and BOLD responses to auditory sentence comprehension, this resulted in the following ROIs: right frontal pole, right IFG, pars opercularis, right central operculum, and right posterior STG. Comparing BOLD responses of the two verbal fluency median split groups showed that both groups had a mean negative BOLD response to auditory sentence comprehension in all of these ROIs. However, reflecting the negative correlation in each of those ROIs, the mean BOLD responses of the higher verbal fluency group were more negative than those of the lower verbal fluency group (Appendix B1).

For sentence comprehension in reading, negative covariate effects of verbal fluency were found in different brain areas that are not typically associated with language processing. The following ROIs were defined: bilateral frontal pole, bilateral MFG, right central operculum, bilateral superior lateral occipital cortex, and bilateral precuneous cortex. In all of these ROIs, the lower verbal fluency group had a small positive BOLD response to reading sentences whereas the higher verbal fluency group had a negative BOLD response (Appendix B2).

BOLD responses to phonological processing showed negative correlations with verbal fluency as well as the VCI. The correlation with verbal fluency was located in the left anterior and posterior MTG. Here, the lower verbal fluency group showed a mean positive BOLD signal change whereas the higher verbal fluency group showed a mean negative BOLD signal change. The negative correlations between BOLD responses to phonological processing and the VCI were located in different brain areas, resulting in the following ROIs: bilateral frontal pole, left MFG, bilateral superior lateral occipital cortex, and bilateral posterior cingulate/precuneous cortex. The higher VCI group showed negative signal change in all of those ROIs. The lower VCI group showed negative signal change in the lateral occipital ROI and the cingulate/precuneus ROI, but positive signal change in the frontal pole and MFG (Appendix B3).

3.5 Discussion

The main aim of this study was to investigate the relationship between language ability and brain activity, using neural responses to sentence processing and phonological processing. As expected, sentence comprehension activated the left anterior temporal lobe in the listening and the reading modality which is in line with previous studies (e.g., Constable et al., 2004; Humphries, Willard, Buchsbaum, & Hickok, 2001; Vandenberghe, Nobre, & Price, 2002). Phonological processing, on the other hand, activated areas including the left inferior frontal gyrus, pars opercularis, and precentral gyrus (e.g., Saur et al., 2008). All of these activations are in accordance with theoretical models as well as results from previous neuroimaging studies (Hickok & Poeppel, 2007; Price, 2012; Vigneau et al., 2006).

Building on these findings, we were interested in how individual differences in language ability are related to the recruitment of brain areas and the intensity of brain activity. Previous research has found such relationships but their direction and their locations remain unclear. Whereas previous studies have mainly measured brain activity during language processing in the context of specific task requirements, we employed an fMRI paradigm that focused on processing language in a stimulus-driven manner, in the absence of any additional cognitive demands. For the resulting activations, we found consistent positive correlations with the Verbal Comprehension Index (VCI as measured by the WASI-II) and verbal fluency. In addition, some brain regions outside the core language network showed negative correlations with the VCI and verbal fluency.

3.5.1 Positive correlations between language ability and brain activity

We observed consistent positive correlations between language ability and brain activity during auditory sentence comprehension and during phonological processing in pseudoword repetition. Since the results were very similar for the VCI and verbal fluency, they will be discussed together under the term language ability. All of the positive correlations that we found between language ability and brain activity, were located in left-hemisphere areas typically associated with language processing. Specifically, higher language ability was associated with increased left anterior temporal lobe activity during auditory sentence comprehension and with increased left frontal lobe activity during phonological processing. Thus, cortical areas that are typically involved in sentence processing and phonological processing, respectively, were recruited for these processes to a greater degree by individuals with relatively higher language ability than by individuals with lower language ability. This greater involvement of brain areas by higher-ability subjects was reflected in both, the intensity as well as the extent of neural activations.

Regarding higher intensity of neural activations in higher-ability subjects, evidence was found in brain areas where group activation overlapped with the correlation of activity with language ability. In these brain areas, both, higher- and lower-ability subjects showed positive BOLD responses to sentence processing or phonological processing, respectively. However, this signal change was greater in subjects with higher language ability. Thus, these brain areas are activated during the respective language process by the whole sample but more strongly so by individuals with higher language ability. This pattern can be interpreted as a deeper form of processing of language material in individuals with higher language ability (Van Ettinger-Veenstra et al., 2012).

Regarding greater extent of neural activations in higher-ability subjects, evidence was found in brain areas where we observed a correlation between neural activity and language ability but no group activation. In these areas, higher-ability subjects showed a positive BOLD response to sentence processing or phonological processing, respectively, whereas lower-ability subjects did not. Thus, these brain areas were recruited exclusively by individuals with higher language ability. During sentence processing, the areas recruited by higher-ability individuals only, were located in the left inferior temporal gyrus (ITG). This region has repeatedly been shown to be involved in semantic processing (e.g., Whitney, Jefferies, & Kirchner, 2010) and sentence processing (e.g., Ikuta et al., 2006; Halai, Parkes, & Welcourne, 2015). During phonological processing, the areas recruited by higher-ability individuals only, were located in the left precentral gyrus. This area is known to support phonological processing (Szenkovits, Peelle, Norris, & Davis, 2012), for example during pseudoword repetition (Saur et al., 2008). The lack of a group activation in these brain areas suggests that their involvement is not crucial for sentence processing or phonological processing, respectively. However, the recruitment of these process-specific cortical areas in addition to the areas of group activation might allow individuals with higher language ability an enhanced processing of language stimuli.

Contrary to our prediction, we did not find any positive correlations between language ability and brain activity for sentence comprehension in the reading modality. This is in contrast to the consistent positive correlations of both language ability measures with brain activity in the listening and repetition conditions. In the current study, the VCI and the verbal fluency task were used as measures of language ability. Both of these verbal tasks rely on receiving auditory input and generating spoken output. In that respect, they are similar to the listening and repetition part of the fMRI paradigm of the current study. In contrast, they are dissimilar to the reading part of the fMRI paradigm, which was entirely reliant on visual input and visual stimulus processing. This lack of similarity with regards to cognitive demands could explain the lack of a significant positive correlation in this study. Although this explanation remains speculative, it has previously been argued that a close proximity in cognitive demands posed by an ability measure and by an fMRI task increases the likelihood of correlations with activity (Neubauer & Fink, 2009). Indeed, previous studies that have found correlations between language ability and neural activity, often used ability measures and fMRI paradigms that shared task demands. For example, reading span, a frequently used measure of language ability, shares the input modality with fMRI reading paradigms (e.g., Buchweitz et al., 2009). As another example, a measure of high-level language ability, such as the BeSS, might share high-level cognitive demands with semantic decisions required in some fMRI reading paradigms (e.g., Van Ettinger-Veenstra, 2016). Further studies could clarify the role that task similarity, e.g. with regard to modality, plays for correlations between ability and brain activity.

3.5.2 Negative correlations between language ability and brain activity

While the current study found some brain areas with decreased activity in high-ability subjects as compared to lower-ability subjects, the pattern of negative correlations was less clear across ability measures and across language processes than it was for positive correlations. None of the negative correlations were located in brain areas that were overlapping with group activations for the respective contrast. In fact, the majority of correlations were located in areas that are not typically thought to be part of the core language network. One exception was a negative correlation in the left MTG between verbal fluency and BOLD responses to phonological processing. Here, subjects with comparably higher verbal fluency showed negative BOLD signal change whereas subjects with lower verbal fluency did not. While this could be interpreted as a deactivation or suppression of the left MTG in higher-ability subjects, an alternative explanation is at least equally likely. A negative correlation of verbal fluency with BOLD responses to pseudoword repetition versus word repetition is mathematically equivalent to a positive correlation with word repetition versus pseudoword repetition. Thus, the result can also be interpreted as increased activation of the left MTG during word repetition in higher-ability subjects compared to lower-ability subjects. In the present study, word repetition was chosen as a control for pseudoword repetition because, in contrast to pseudowords, words have a stored sensory and motor representation, based on regular usage of the words (Hickok, 2009; Hickok & Poeppel, 2007). This makes pseudowords phonologically more demanding than words and contrasting the two has frequently been used as a means to assess phonological processing (e.g., Hartwigsen, Saur, Price, Baumgaertner, Ulmer, & Siebner, 2013; Hagoort, Indefrey, Brown, Herzog, Steinmetz, & Seitz, 1999; Saur et al., 2008). However, words and pseudowords do not only differ in terms of their phonological demand. They also differ in terms of their semantics. Words elicit semantic processing whereas pseudowords generally do not. During word repetition, we would therefore expect activation in the left MTG, an area strongly associated with semantic processing (e.g., Giesbrecht, Camblin, & Swaab, 2004). Indeed, we did find left MTG activation when contrasting words with pseudowords. This activation partly overlapped with the area in which activity correlated with verbal fluency. A positive correlation between verbal fluency and activation in this region during word processing could then be interpreted as higher-ability subjects engaging semantic areas more strongly than lower-ability subjects during semantic processing. This would be in line with the findings described above, that auditory sentence processing and phonological processing elicit stronger responses in process-specific cortical areas in individuals with higher language ability.

Other negative correlations between the VCI or verbal fluency and neural activation observed in the current study were mainly located in the right hemisphere and in bilateral cognitive control areas. Some of these correlations resulted from negative BOLD signal changes in higher-ability as well as lower-ability participants which were more negative in participants with higher language ability. This was, for example, the case in the right IFG, pars opercularis and the right posterior STG during auditory sentence processing. Negative BOLD responses in these areas could be interpreted as a suppression effect. If a dominance of the left hemisphere in language processing is assumed to be beneficial (e.g., Gutierrez-Sigut, Payne, & MacSweeney, 2015), a reduced involvement, or “deactivation”, of right-hemispheric homologues could be necessary or helpful for language processing. Individuals with higher language ability might be better at suppressing right-hemispheric areas such as the right IFG or right STG, explaining the stronger negative BOLD response that we found. Alternatively, the result could be explained by a positive correlation for the reversed contrast, in the same way as was described above for the left MTG involvement in word repetition. Thus, the negative correlation for sentence processing versus processing of reversed pseudospeech could, in fact, reflect a positive correlation between verbal fluency and processing of reversed pseudospeech. Processing unusual language stimuli, such as pseudospeech or artificially manipulated speech sounds, has previously been associated with right-hemispheric activation (Binder et al., 2000; Meyer, Alter, Friederici, Lohmann, & von Cramon, 2002; Meyer, Steinhauer, Alter, Friederici, & von Cramon, 2004). Similarly, processing of reversed pseudospeech might elicit an engagement of the right hemisphere. All of the correlations that were found between verbal fluency and activity for sentence processing versus processing of reversed speech are located in brain areas associated with auditory or phonological processing (e.g., Heschl's gyrus, IFG opercularis, posterior STG). It is conceivable that higher-ability subjects engaged those areas to a greater degree during processing of reversed pseudospeech than did lower-ability subjects.

The results also revealed negative correlations originating from negative BOLD responses in subjects with higher language ability and positive BOLD responses in subjects with lower language ability. Thus, subjects with lower language ability engaged brain areas in addition to the ones that are being engaged by the whole sample for a particular language process. This finding could be interpreted as a failure to suppress them when they should not be involved or as a mechanism to cope with increased demands by recruiting more resources. This pattern was found, for example, for frontal areas (e.g., frontal pole and MFG) that are known to be involved in cognitive control and executive functions (Breukelaar et al., 2016; Cole & Schneider, 2007; Niendam et al., 2012). It is possible that individuals with comparably lower language ability need to recruit these areas during sentence reading and phonological processing whereas individuals with higher language ability can rely on primary language areas only, without requiring additional support from the cognitive control network. Activity in the MFG during language processing has been found to be negatively correlated with language ability in previous studies (e.g., Buchweitz et al., 2009, Prat et al., 2007, 2012). This has typically been interpreted in the light of the MFG's involvement in cognitive control, strategic processes and working memory. Due to increased effort in language processing, individuals with lower language ability are thought to rely on these functions to a greater degree than individuals with higher ability.

Since none of these negative correlations were consistent across the two language ability measures or across the different language processes, these results and their interpretations should be seen as tentative.

Negative correlations between the VCI and verbal fluency on the one hand and BOLD responses on the other hand support the concept of neural efficiency. Neural efficiency has previously been proposed as an explanation for decreased activity in individuals with lower language ability (Prat et al., 2011; 2012). However, our finding of consistent positive correlations in the left temporal lobe and the left frontal lobe for both measures of language ability, contradict the neural efficiency hypothesis. In these two brain regions, higher-ability subjects showed more intense and more widespread activations during sentence processing and phonological processing, respectively, as compared to lower-ability subjects. The robustness of this finding across two different language processes, two different cortical regions, and two different measures of language ability is noteworthy.

The clear pattern in our results also diverges from the large variation of results in other studies on the relationship between language ability and brain activity. One explanation for this divergence might result from the differences between the fMRI paradigms that were used in this and other studies. The current study measured neural responses to different language processes in a stimulus-driven manner that was very low in non-linguistic cognitive demands. Other studies have usually used language tasks that additionally involved non-linguistic cognitive processes, such as working memory processes (e.g., Prat & Just, 2010; Prat et al., 2012), or decision making (e.g., Buchweitz et al., 2009; Van Ettinger-Veenstra et al., 2016). It is difficult to determine the extent to which these non-linguistic task components contributed to the correlations. Thus, differences in brain activity between higher-ability individuals and lower-ability individuals might not solely reflect differences in activity associated with language processing but rather differences in activity associated with dealing with cognitive demand in general. This is especially true if brain activity for those tasks was correlated with language ability measures that tap into skills that are not predominantly linguistic in nature but rather related to more fluid aspects of language ability (e.g., verbal working memory).

A review on the relationship between brain activity and intelligence has suggested a differentiation between cognitive processes and brain regions associated with fluid intelligence, such as executive control in frontal areas, and processes and regions that are more domain-specific, such as memory in parietal areas (Neubauer & Fink, 2009). The authors even concluded that neural efficiency might be a concept that primarily applies to frontal brain areas. These areas are often found to show decreases in activity with increasing cognitive ability, whereas process-specific areas have been found to show increases. This pattern was proposed to be particularly true for tasks or cognitive processes that have been automated due to extensive practice. For such processes, subjects increasingly rely on specialized brain regions rather than frontal executive areas and might then show increased activations in these specialized brain regions with increasing ability. While the review discusses memory processes in the parietal lobe as an example, it is conceivable that the same mechanisms apply to other cognitive functions, indicating a general principle of how cognitive ability is reflected in brain activity.

If applied to language processes, the proposition of increased activity in specialized brain areas is fully in line with the results of the present study. In process-specific cortical areas (i.e., temporal gyrus for sentence processing and IFG opercularis/precentral gyrus for phonological processing), positive relationships between language ability and activity were found. On the other hand, in brain areas associated with cognitive demand and executive control (e.g., MFG), negative relationships between language ability and activity were found, supporting the neural efficiency hypothesis.

A recent meta-analysis provided further evidence for increased activity in process-specific brain areas with increased cognitive ability (Neumann, Lotze, & Eickhoff, 2015). Across various areas of expertise (e.g., musical, arithmetic, or chess expertise), individuals with higher levels of ability showed increased activity in brain areas that were associated with their area of expertise (e.g., auditory cortex for auditory stimulation). While all of the twenty-six studies included in the meta-analysis showed positive relationships, only two of these twenty-six studies additionally reported brain areas of decreased activation in higher-ability individuals, supporting the neural efficiency hypothesis.

The use of neural efficiency as an explanation for decreased activations associated with higher ability has previously been criticized. According to Poldrack (2015), true neural efficiency means that "the same neural computation is performed with identical time and intensity, but the metabolic expenditure differs between groups" (p.14). However, this is impossible to investigate based on studies like the one reported here or similar studies discussed in this paper. First, fMRI data do not lend themselves to conclusions about underlying patterns of neuronal firing so that the exact duration and intensity of neural processes remains unclear. Second, paradigms that are typically used to assess, for example, language processing, do not allow full insight into the exact cognitive processes that are performed by participants. Even if the task can be assumed to be equally difficult for all participants, as was the case in our paradigm, there is no guarantee that the exact same processes were carried out by all participants. This is not only true for the interpretation of negative correlations as neural efficiency, but for the interpretation of positive correlations as well.

For example, explaining increased activations in higher-ability subjects as deeper processing (e.g., Van Ettinger-Veenstra, 2016) may indicate additional cognitive processes taking place in those subjects. Processing sentences might trigger stronger semantic associations in individuals with higher language ability than in individuals with lower language ability, contributing to increased activation in higher-ability subjects. However, it is still noteworthy that, under identical experimental conditions, the same language stimuli trigger different neural responses and potentially different cognitive processes in individuals with higher language ability than in individuals with lower ability. One reason for these differences in responses to language on a functional level could be linked to structural differences between individuals with higher versus lower language ability, for example with regard to grey matter density (Lee et al., 2007; Mechelli et al., 2004;) or structural connectivity (Klingberg et al., 2000; Niogi & McCandliss, 2006).

3.5.3 Limitations of the study

When interpreting the present results, the sample composition should be borne in mind. First, all participants were highly educated university students and their VCI was considerably higher than the population average. It is plausible that the mechanisms that underlie the relationship between language ability and neural activity, are the same across the entire range of language ability. Still, the generalizability of the findings to a sample that is more representative of the population should be subjected to further investigation. Second, the variability of language ability in our sample was smaller than it is in the general population. Performing median splits on the VCI and verbal fluency scores allowed us to directly compare those individuals in our sample who had comparably higher ability to those with comparably lower ability. However, for the VCI as well as verbal fluency, the means of the higher and the lower groups did not differ as much as you would expect when performing a median split on a more representative sample. The fact that we still found consistent differences in neural activations in these comparisons suggests that the relationship between language ability and neural activity is robust even when investigating only a reduced range of the ability spectrum.

In conclusion, we found strong evidence for a relationship between language ability and neural activity across different language processes, modalities, and brain regions. Specifically, the VCI as well as verbal fluency was positively related to activations in typical cortical language areas. Individuals with relatively higher language ability showed more intense and more extensive activations in left temporal areas during auditory sentence comprehension and in left frontal areas during phonological processing. This increased involvement of process-specific cortical areas suggests deeper processing in individuals with higher language ability compared to individuals with lower language ability. Evidence for decreased activations in higher-ability individuals, previously interpreted as neural efficiency, was less consistent and restricted to brain areas that are not typically associated with language processing, such as areas of the cognitive control network. The results of the current study suggest that previous findings supporting the concept of neural efficiency, may have partially been driven by general cognitive demand rather than language processing per se. The stimulus-driven paradigm used in the current study allowed us to investigate the relationship between language ability and brain activity during language processing in the absence of additional task demands. Under these circumstances, higher ability seems to be linked to increased rather than decreased neural activity. Combined with similar findings in a variety of other cognitive domains, the current results suggest that the increased engagement of process-specific brain regions in subjects with higher ability might be a general mechanism of brain functioning.

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3.7 Appendix

Table A1

Details for correlations between brain activity for auditory sentence processing and language ability measures

	Size (k)	Sig. (p)	Peak (x y z)	Z-value	Brain areas covered
VCI (WASI-II)					
Positive	1624	<.001	-50 -4 -12	4.78	temporal pole, aSTG, aMTG, aITG, pSTG, pMTG, pITG, SMG
Negative	-	-	-	-	-
Verbal Fluency					
Positive	1279	<.001	-42 -16 -30	4.52	temporal pole, aSTG, aMTG, aITG, pSTG, pMTG, pITG, SMG
Negative	1001	<.001	70 -28 6	4.52	SMG, pSTG, planum temporale, Heschl’s g, central opercular c, precentral g, IFGop
	638	.015	42 42 2	4.09	frontal pole, MFG, IFGtri

Peak locations are given in mm in MNI-152 standard space. Probabilistic locations are derived from the Harvard-Oxford Cortical Structural Atlas. Abbreviations: see Table 2.

Table A2

Details for correlations between brain activity for visual sentence processing and language ability measures

	Size (k)	Sig. (p)	Peak (x y z)	Z-value	Brain areas covered
VCI (WASI-II)					
Positive	-	-	-	-	-
Negative	-	-	-	-	-
Verbal Fluency					
Positive	-	-	-	-	-
Negative	5516	<.001	20 -50 6	5.69	precuneous c, lingual g, angular g, SMG, intracalcarine c, p cing g
	4864	<.001	44 58 -8	5.80	frontal pole
	2159	<.001	-54 -74 28	4.74	lat occip c
	1311	<.001	36 16 42	5.31	MFG, SFG, precentral g
	692	.014	44 2 10	4.02	central opercular c, Heschl’s g, insular c

Peak locations are given in mm in MNI-152 standard space. Probabilistic locations are derived from the Harvard-Oxford Cortical Structural Atlas. Abbreviations: see Table 2.

Table A3

Details for correlations between brain activity for phonological processing (repetition) and language ability measures

	Size (k)	Sig. (p)	Peak (x y z)	Z-value	Brain areas covered
<u>VCI (WASI-II)</u>					
Positive	652	.013	-50 4 28	4.95	IFGop, precentral g, insular c
Negative	4386	<.001	48 -70 40	4.78	bilateral: precuneous c, post cing c, lat occip c RH: angular g, supracalcarine c
	2113	<.001	6 34 -22	4.19	bilateral: ant cing c, subcollosal c, frontal medial c LH: paracing c, frontal pole, SFG, MFG
<u>Verbal Fluency</u>					
Positive	1608	<.001	-50 2 20	4.96	IFGoper, precentral g, postcentral g, central opercular c, SMG
	1509	<.001	4 -90 -4	3.48	lingual g, intracalcarine c, occip pole
Negative	633	.016	-54 -2 -22	4.19	aMTG, pMTG, pITG

Peak locations are given in mm in MNI-152 standard space. Probabilistic locations are derived from the Harvard-Oxford Cortical Structural Atlas. Abbreviations: see Table 2.

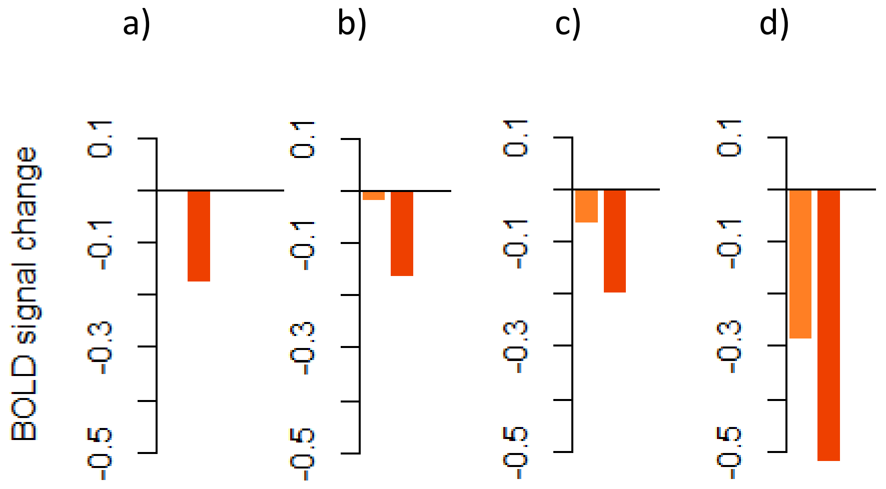

Figure B1. BOLD signal changes for auditory sentence processing in different ROIs averaged across participants of the lower verbal fluency group (light red) and the higher verbal fluency group (dark red). All ROIs are brain areas where activity for auditory sentence processing correlated negatively with VCI scores. a) right hemisphere (RH) frontal pole, b) RH IFG, pars opercularis, c) RH central operculum, d) RH posterior STG

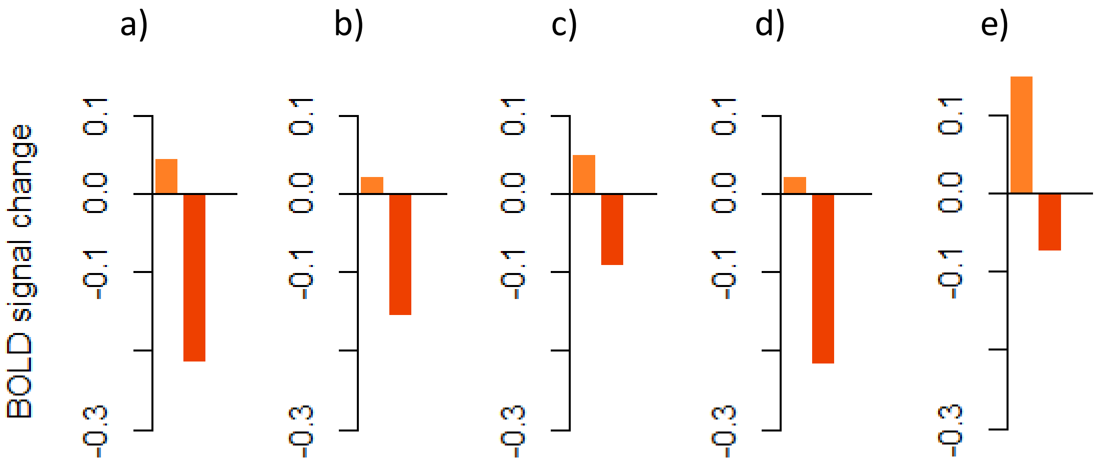

Figure B2. BOLD signal changes for visual sentence processing in different ROIs averaged across participants of the lower verbal fluency group (light red) and the higher verbal fluency group (dark red). All ROIs are brain areas where activity for visual sentence processing correlated negatively with VCI scores. a) frontal pole, b) MFG/SFG, c) RH central operculum, d) lateral occipital cortex, e) precuneus

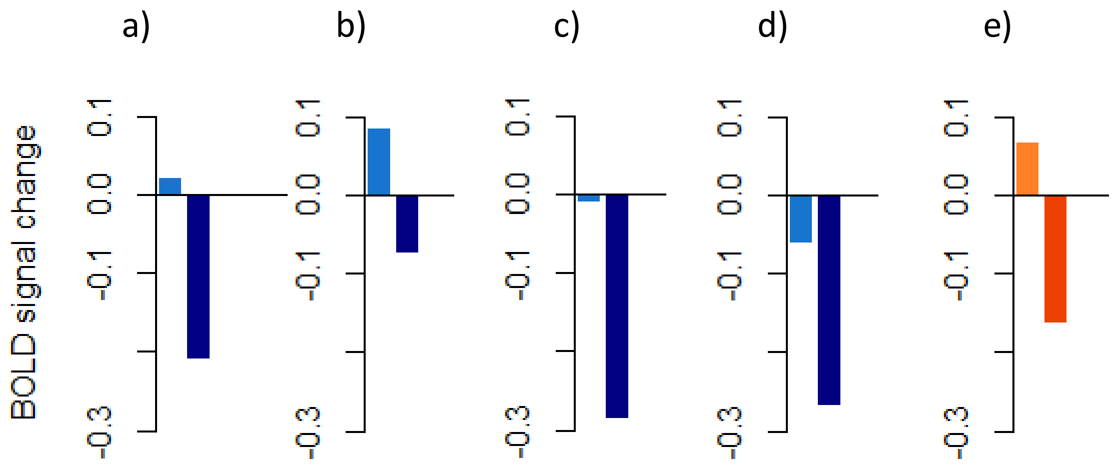

Figure B3. BOLD signal changes for phonological processing in different ROIs averaged across participants of the lower VCI group (light blue) and the higher VCI group (dark blue) for a) to d) and across participants of the lower verbal fluency group (light red) and the higher verbal fluency group (dark red) for e). All ROIs are brain areas where activity for auditory sentence comprehension correlated negatively with verbal fluency scores (red) or VCI scores (blue). a) frontal pole, b) left MFG, c) lateral occipital cortex, d) posterior cingulate cortex

Chapter 4

Degrees of Left-Lateralization Across Different Language Processes and Relationship with Verbal Ability

4.1 Abstract

While there is existing evidence for a relationship between language lateralization and verbal ability, the direction and the strength of this relationship differ substantially between studies. In particular, the specific tasks employed to assess language lateralization, seem to affect the degree of lateralization and, consequently, the relationship with verbal ability. In the current study, fMRI data were acquired to explore effects of different language processes and modalities on language lateralization. Twenty-two healthy adult participants engaged in phonological, semantic, and sentence processing during passive listening, reading and repetition. Based on the fMRI activity, laterality indices (LIs) were calculated for each language process and modality. Outside the MRI scanner, participants performed two well-established behavioral tests of language lateralization (i.e., dichotic listening and a visual half-field task). Furthermore, verbal ability was assessed with the Verbal Comprehension Index (WASI-II) and verbal fluency. Results showed left-lateralized brain activity for all language processes across all modalities, with phonological processing being most strongly lateralized. The processing modality did not affect language lateralization. LIs calculated from brain activity corresponded with those from behavioral lateralization tasks, with positive correlations between phonological processing and dichotic listening and between reading and the visual half-field task. Furthermore, lateralization of brain activity showed positive relationships with verbal ability, although some correlations failed to reach significance. The results demonstrate the importance of considering the multidimensionality of language when investigating degrees of language lateralization and its relationship with behavioral measurements of lateralization and verbal ability.

4.2 Introduction

Language is one of the most reliably lateralized cognitive functions in the human brain. The left cerebral hemisphere is dominant for language processing in over 90% of right-handers and at least 70% of left-handers (Rasmussen & Milner, 1977; Knecht et al., 2000). This strikingly pervasive bias has led many researchers to suggest that a left-lateralized representation of language functions in the brain might be adaptive, for example by allowing parallel processing in the two hemispheres (e.g., Hirnstein, Hausmann, Güntürkün, 2008).

Historically, the degree of language lateralization has been assessed by measuring relative differences in task performance for each cerebral hemisphere. In behavioral lateralization tasks, stimuli are presented only to one side of the auditory or the visual system (i.e., one ear or one visual half-field) (Westerhausen & Hugdahl, 2008; Bourne, 2006). Due to the organization of the auditory and the visual system, lateralized stimulus presentation results in the stimuli being initially processed by the cerebral hemisphere that is contralateral to the side of presentation. This allows for a comparison of responses to stimuli when they are initially processed by the left hemisphere (LH) versus when they are initially processed by the right hemisphere (RH). For language tasks, participants typically show superior performance for stimuli presented to the right side of the auditory or visual system, reflecting the superiority of the left hemisphere for processing language (Kimura, 1967; Hunter & Brysbaert, 2008). The strength of this bias for a given individual for a particular task is typically expressed with a laterality index (LI), indicating the degree of lateralization.

A well-established behavioral paradigm of language lateralization is the dichotic listening (DL) task (Kimura, 1961; Bryden, 1988; Hugdahl, 1995). In DL tasks, participants are presented with two different auditory stimuli played simultaneously, one to each ear, via headphones. When participants are asked to report what they heard, they typically show a preference to report the stimulus presented to the right ear rather than the stimulus presented to the left ear. This is thought to reflect the advantage of the left cerebral hemisphere over the right hemisphere in processing language stimuli. Another well-established paradigm to assess language lateralization is the visual half-field (VHF) paradigm (Bourne, 2006; Hunter & Brysbaert, 2008). In VHF tasks, language stimuli are presented either to the left or to the right visual field while preventing saccades to the stimulus that would allow bilateral processing. Participants typically show better performance for language stimuli presented in the right visual field, reflecting the advantage of the left cerebral hemisphere for processing language.

Investigating potential benefits of lateralization, some studies have correlated the degree of language lateralization as assessed with DL or VHF tasks with the overall performance on these tasks (i.e. averaged across ears or visual half-fields). Results have revealed significant relationships between language lateralization and performance, although the direction of these relationships is less clear. Specifically, mostly positive correlations between lateralization and performance have been reported for DL (Boles, Barth, & Merrill, 2008; Hellige, Zatkin, & Wong, 1981) whereas mostly negative correlations have been reported for VHF tasks (Boles et al., 2008; Hirnstein, Leask, Rose, & Hausmann, 2010). A general issue in studies that investigate the relationship between DL or VHF lateralization and performance, is that LIs and performance scores are usually calculated from the same data, resulting in statistical interdependence of the two measures (Hirnstein, Hugdahl, & Hausmann, 2014). Furthermore, although accuracy and response times in DL and VHF tasks might be an indicator of verbal ability, they only assess one very specific aspect of language processing and do not necessarily allow conclusions about the general relationship between language lateralization and verbal ability. In contrast, Chiarello, Welcome, Halderman, and Leonard (2009) assessed verbal ability separately from language lateralization in a VHF task, measuring more general verbal abilities (i.e., verbal IQ and reading skills). The authors found small but consistently positive correlations between language lateralization and verbal ability.

Other studies have assessed language lateralization by comparing brain activity in the left versus the right cerebral hemisphere during language processing. For example, functional Transcranial Doppler sonography (fTCD) offers an indirect measure of brain activity in the two hemispheres by estimating blood flow in the arteries that supply the LH and the RH during a given cognitive task. In children, language lateralization as assessed with fTCD during a cartoon description task has been shown to be positively related to vocabulary knowledge and reading skill (Groen, Whitehouse, Badcock, & Bishop, 2012). However, fTCD lateralization during a word generation task did not show any significant relationships with a number of language ability measures in adults (Knecht et al., 2001).

In comparison to fTCD, functional Magnetic Resonance Imaging (fMRI) offers a more direct measurement of brain activity and allows for the localization of activity and, hence, investigation of functional lateralization in specific brain areas. In children, language lateralization as assessed with fMRI has repeatedly been shown to increase with age (Everts et al., 2009; Holland, Plante, Weber, Byars, Strawsburg, Schmithorst, & Ball, 2001; Lidzba, Schwilling, Grodd, Krägeloh-Mann, & Wilke, 2011), suggesting stronger left-lateralization as children develop their verbal abilities. Furthermore, lateralization in fMRI activity during a vowel detection task and during a synonym detection task showed positive correlations with verbal IQ in children (Everts et al., 2009). In contrast, in an adult sample, fMRI lateralization during a word generation task was not significantly correlated with verbal ability (Powell, Kemp, & García-Finaña, 2012). However, a recent large-scale fMRI study (N=297) did find a link between verbal ability and language lateralization (Mellet et al., 2014). Subjects with weakly lateralized brain activity during a sentence generation task performed significantly worse on a number of language tasks performed outside the MRI scanner (e.g., verb generation, synonym generation, rhyming, listening and reading span) than subjects with strongly lateralized brain activity. But the effect size was very small, accounting for only 3% of the variance in the sample, suggesting only subtle differences in language ability between the lateralization groups. Further evidence for a positive relationship between language lateralization and verbal ability comes from lateralization in fMRI resting state activity in the cortical language network. The degree of left-lateralization in cortical interactions of the temporal lobe has been found to show moderate positive correlations with vocabulary knowledge (Gotts, Jo, Wallace, Saad, Cox & Martin, 2013).

In summary, the majority of studies suggest a relationship between language lateralization and verbal ability. However, the exact nature of the relationship is unclear. Behavioral measures of language lateralization have shown positive relationships between lateralization and task performance in some studies but negative relationships in others. Assessing language lateralization and verbal ability separately from each other, some fTCD and fMRI studies have confirmed a link between the two, with increasing evidence for positive associations between LIs and verbal ability. Inconsistencies in results could stem from differences in the tasks that were used, and hence the language processes that were studied, or differences in the way that LIs were generated.

4.2.1 Factors affecting brain lateralization during language processing

When investigating language lateralization, both, the way that language processing is operationalized, and the way that lateralization is assessed, can affect the resulting degree of language lateralization. When using fMRI or fTCD, LIs are oftentimes generated based on brain activation data from one specific task, such as word generation, despite concerns that language lateralization might not be a unitary concept (Bishop, 2013). Indeed, it has been shown that degrees of brain lateralization can differ significantly for different language tasks (Hund-Georgiandis, Lex, & Von Cramon, 2001; Stroobant, Buijs, & Vingerhoets, 2009). Furthermore, correlations between LIs for different tasks vary considerably, ranging from non-significant to large (Hund-Georgiandis et al., 2001; Badcock, Nye, & Bishop, 2012; Häberling, Steinemann, & Corballis, 2016). In an attempt to understand these findings, it has been proposed that productive language tasks lateralize more strongly than receptive language tasks (Badcock et al., 2012; Gutierrez-Sigut, Payne, & MacSweeney, 2015), suggesting an effect of the processing modality on the degree of lateralization. Furthermore, it has been argued that left-lateralization of brain activity is more pronounced for phonological tasks than for semantic tasks (Gutierrez-Sigut et al., 2015), suggesting an effect of the language process on the degree of lateralization. However, the majority of studies that compare LIs for different language tasks, employ tasks that comprise a range of linguistic and other cognitive functions. Thus, the tasks under comparison differ on several dimensions which could have confounding effects (Gutierrez-Sigut et al., 2015). For example, comparing fTCD LIs for letter-cued word generation with fTCD LIs for auditory sentence comprehension with an accuracy judgement task resulted in stronger lateralization for the word generation task (Buchinger, Flöel, Lohmann, Deppe, Henningsen, & Knecht, 2000). This was interpreted as expressive language tasks being more strongly lateralized than receptive language tasks. However, it is possible that it was not the difference in modality that drove the effect but instead differences in the language processes required, i.e. predominantly phonological processes in the letter-cued word generation and predominantly semantic and syntactic processes in the sentence comprehension task. Furthermore, the role of additional, non-linguistic task demands, such as inhibition of non-target words during word generation or decision making during sentence judgement, is unknown.

In an fMRI study, the lack of a significant difference in LIs for a letter-cued word generation task and a synonym judgement task was interpreted as equal degrees of lateralization for language production and comprehension (Häberling et al., 2016). However, the two tasks confounded the factors modality (production versus comprehension) and language process (phonological versus semantic processing) as well as non-linguistic, task-specific cognitive demands. It is possible that these factors each had opposite effects on lateralization which cancelled each other out, leading to a null-result in the task comparison.

There are few studies that have compared either processing modalities or language processes directly while holding other elements of the tasks constant. Hund-Georgiadis et al. (2001) investigated the effect of modality on brain lateralization by comparing fTCD LIs for two language tasks performed in the listening and in the reading modality. Participants engaged in a semantic task (concrete-abstract judgement of words) and a lexical task (noun-verb discrimination of words), with auditorily presented stimuli as well as with visually presented stimuli. The authors did not find a significant effect of modality and LIs for the listening and the reading version of the tasks were strongly correlated.

The effect of language process on lateralization was investigated in an fTCD study using a word generation task with two conditions (Gutierrez-Sigut et al., 2015). In a phonological condition, participants generated words starting with certain cue letters. In a semantic condition, participants generated words belonging to certain categories. While LIs were numerically larger for phonological processing than for semantic processing, this difference was not statistically significant.

Apart from the question of how language is operationalized, the way that lateralization is assessed (i.e. how LIs are generated from brain activity data), can be another source of variation in LIs. In behavioral studies, LIs are typically calculated by subtracting performance for stimuli presented to the left ear/VHF (i.e., processed by the RH) from stimuli presented to the right ear/VHF, and dividing it by the overall performance (e.g., Hirnstein et al., 2008; Hugdahl, Westerhausen, Alho, Medvedev, & Hämäläinen, 2008). Similarly, in fMRI studies, an LI for a single participant in a given task is typically calculated by subtracting the degree of RH activity from the degree of LH activity, and dividing the result by the total amount of activity. However, there are several ways to define the degree of RH and LH activity. One approach is to compare the extent of activity in the two hemispheres, that is, the number of active voxels. This approach requires a decision on an intensity threshold above which a voxel is counted as “active”. Previous studies have used a variety of different fixed thresholds (e.g., Hund-Georgiadis et al., 2001; Ramsey, Sommer, Rutten, & Kahn, 2001; Lopes, Yasuda, de Campos, Balthazar, Binder, & Cendes, 2016) or used an individual threshold for each participant (e.g., Fernández et al., 2003; Niskanen et al., 2012). However, this method does not take into account the intensities of above-threshold voxels. Thus, the calculation would always result in an LI of zero if an equal number of voxels was activated above threshold in both hemispheres, regardless of their intensities. However, stronger intensity of voxels in one hemisphere than in the other would indicate a stronger involvement of that hemisphere in the cognitive process under study, which would not be reflected in the resulting LI of zero (Seghier, 2008). An alternative approach to counting the number of active voxels is comparing the magnitude of activity in the two hemispheres, i.e. voxel intensities (usually in the form of t-values). However, this method is very sensitive to the effect of outliers (Wilke & Lidzba, 2007).

Addressing these issues, Wilke and Schmithorst (2006) developed an approach that offers more robust and reliable LIs. The authors first use a bootstrapping technique to generate multiple LIs at different thresholds. In order to minimize the effect of outliers, the range of LIs is then trimmed to only use the central 50% for further calculation. Subsequently, a mean of these LIs is calculated, using a weighting factor that favors LIs generated at higher thresholds, since voxels surviving higher thresholds are thought to have stronger correlations with the task. This method has been made available in an SPM toolbox (Wilke & Lidzba, 2007) and has since been increasingly used by other authors investigating lateralization in fMRI data (e.g., Powell et al., 2012; Häberling et al., 2016). Concordance between studies with regard to the methods used to calculate LIs should reduce some of the variance in results and facilitate comparisons between different studies in the future (Wilke & Lidzba, 2007).

Another factor to consider when calculating LIs based on fMRI data, is the choice of brain areas that are included. Research has shown that not all regions of the brain are equally strongly lateralized, even within a single task (Lopes et al., 2016). In addition, previous studies have found conflicting evidence regarding correlations between lateralization in different regions of interest (ROIs) for the same task within participants, ranging from negative (Seghier, Kherif, Josse, & Price, 2011) over non-significant or weak (Pinel & Dehaene, 2010) to strong positive correlations (Häberling et al., 2016).

An alternative approach to restricting analyses to specific ROIs, is to base LI calculations on activity in the entire grey matter of the LH versus the RH, generating a whole-brain LI. This can increase the size of LIs compared to ROI-specific calculations

(Lopes et al., 2016). However, relationships between language LIs and verbal performance measures have been found to be stronger for ROI-specific LIs than for whole-brain LIs, for example when using an ROI in the inferior frontal gyrus for word generation (Powell et al., 2012). A review on methodological issues in fMRI lateralization assessment concluded that both, whole-brain as well as regional LIs are informative and should be studied together in order to obtain a complete picture of lateralization patterns (Seghier, 2008).

In the current study, we addressed these potential sources of variation in LIs in order to systematically investigate language lateralization and its relationship to verbal ability. Language lateralization was assessed based on fMRI activations for different language processes (i.e., phonological processing, semantic processing, sentence processing) in different modalities (i.e., listening, reading, speaking). The fMRI paradigm was designed in such a way that non-linguistic task demands (e.g., decision making, working memory) were kept to a minimum and held constant across language processes and modalities. LIs for the different language processes were calculated based on activity in the two hemispheres as a whole, using a grey matter mask, and based on activity in specific ROIs only. While we expected similar patterns for whole-brain LIs and ROI-specific LIs overall, ROI-specific LIs were hypothesized to be more reflective of lateralization in language-specific brain areas (Wilke & Lidzba, 2007) and to show stronger correlations with verbal ability (Powell et al., 2012).

For each language process, a separate anatomical ROI was chosen to reflect brain areas that are known to be involved in phonological, semantic, and sentence processing, respectively. This was done in line with results from previous research localizing different language functions in the brain and in accordance with the dual stream model of language processing (Hickok & Poeppel, 2007), as a widely-accepted model of speech processing and production. The dual stream model proposes that speech is analyzed to extract meaning within a ventral processing stream along the temporal lobe. The ventral stream departs from the posterior superior temporal gyrus (STG) and sulcus (STS), where speech is analyzed with regard to phonological properties. Phonological processing is hypothesized to be asymmetrical, with the left and the right hemisphere showing preferences for processing different elements of the speech signal. While the LH integrates information in speech signals over short as well as long time periods, the RH specializes in integration of information over longer time periods (Hickok & Poeppel, 2007). These speech elements are then combined to form larger units of speech, such as syllables, which primarily engage the left STG/STS and, to a lesser degree, the right STG/STS (Rimol, Specht, Weis, Savoy, & Hugdahl, 2005; Specht, Osnes, & Hugdahl, 2009). According to the dual stream model, semantic processing of language stimuli takes place in a “lexical interface”, located in the posterior middle temporal gyrus (MTG) and inferior temporal sulcus (ITS). Semantic processing is hypothesized to be bilateral although the LH is thought to be dominant. Sentence processing is thought to take place in a “combinatorial network” in the anterior temporal lobe. Hickok and Poeppel (2007) proposed a strong lateralization to the left hemisphere at this stage of processing. Thus, the dual stream model suggests an overall bilateral organization of the ventral stream, i.e. involvement of the LH and the RH, but varying degrees of LH over RH dominance for the different language processes phonology, semantics, and sentence processing.

These predictions are in line with previous suggestions that the language process can affect the degree of lateralization in brain activity. However, as discussed above, previous studies have usually confounded language process with modality. Therefore, differences between LIs for different language tasks could only be ascribed to an effect of the tasks, without being able to determine if it was differences in language process or modality that drove the effects. In contrast, the fMRI paradigm in the current study allowed to investigate effects of modality and language process independently. Based on the predictions of the dual stream model (Hickok & Poeppel, 2007), it was hypothesized that it is language processes rather than modality that affects language lateralization. Specifically, we expected different degrees of left-lateralized brain activity for phonological, semantic and sentence processing, regardless of the processing modality (listening, reading, speaking), since all three language processes are higher-level cognitions that should be relatively independent from modality-related lower-level perceptual or motor processes.

As a secondary goal, we were interested in how LIs derived from fMRI activation for different language processes and modalities relate to behaviorally assessed language lateralization. Previous fMRI studies have shown left-lateralized brain activity during dichotic listening (DL) (e.g., Hugdahl, Brønnick, Kyllingsbæk, Law, Gade, & Paulson, 1999; Van den Noort, Specht, Rimol, Ersland, & Hugdahl, 2008) and visual half-field (VHF) tasks (e.g., Weis, Hausmann, Stoffer, Vohn, Kellermann, & Sturm, 2008). Nevertheless, relating behavioral LIs from DL or VHF tasks outside the MRI scanner to language lateralization assessed with fMRI or fTCD has led to mixed results. Correlations between behavioral LIs and fMRI or fTCD LIs are typically positive, but range from small to large (Bethmann, Tempelmann, De Bleser, Scheich, & Brechmann, 2007; Hund-Georgiadis, Lex, Friederici, & Von Cramon, 2002; Hunter & Brysbaert, 2008; Krach, Chen, & Hartje, 2006; Van der Haegen, Cai, Seurinck, & Brysbaert, 2011).

The current study also investigated relationships between fMRI-based LIs and LIs derived from a DL and a VHF task. The DL paradigm employed here (Hugdahl, 1995), requires auditory processing of syllables, hence relying on phonological processes. Therefore, we expected a positive correlation between DL LIs and fMRI LIs for phonological processing in the listening modality. The VHF task employed here (Hirnstein et al., 2008), required word-pseudoword decisions, hence relying on phonological as well as semantic processing of visual stimuli. Therefore, we expected a positive correlation between the VHF LIs and fMRI LIs for phonological processing and for semantic processing in the reading modality.

Finally, we expected a positive relationship between brain lateralization and verbal ability, assessed outside the MRI scanner, using two established measures, the verbal scale (Verbal Comprehension Index, VCI) of the Wechsler Abbreviated Scale of Intelligence

(WASI-II; Wechsler, 2011) and a verbal fluency task (e.g., Birn et al., 2010; Costafreda et al., 2006). The VCI tasks require participants to define words and describe semantic resemblances of different concepts. The verbal fluency task requires the generation of single words. Both, the VCI and verbal fluency, thus rely heavily on semantic knowledge and semantic processing of language stimuli. Therefore, we expected performance on both measures of language ability to be most strongly related to fMRI LIs for semantic processing.

4.3 Methods

4.3.1 Subjects

Twenty-six right-handed native English speakers took part in the current study after giving informed consent. All participants had normal or corrected-to-normal vision and normal self-reported hearing. All participants reported not having a history of any psychiatric conditions. Motion correction revealed that four participants had head movements greater than one voxel size between volumes. They were excluded from the study, leaving a final sample of twenty-two subjects (14 female, mean age 22.05 years, *SD* = 7.66). The Edinburgh Handedness Inventory (Oldfield, 1971) revealed a mean handedness index of 83.13 (*SD* = 20.18). Handedness indices ranged from 41.18 to 100, with 45% of participants with a handedness index of 100. The study was approved by the Durham University Ethics Committee and conformed to the guidelines of the Declaration of Helsinki.

4.3.2 Stimuli

To investigate different language processes across different modalities, several types of language stimuli as well as modality-specific control stimuli were presented in a passive listening task, a silent reading task, and a repetition task. The language stimuli included words, sentences, scrambled sentences, pseudowords, and pseudosentences (results on scrambled sentences and pseudosentences not included in this paper). All words were taken from the MRC Psycholinguistic Database (Coltheart, 1981) and pseudowords were derived from these words, using the Wuggy software (Keuleers, & Brysbaert, 2010).

For all nouns, either used in word lists in the word condition or used in sentences in the sentence condition, the mean number of letters was 6.11 (*SD* = 2.00), mean word frequency (Kucera & Francis, 1967) was 74.13 (*SD* = 118.04), mean familiarity was 528.82 (*SD* = 76.71), and mean concreteness was 514.31 (*SD* = 101.40). Across subjects, the same stimuli were used in the three modalities, listening, reading, and repetition.

To avoid effects of potential differences between words (e.g., with regard to length or frequency), the same words were used in the word condition, the sentence condition, and the scrambled sentence condition across subjects. This was achieved by generating sentences with multiple possible ending words. One of these ending words was then presented in the sentence condition whereas the other ones were presented in the word condition. The distribution of ending words to either the word condition or the sentence condition differed between subjects (see Table 1 for examples). All sentences consisted of six or seven words and had the same grammatical structure. In total, 1009 content words were used in the study: 533 nouns, 238 verbs, and 238 adjectives.

For the auditory control condition, pseudowords were temporally reversed, using the Audacity software (version 2.0.5). The resulting stimuli therefore required auditory processing, but lacked phonological information. For the visual control condition, strings of slashes and backslashes were created (e.g., “/ / \ /” or “\ / / / \ /”) by replacing half of the letters of the alphabet with a forward slash and the other half with a backward slash. The resulting symbol strings lacked any orthographic information but required visual processing. In the repetition control condition, participants had to repeat the word “against”. This particular word was chosen because it is comparable in length and phonological complexity (840 ms, 6 phonemes) to the pseudowords used in this study. However, due to its extensive usage (Kucera-Francis written frequency of 626) it is phonologically less demanding than unfamiliar pseudowords and will, therefore, serve as a control for the pseudoword condition.

Table 1
Example of stimuli used in the sentence condition and in the word condition across participants

	Participant A	Participant B
Sentence condition	The customer tries the spicy <u>soup</u> The nephew finds the hidden <u>toy</u>	The customer tries the spicy <u>meal</u> The nephew finds the hidden <u>box</u>
Word condition	meal … stew … box … sweets …	soup … stew … toy … sweets …

4.3.3 Procedure

All participants took part in two fMRI scanning sessions as well as a session of behavioral testing, in which participants' handedness, verbal ability, and language lateralization was assessed with a variety of tasks. The behavioral testing lasted approximately one hour and typically took part on the day before the scanning sessions.

4.3.3.1 Behavioral lateralization measurements

Dichotic Listening. The Bergen Dichotic Listening paradigm (Hugdahl, 1995) was used as a behavioral measure of brain lateralization for phonological processing. Stimuli consisted of a range of CV-syllables (i.e., /ba/, /da/, /ga/, /ka/, /pa/, /ta/), recorded from a native English speaker and presented to participants via headphones. Participants were instructed to report which syllable they heard most clearly and most loudly immediately after it was presented. In 30 trials, participants were simultaneously presented with two different syllables, each played to one ear. In 6 control trials, the same syllable was presented to both ears. These control trials served as a confirmation that all participants were able to perform the task and were not included in the LI calculation. The DL LI was calculated with the following formula: [(correct right ear (%) - correct left ear (%)) / (correct right ear (%) + correct left ear (%))] * 100. This formula results in possible LIs from +100 to -100, indicating consistent left-lateralization and right-lateralization, respectively.

Visual Half-Field task. Participants performed a visual half-field task with word-pseudoword decisions (Hirnstein et al., 2008). Participants were presented with the stimuli on a computer screen while resting their head on a chin rest. The distance between the participants' eyes and the screen was measured to be 57 cm so that one cm on the screen corresponded to one degree of visual angle. Each trial started with a black fixation cross presented in the center of a white screen. After 2 s two black frames appeared, one 2.2 cm to the left of the fixation cross, and one 2.2 cm to the right of the fixation cross. One of the frames contained either a word or a pseudoword, staying on the screen for 185 ms. The short presentation time in combination with the distance between the fixation cross and the stimuli ensured that stimuli were only presented to one visual half-field. Participants were instructed to keep fixating the cross the whole time and to make a decision on whether the appearing stimulus was a word or a pseudoword. They indicated their chose with a button press. The responding hand was changed after the first half of the trials and the order of the starting hand was counterbalanced across participants. The total number of trials was 100, excluding 10 practice trials. The VHF LI was calculated with the following formula: [(correct right VHF (%) - correct left VHF (%)) / (correct right VHF (%) + correct left VHF (%))] * 100. This formula results in possible LIs from +100 to -100, indicating consistent left-lateralization and right-lateralization, respectively.

4.3.3.2 Verbal ability measurements

Verbal Comprehension Index. The Vocabulary test and the Similarity test of the Wechsler Abbreviated Scale of Intelligence (WASI-II, Wechlser, 2011) were administered. Together, the two tests form the verbal subscale of the WASI-II and their scores constitute the Verbal Comprehension Index (VCI; called “verbal IQ” in previous versions of the WASI). In the Vocabulary subtest, participants were asked to give a description of the meaning of a range of given stimulus words. In the Similarity subtest, participants were asked to describe in what way given pairs of words were alike.

Verbal Fluency. Participants performed a verbal fluency task, consisting of a semantic (e.g., Basho, Palmer, Rubio, Wulfeck, & Müller, 2007; De Carli et al., 2007; Birn et al., 2010) and a phonological part (Controlled Word Association Test, COWAT (e.g., Loonstra, Tarlow, & Sellers, 2001; Rodriguez-Aranda & Martinussen, 2006)). Both parts consisted of three two-minute periods in which participants generated as many words as they could. In the semantic part, the generated words had to belong to a certain category (i.e., animals, fruits, jobs). In the phonological part, the generated words had to start with the letter F, A, and S.

4.3.3.3 fMRI paradigm

All participants took part in two identical sessions with three runs each (listening, reading, repetition), only changing the specific stimuli that were presented. The order of the runs was counterbalanced and the order of conditions in each run was determined by one of four pseudorandomly generated lists of conditions.

Participants performed a passive listening task, a silent reading task and a repetition task. After each stimulus, participants pressed a response box button with their index finger. Participants used different hands for responding in the two sessions, counterbalancing the order of left and right hand across participants. The button press ensured that participants attended the stimuli appropriately but kept language-unrelated cognitive demands minimal and constant across modalities and conditions. In the repetition runs, participants repeated the stimulus out loud after pressing the button.

The listening runs lasted 19.2 min and consisted of four blocks per condition (i.e., a total of eight blocks per condition for the entire study): control, pseudowords, words, pseudosentences, scrambled sentences, and sentences. For control stimuli, pseudowords, and words, 14 stimuli were presented per block. For pseudosentences, scrambled sentences and sentences, 6 stimuli were presented per block. Interstimulus intervals (ISI) were jittered. The mean length of the stimuli and their ISI were as follows: 812 ms (ISI 2991 ms) for control, 811 ms (ISI 2999 ms) for pseudowords, 843 ms (ISI 2997) for words, 2424 ms (ISI 6350 ms) for pseudosentences, 3057 ms (ISI 6349 ms) for scrambled sentences, and 2388 ms (ISI 6342 ms) for sentences. fMRI compatible in-ear headphones were used for stimulus presentation and the listening volume was confirmed by the participant before each session. During the auditory stimulus presentation, participants were instructed to fixate a white cross presented at the center of a screen in front of them. The reading runs lasted 15.0 min, including four blocks per condition: control, pseudowords, words, pseudosentences, and sentences. For control stimuli, pseudowords, and words, 14 stimuli were presented per block (presentation time of 1000 ms). For pseudosentences, and sentences, 6 stimuli were presented per block, each (pseudo-)sentence divided into three chunks of 1400 ms (e.g., The customer – finds – the hidden toy). ISI were jittered, with the following means: 2487 ms for control, 2506 ms for pseudowords, 2517 ms for words, 5865 ms for pseudosentences, and 5877 ms for sentences. Stimuli were presented via a BOLD screen (Cambridge Research Systems) and a mirror mounted on the head coil. Stimuli were presented in white on a black background in the center of the screen. The repetition runs lasted 13.1 min, including four blocks per condition: control, pseudowords, words, and sentences. For control stimuli, pseudowords, and words, 7 stimuli were presented per block. In the sentence condition, 3 stimuli were presented per block. ISI were jittered. The mean length of the stimuli and their ISI were as follows: 840 ms (ISI of 5563 ms) for control, 811 ms (ISI of 5590 ms) for pseudowords, 843 ms (ISI of 5478) for words, and 2388 ms (ISI of 12188ms) for sentences. Stimulus presentation in the repetition runs was the same as in the listening runs, except for longer ISI to allow for repetition of the stimuli by the participant. Each run also included four blocks of a low-level baseline condition (looking at a fixation cross for 37.5 s). Each condition block started with a 2-second prompt screen, providing a brief reminder of the task and condition. Stimulus presentation was run with the Psychtoolbox-3 software (MATLAB version R2014a).

Each scanning session lasted about one hour, including short breaks between the three runs and a structural scan (T1 or DTI) at the end of the session. Between the two sessions, participants were given a break of approximately one to two hours.

4.3.4 fMRI data acquisition

Data were acquired at the Durham University Neuroimaging Centre at James Cook University Hospital, Middlesbrough, UK, using a Siemens 3T Magnetom Trio Scanner with a 32 channel head coil. EPI imaging of the whole head was performed, using a 96 x 96 matrix with a field of view of 210 x 210 and a voxel size of 2.1875 x 2.1875 x 3 mm. 35 axial slices were collected in ascending acquisition with a 10% gap in between slices. The TR was 2.16 s, TE 30 ms and the flip angle was 90°. The total number of volumes acquired per person (across the two sessions) was 2660 (i.e., 1080 for listening runs, 844 for reading runs, and 736 for repetition runs).

Anatomical data was acquired with a T1-weighted 3D sequence comprising 192 slices (TR = 2250 ms, TE = 2.52 ms, TI = 900 ms, flip angle 9°, FOV = 25.6 cm, 512x512 matrix, voxel size = 0.5x0.5 mm).

4.3.5 Data preprocessing and analysis

Data were preprocessed and analyzed using FMRIB's Software Library, version 4.1 (FSL, http://www.fmrib.ox.ac.uk/fsl). A custom-made symmetric template brain was used for coregistration. This template was generated by averaging the original MNI template with its mirrored version (i.e., flipped by 180° with respect to the midline). Using this template will allow the direct comparison of activations in the left and the right hemisphere on a voxel-by-voxel-basis. In the initial analysis, the two scanning sessions were analyzed separately. The data were smoothed with a full-width half-maximum kernel of 6 mm. The high-pass filter cut-off was set to twice the maximum cycle length for each of the runs (Poldrack, Mumford, & Nichols, 2012), resulting in 168 s for listening runs, 140 s for reading runs and 152 s for repetition runs. The FSL FILM tool was used for prewhitening. Motion correction was carried out using FSL’s MCFLIRT and motion parameters were included in the model as regressors of no interest. In an event-related analysis (i.e., using timings of single stimulus onsets and durations rather than blocks), each stimulus type was modelled as an explanatory variable and convolved with a double gamma hemodynamic response function. Resting blocks were used as an implicit baseline not specified in the model.

In a second step, the results from the first-level analysis were combined for each subject in a fixed-effects analysis. In a third step, a group analysis was carried out, using FSL FLAME 1+2. Outliers were automatically de-weighted by FSL.

For each of the three modalities, three contrasts were chosen to reflect the different language processes under investigation. Phonological processing was assessed by contrasting pseudowords with the modality-specific control conditions (i.e., reversed pseudowords, symbol strings, or repeating “against”). Semantic processing was assessed by comparing words with pseudowords. Sentence processing was assessed by comparing sentences with words.

For each language process in each modality, activations in the LH and the RH were directly compared on a voxel-by-voxel level. Employing paired t-tests, the t-maps for all nine contrasts were contrasted with their respective mirrored versions (i.e., flipped by 180° with respect to the midline). This approach will identify, for each language process in each modality, brain regions that are significantly more activated in the LH than in the RH and those areas that are significantly more activated in the RH than in the LH.

4.3.5.1 LI calculations

In order to quantify degrees of lateralization in brain activity during language processing, LIs were calculated based on the fMRI data, using the bootstrapping method provided by the SPM8 LI toolbox (Wilke & Lidzba, 2007). For each of the three language processes (i.e., phonological processing, semantic processing, sentence processing) in each of the three modalities (i.e., listening, reading, repetition), two types of LIs were calculated. First, whole-brain LIs were calculated, using the gray matter mask provided by the SPM LI toolbox, excluding 5mm to the left and to the right side of the interhemispheric fissure. This resulted in nine (3 x 3) whole-brain fMRI LIs.

Second, anatomical ROIs were used to investigate lateralization in specific areas in the brain. Specifically, for each of the three language processes, one ROI was chosen based on its well-established involvement in the respective language process. The ROI chosen for phonological processing was the posterior superior temporal gyrus (pSTG), while the posterior middle temporal gyrus (pMTG) was chosen for semantic processing and the anterior temporal lobe (ATL) for sentence processing. For each ROI, an anatomical mask was created using the Harvard-Oxford Cortical Atlas (Figure 1). These masks were used to calculate nine ROI-based fMRI LIs, i.e., three LIs (for listening, reading, repetition) for phonological processing based on activity in the pSTG, three LIs for semantic processing based on activity in the pMTG and three LIs for sentence processing based on activity in the ATL.

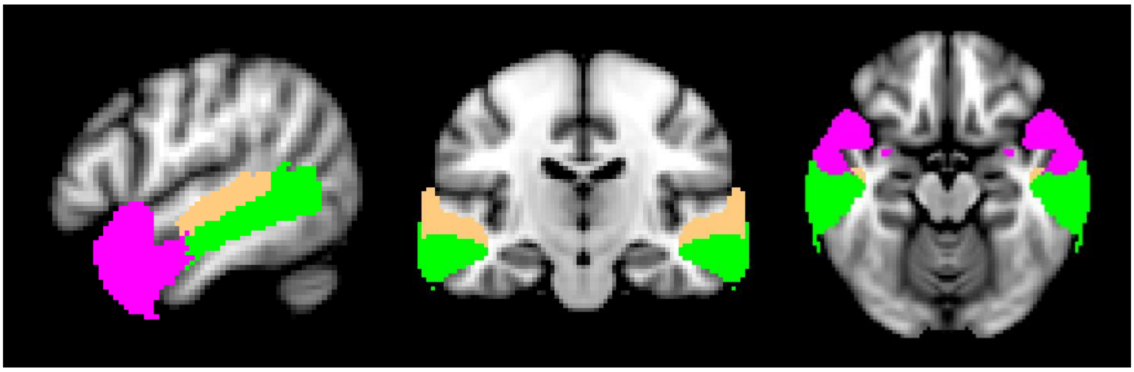

Figure 1. Anatomical masks used for the calculations of the ROI-specific LIs. Beige: pSTG mask for phonological processing; green: pMTG mask for semantic processing; pink: ATL mask for sentence processing.

To investigate the relationship between language lateralization as assessed with fMRI and with behavioral laterality measures, Pearson correlation analyses were performed with the fMRI LIs and LIs from DL and the VHF task. Specifically, for both behavioral laterality measures, one fMRI contrast was chosen to best reflect the language process assessed in the behavioral laterality task. This was done to maximize correlation between fMRI LIs and behavioral LIs. DL involves listening to syllables and assesses lateralization of phonological processing. Therefore, DL LIs were correlated with fMRI LIs for phonological processing in the listening modality (i.e., pseudowords > reversed pseudowords). The VHF task involves reading of words and pseudowords and making a word-nonword decision. Thus, the task requires phonological as well as semantic processing. VHF LIs were therefore correlated with fMRI LIs for phonological processing and fMRI LIs for semantic processing.

Finally, the relationship between lateralization and verbal ability was investigated by performing Pearson correlation analyses with VCI scores and fMRI LIs and with verbal fluency scores and the fMRI LIs. Since both verbal ability tests rely on semantic processing and language production, fMRI results for semantic processing in repetition were expected to show the strongest correlation with VCI and verbal fluency scores.

4.4 Results

4.4.1 Behavioral language lateralization results

Dichotic Listening. To test whether the DL paradigm revealed the expected right ear advantage, the number of correct responses for each ear was subjected to a paired t-test. The results revealed a significant difference between right-ear and left-ear reports, $t(21) = 2.95$, $p = .008$. Participants correctly reported syllables that were presented to the right ear ($M = 49.55\%$, $SD = 13.70$) more frequently than syllables presented to the left ear ($M = 34.85\%$, $SD = 11.44$). The mean DL LI in the sample was 16.93 ($SD = 26.55$). This LI was significantly greater than zero, $t(21) = 3.00$, $p = .007$

Visual half-field task. To investigate whether the task elicited the expected right VHF advantage, the number of correct responses for each visual field were subjected to a paired t-test. The results revealed a significant difference between the right and the left visual field, t(21) = 2.19, $p = .04$. As expected, participants made more correct word-pseudoword decisions in the right visual field ($M = 78.73\%$, $SD = 10.84$) than in the left visual field ($M = 75.27\%$, $SD = 11.19$). The mean VHF LI in the sample was 2.31 ($SD = 4.92$). This LI was significantly greater than zero, $t(21) = 2.20$, $p = .039$.

4.4.2 Verbal ability results

Verbal Comprehension Index (VCI). The mean VCI as assessed with the WASI-II was *M* = 120.14 (*SD* = 14.80), indicating an above-average verbal ability in the sample.

Verbal Fluency. The semantic as well as the phonological fluency task showed good reliability (Cronbach's alpha of .80 for category fluency and .87 for letter fluency). In the semantic part, participants generated a mean of 27.08 words (*SD* = 4.74) per two-minute time period. In the phonological part, participants produced a mean of 22.15 words (*SD* = 6.27) per two-minute time period. Performances on the semantic and the phonological part of the task were significantly correlated, *r*(20) = .67, *p* = .001. The overall verbal fluency was calculated as the average of the semantic part and the phonological part and resulted in a mean of *M* = 24.61 (*SD* = 5.04). Verbal fluency was significantly correlated with the VCI, *r*(20) = .460, *p* = .031.

4.4.3 fMRI group activations

In a first step of fMRI data analysis it was ensured that the different language processes under investigation engaged the cortical areas that were hypothesized to be involved. In three instances, contrasts for phonological or semantic processing did not result in significant activations when applying standard thresholding and correction for multiple comparisons. This lack of significance when comparing words, pseudowords and reversed speech is in line with previous studies (e.g., Binder et al., 2000). However, since the focus of the current study was not the strength of activations per se, but rather the relative engagement of the LH compared to the RH, thresholds for initially non-significant contrasts were lowered to explore subthreshold activations and ensure that they were located in the expected brain areas. Phonological processing activated the left posterior superior temporal gyrus (pSTG) in listening, reading and repetition [-56 -40 2, z=2.76 for listening, z=1.67 for reading, z=2.73 for repetition] (Figure 2). In repetition, there were additional activations in the right pSTG [60 -2 -4, z=4.52] and the left inferior frontal gyrus (IFG) [-56 14 30, z=6.05].

Activations were considerably weaker for listening and reading than for repetition and are displayed with a threshold of z = 1.65, uncorrected for multiple comparisons. Semantic processing activated posterior temporal regions but there was less overlap between the three modalities than there was for phonological processing (Figure 3). In listening, semantic processing engaged the left anterior MTG [-62 0 -22, z=2.78] and bilateral angular gyrus [-60 -52 36, z=3.21]. In reading, activations were located in the left posterior STG and MTG [-60 -42 12, z=4.75] as well as frontal and occipital regions. In repetition, activations were located in left anterior MTG [-60 -12 -16, z=3.77] and bilateral lateral occipital cortex [-44 -82 24, z=4.97], reaching into posterior MTG [56 -58 4, z=4.01] and angular gyrus [58 -46 22, z=3.93] in the RH. Activations for semantic processing in the listening modality were weaker than in reading and repetition and are displayed with a threshold of z = 1.65, uncorrected for multiple comparisons. Sentence processing elicited stronger activations in all three modalities than did phonological and semantic processing (Figure 4). In addition to modality-specific activations in posterior temporal regions, sentence processes significantly activated the left anterior temporal lobe (ATL) [-56 -4 -14] in all three modalities, with considerable overlap in the temporal pole [-52 10 -18].

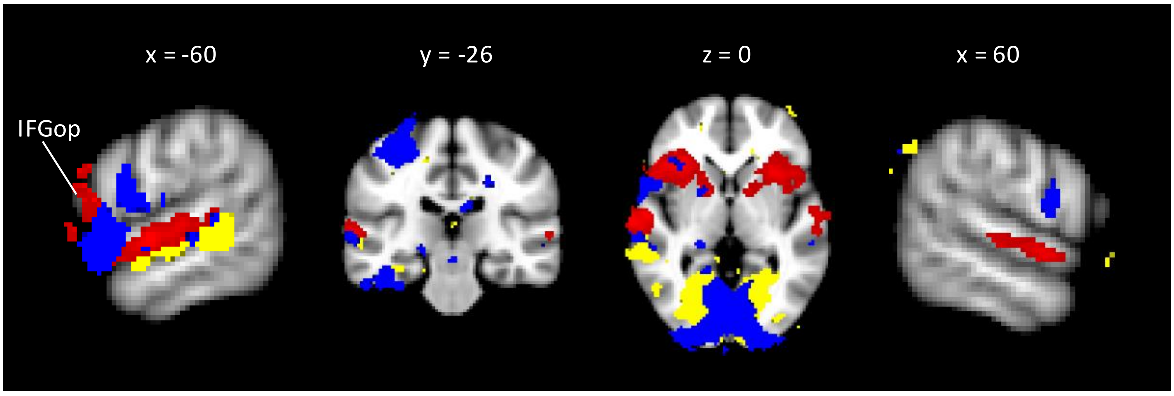

Figure 2. Group activations for phonological processing in the different modalities. Yellow = listening, blue = reading, red = repetition. Results for repetition are cluster-corrected at z = 2.3, p < .05. Results for listening and reading are thresholded at z = 1.65, uncorrected for multiple comparisons.

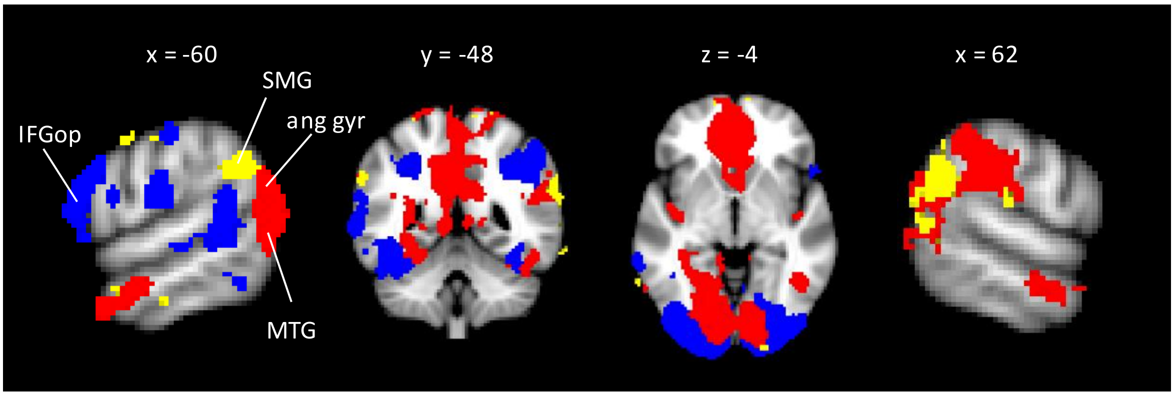

Figure 3. Group activations for semantic processing in the different modalities. Yellow = listening, blue = reading, red = repetition. Results for reading and repetition are cluster-corrected at z = 2.3, $p < .05$. Results for listening are thresholded at z = 1.65, uncorrected for multiple comparisons.

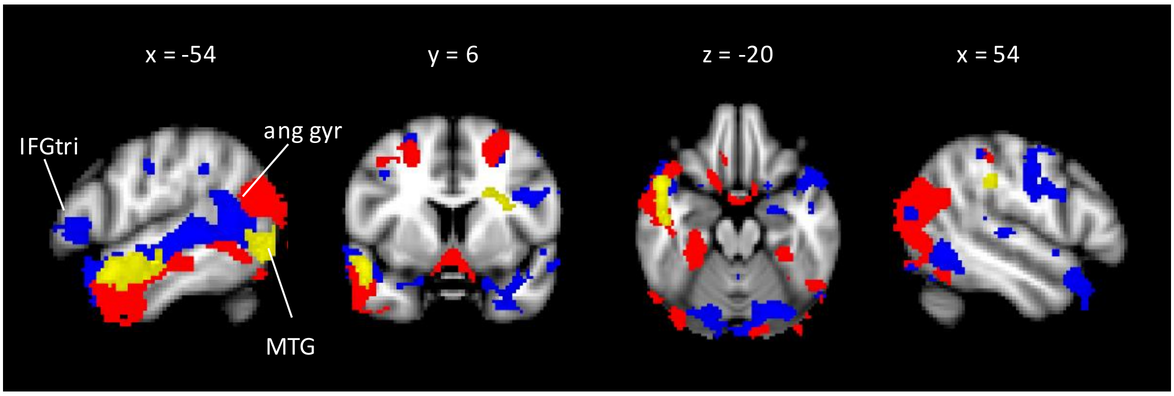

Figure 4. Group activations for sentence processing in the different modalities. Yellow = listening, blue = reading, red = repetition. All results are cluster-corrected at z = 2.3, $p < .05$.

Paired t-tests for direct comparisons of LH and RH activation resulted in several significant clusters for each language process (Figures 5-7). For phonological processing, all of these clusters were located in the LH, predominantly centering around the left STG/STS with additional clusters in the left SMG and parietal operculum for listening and repetition and in the left IFG and precentral gyrus for reading and repetition. There were no areas of significantly stronger activation in the RH than in the LH. For semantic processing, the comparison of LH and RH activity resulted in a cluster in the right SMG/angular gyrus for listening and a cluster in the left ITG and temporal and occipital fusiform cortex for reading. For repetition, there were no significant clusters. However, results uncorrected for multiple comparisons revealed some small clusters in both hemispheres, one of which overlapped with the cluster in the right SMG/angular gyrus found for the listening modality. For sentence processing, comparisons of LH and RH activity resulted in clusters centering around the left STG/MTG for all three modalities. Furthermore, there were some clusters in the RH for all modalities, predominantly centering around the SMG.

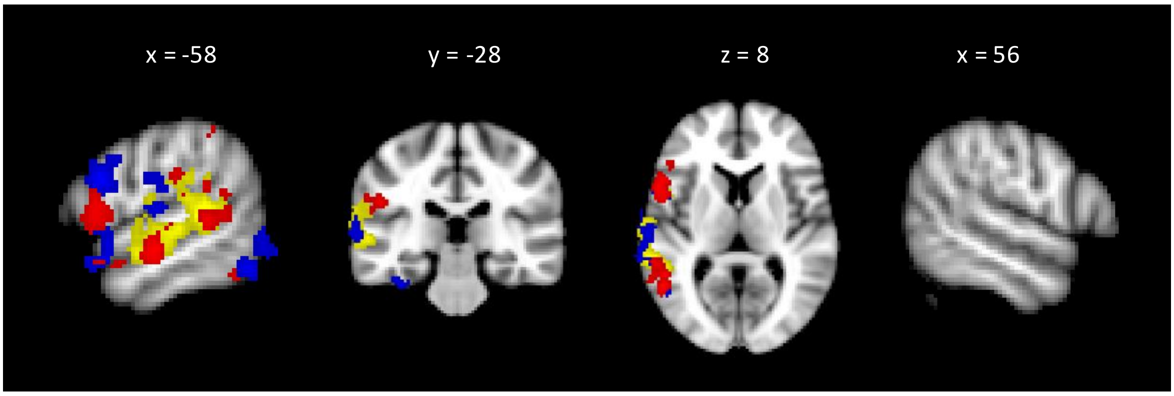

Figure 5. Comparison of LH and RH activity for phonological processing in the three modalities. Yellow = listening, blue = reading, red = repetition. Activated areas indicate significantly greater activation in the original z statistic than in the mirrored version. All results are cluster-corrected at *z* = 2.3, *p* < .05.

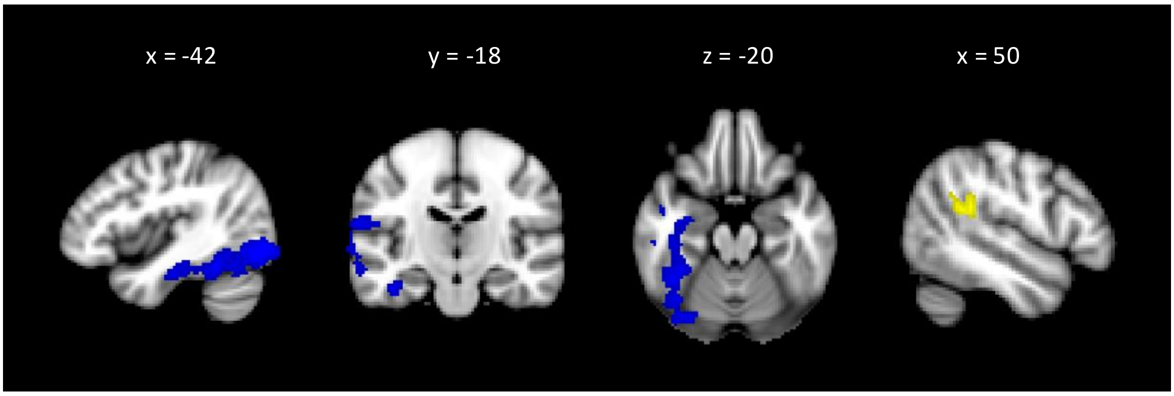

Figure 6. Comparison of LH and RH activity for semantic processing in the three modalities. Yellow = listening, blue = reading, red = repetition. Activated areas indicate significantly greater activation in the original z statistic than in the mirrored version. All results are cluster-corrected at *z* = 2.3, *p* < .05.

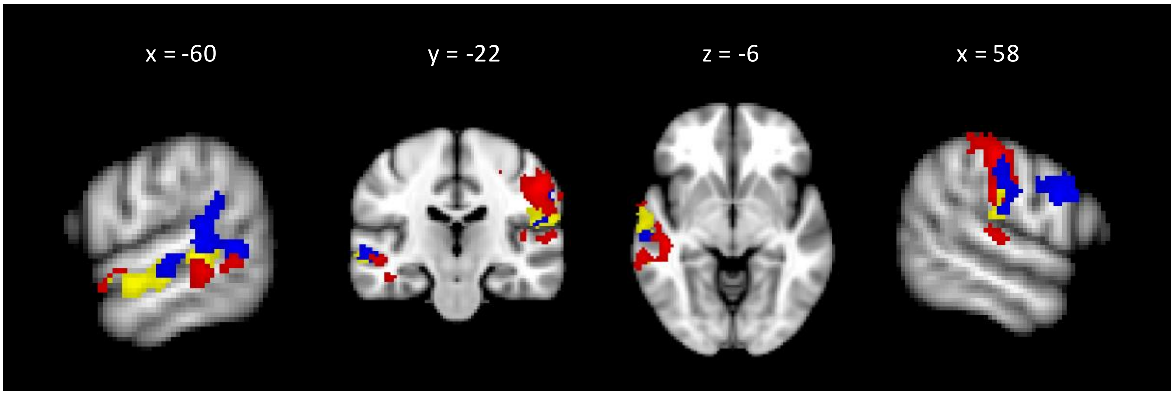

Figure 7. Comparison of LH and RH activity for sentence processing in the three modalities. Yellow = listening, blue = reading, red = repetition. Activated areas indicate significantly greater activation in the original z statistic than in the mirrored version. All results are cluster-corrected at $z = 2.3$, $p < .05$.

4.4.4 Lateralization indices

Whole-brain LIs. All of the nine whole-brain LIs were positive, 3 of them being significantly greater than zero, that is, significantly left lateralized (Bonferroni-corrected) (Figure 8, left panel). The nine whole-brain LIs were entered into a 3 x 3 repeated measures ANOVA with Modality (listening, reading, repetition) and Language process (phonology, semantics, sentence processing) as within-subject factors. Modality did not show a significant main effect, $F(2, 42) = 0.13$, $p = .880$. LIs for all three modalities were significantly left lateralized (Bonferroni-corrected). Language Process showed a significant effect, $F(2, 42) = 4.08$, $p = .024$. However, in pairwise comparisons, none of the LIs were significantly different ($p = .149$ for phonology vs. semantics, $p = .070$ for phonology vs. sentences, $p = 1.00$ for semantics vs. sentences). Only LIs for phonological and semantic processing were significantly greater than zero, $t(21) = 4.63$, $p <.001$ for phonology, $t(21) = 3.60$, $p =.002$ for semantics, $t(21) = 1.92$, $p = .07$ for sentences. The interaction of Modality x Language Process was not significant, $F(4, 84) = 2.08$, $p = .091$.

ROI-specific LIs. All of the nine ROI-specific LIs were positive, two of them being significantly greater than zero (Bonferroni-corrected) (Figure 8, right panel). The nine ROI-specific LIs were entered into a 3 x 3 repeated measures ANOVA with Modality and

Language process as within-subject factors. Modality did not show a significant main effect, *F*(2, 42) = 0.14, *p* = .869. LIs for all three modalities were significantly left lateralized (Bonferroni-corrected). Language Process showed a significant effect, *F*(2, 42) = 4.14, *p* = .023. However, in pairwise comparisons, LIs for the three language processes were not significantly different (*p* = .067 for phonology vs. semantics, *p* = .141 for phonology vs. sentences, *p* = 1.00 for semantics vs. sentences). Only LIs for phonological and sentence processing were significantly greater than zero, *t*(21) = 4.86, *p* <.001 for phonology, *t*(21) = 1.71, *p* =.10 for semantics, *t*(21) = 3.38, *p* = .003 for sentences. The interaction of Modality x Language Process was not significant, *F*(4, 84) = 0.80, *p* = .528.

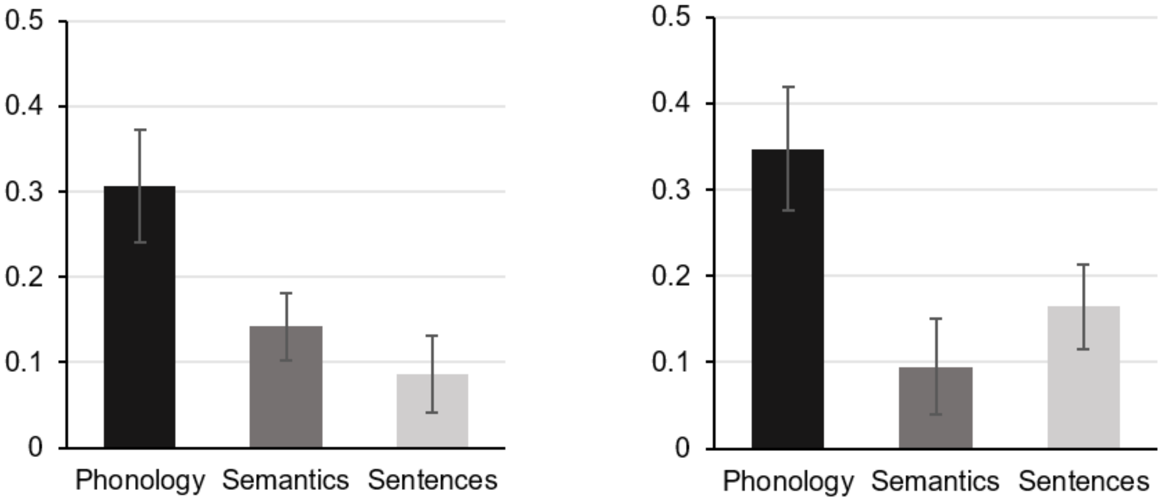

Figure 8. Mean fMRI LIs (and standard error means) for the different language processes. Left panel: whole-brain LIs; right panel: ROI-specific LIs.

Furthermore, an overall language LI was calculated, reflecting language lateralization across language processes and modalities. This was done twice, once by taking the mean of the nine ROI-specific LIs and once by taking the mean of the nine whole-brain LIs. The mean ROI-specific language LI across subjects was *M* = 0.20 (SD = 0.13). Twenty subjects (90.91%) had a language LI numerically larger than zero, that is, left-lateralized. Two subjects had language LIs just below zero (-0.02 and -0.06). The mean whole-brain language LI across subjects was *M* = 0.17 (SD = 0.10). Twenty-one subjects (95.45%) had a language LI numerically larger than zero, that is, left-lateralized. One subject had a language LI below zero (-0.08).

4.4.5 Relationships between fMRI LIs and behavioral LIs

Dichotic Listening. LIs generated from DL performance did not show significant correlations with LIs for phonological processing in listening ($p > .53$). Correlations between DL LIs and fMRI LIs for phonological processing averaged across modalities were larger but did not reach significance, $r(20) = .31$, $p = .157$, for whole-brain LIs and $r(20) = .27$, $p = .220$, for ROI-specific LIs from the pSTG. Based on the idea that DL is “a measure of temporal lobe function” and “hemispheric language asymmetry” (Hugdahl, 1995), we further calculated correlations between DL LIs and fMRI LIs for phonological processing based on activity in the entire temporal lobe rather than just the pSTG as well as correlations between DL LIs and the whole-brain overall language LI rather than only phonological processing. DL LIs showed a significant positive correlation with phonological processing in the temporal lobe, $r(20) = .51$, $p = .016$. DL LIs did not show a significant correlation with the overall language LI, $r(20) = .32$, $p = .142$.

Visual half-field task. LIs for the VHF task showed non-significant correlations with fMRI LIs for phonological processing in reading, $r(20) = .35$, $p = .109$ for whole-brain LIs and $r(20) = .35$, $p = .110$ for ROI-specific LIs from the pSTG. For semantic processing in reading, correlations were at $r(20) = .30$, $p = .173$, for whole-brain LIs and $r(20) = -.18$, $p = .434$ for ROI-specific LIs from the pMTG. The average whole-brain LI for reading (across language processes) showed a strong positive correlation with the VHF LI, $r(20) = .53$, $p = .012$.

4.4.6 Relationships between fMRI LIs and verbal ability

Correlations between the two verbal ability measures and different fMRI LIs are shown in Table 2. Contrary to our prediction, the WASI-II VCI did not show significant correlations with LIs for semantic processing or with the overall language LI.

Verbal fluency on the other hand, showed significant correlations with fMRI LIs for semantic processing in the pMTG during repetition and with fMRI LIs for semantic processing in the pMTG across modalities. However, verbal fluency did not correlate significantly with the global fMRI language LI.

Table 2
Correlations (and p values) between verbal ability and fMRI LIs.

	LI for semantic processing in the pMTG during repetition	LI for semantic processing in the pMTG across modalities	Overall language LI (across processes, modalities and ROIs)
VCI	.21 (.352)	.09 (.683)	.36 (.102)
Verbal fluency	.48 (.023*)	.52 (.013*)	.17 (.438)

* $p < .05$

4.5 Discussion

4.5.1 Brain activations for different language processes

The primary aim of this study was to investigate patterns of brain lateralization for different language processes and modalities in a task-independent manner, applying process-specific ROI masks and whole-brain activity masks. Second, we explored relationships between lateralization of brain activity and behavioral language lateralization. Finally, we were interested in the relationship between language lateralization and verbal ability.

Language lateralization was assessed with fMRI LIs, based on brain activity for listening, reading, and repetition with different types of language stimuli that elicited phonological, semantic and sentence processing, respectively. Overall, the three language processes activated the expected brain areas, although not all activations reached the threshold of significance.

As hypothesized, activations for phonological processing were predominantly located in the left pSTG in listening, reading and repetition (Hickok & Poeppel, 2007; Price, 2010; Vigneau et al., 2006). Semantic processing activated posterior temporal regions, as hypothesized (Hickok & Poeppel, 2007; Price, 2010; Vigneau et al., 2006). However, activations for semantic processing showed less overlap between the three modalities than phonological processing. Furthermore, there was a greater extent of RH involvement in semantic processing compared to phonological processing, particularly for listening and repetition. Sentence processing resulted in strong activations in the left ATL in listening, reading and repetition. This brain region has repeatedly been shown to be involved in sentence processing, predominantly using listening and reading paradigms (Constable et al., 2004; Humphries, Willard, Buchsbaum, & Hickok, 2001; Vandenberghe, Nobre, & Price, 2002). The results of the current study confirm the involvement of the left ATL in the production of sentences and show a large overlap of activation for all three modalities.

For all three language processes in all three modalities, fMRI LIs were positive, when based on whole-brain activity and when based on ROI-specific activity, indicating a LH language dominance in the sample.

4.5.2 Lateralization and modality

The degree of language lateralization did not vary with the modality of processing. LH dominance was similarly large for listening, reading and repetition, regardless of whether whole-brain activity or ROI-specific activity was taken into account. A lack of a modality effect on language lateralization has previously been shown in a comparison of listening and reading (Hund-Georgiadis et al., 2001). However, with regard to productive versus perceptive tasks, it has been suggested that modality can have an effect on the degree of lateralization, with production of language being more strongly lateralized than perception (Badcock et al., 2012; Gutierrez-Sigut et al., 2015). The current results do not support this claim. Modality did not affect the degree of lateralization when confounding effects of other task elements, such as language processes, were minimized. The lack of modality effects on language lateralization is in line with the substantial overlap of activations for language processing across different modalities, as found in the current study and others (e.g., Jobard, Vigneau, Mazoyer, & Tzourio-Mazoyer, 2007; Lindenberg & Scheef, 2007). The concordance of results in different modalities, with regard to lateralization and activations, suggest that phonological, semantic and sentence processing are higher-level, supra-modal cognitive processes, which are relatively independent from lower-level perceptual or motor processes.

4.5.3 Lateralization and language processes

In contrast to modality, language process had a significant effect on the degree of lateralization. Phonological processing was most strongly LH-lateralized compared to semantic and sentence processing in both, whole-brain and ROI-specific LIs. Previous comparisons of tasks involving phonological processing and tasks involving semantic or sentence processing have also resulted in larger lateralization for phonological tasks (Buchinger et al., 2000). However, as discussed earlier, these tasks confounded the type of linguistic processing with modality and non-linguistic task demands, for example when comparing a verbal fluency task to a synonym judgement task or a story listening task. In contrast, the current study systematically compared different language processes in different modalities, allowing for a differentiation of effects for the two variables. Therefore, the effect of language process can be directly attributed to the role of linguistic processes in lateralization, independent of processing modality or additional, non-linguistic task demands. The effect of language process on the degree of lateralization in the current study contradicts a recent fTCD study that compared lateralization for a phonological and a semantic condition of the verbal fluency task (Gutierrez-Sigut et al., 2015). The authors did not find a significant difference between the degree of lateralization for phonological and semantic fluency, although the phonological task produced numerically larger LIs. In comparison to the fMRI paradigm used in the current study, the verbal fluency paradigm required a larger amount of cognitive effort that was specific to the task rather than related to the linguistic processes required for the phonological versus the semantic condition. These non-linguistic processes were shared between the two conditions of the paradigm, possibly accounting for the lack of a significant difference in brain activation and, hence, lateralization. In contrast, in the current study the shared variance in the phonological and the semantic condition was minimal due to low general task demands, thus giving more weight to differences in linguistic demands between the phonological and semantic condition. Furthermore, even the phonological condition of the verbal fluency paradigm relies on the retrieval and production of words and, thus, necessarily involves semantic processing. This further increases the shared variance between the phonological and the semantic condition of the verbal fluency task, possibly accounting for similarities in the degree of lateralization in the two conditions. In contrast, the current study assessed phonological processing with pseudoword stimuli which did not involve any semantic information. Although speculative, these two aspects might explain the difference in findings between the current study and Gutierrez-Sigut et al. (2015).

Semantic and sentence processing were numerically less strongly lateralized than phonological processing in both, whole-brain LIs and ROI-specific LIs. However, the exact patterns of lateralization for semantic and sentence processing differed between whole-brain LIs and ROI-specific LIs. For whole-brain LIs, sematic processing was significantly left-lateralized, whereas sentence processing was not. For process-specific ROIs in the temporal lobe, sentence processing was significantly lateralized, whereas semantic processing was not. Only in the reading modality did semantic processing approach significance. It should be noted that direct LH-RH comparison revealed significantly more activation in the left than in the right fusiform gyrus, a region located in close proximity to the pMTG, which was used as an ROI for the semantic LI calculation. The fusiform gyrus is known to be involved in word reading and has been found to show left-lateralized activity (Dehaene, Le Clec'H, Poline, Le Bihan, & Cohen, 2002; Turkeltaub, Eden, Jones, & Zeffiro, 2002). Furthermore, it has been found to be engaged in non-linguistic semantic processing, such as object recognition, and has been suggested to integrate information about the visual form of the word and its meaning (Devlin, Jamison, Gonnerman, & Matthews, 2006).

The unexpected lack of a significant lateralization of semantic processing in the pMTG across modalities is in contradiction with the dual stream model's prediction of left-dominant representation of semantic processes, although the model predicts some RH involvement in semantic processing (Hickok & Poeppel, 2007). Since semantic processing resulted in relatively weak activations in the current study, we cannot rule out that stronger overall activity would have enhanced lateralization. However, activations for phonological processing were of similar intensity and resulted in robust and large LIs. Therefore, we suggest another explanation for the lack of a clear left-lateralization in semantic processing in the pMTG. In addition to a "lexical interface" for semantic processing in the left and right pMTG, the dual stream model also proposes a "conceptual network" that is distributed across the entire brain. This idea is supported by empirical evidence of semantic processing activations in a range of frontal, temporal and parietal areas (Binder, Desai, Graves, & Conant, 2009). The results of the current study support this notion of widely distributed brain areas involved in semantic processing, with activations in left frontal and anterior temporal regions, but bilateral posterior temporal, and parietal regions across the three different modalities. These differential patterns of semantic lateralization across different brain areas explain why the whole-brain LI for semantic processing was significantly left-lateralized whereas the ROI-specific LI was not.

The expected left-lateralization of sentence processing in the ATL ROI is in line with the dual stream model. In contrast, activity for sentence processing was not significantly left-lateralized across the entire brain, as reflected in the small whole-brain LI for sentence processing. Direct comparisons of LH and RH activity for sentence processing revealed that although temporal areas showed a significant LH bias in all three modalities, the RH showed more activity than the LH in frontal and parietal areas, especially for reading and repetition. It is possible that sentence processing elicited semantic associations in the form of inferences or situational imagery which would engage the RH to a greater degree than the LH. Indeed, the RH has been associated with processing of the wider context of sentences or stories (Vigneau et al., 2011).

The small but distinct differences between whole-brain LIs and ROI-specific LIs suggest that the choice of mask can be critical when calculating LIs. For focused activations, as in the case of sentence processing in the current study, brain activity in language-specific ROIs might be more informative than activity measures across the entire brain. In contrast, for processes that are less clearly localized to one particular brain region, such as semantic processing in a distributed conceptual network, a mask covering the entire network might be more appropriate to capture lateralization effects.

4.5.4 Other factors affecting the degree of lateralization

Overall, the mean LIs found in the current study are smaller in size than in numerous prior fMRI studies (e.g., Powell et al., 2012, Häberling et al., 2016). There are several possible explanations for these differences in LI sizes between the current and previous studies. First, the majority of previous lateralization studies have used fMRI paradigms that require an active processing or manipulation of language stimuli, such as word generation or semantic decisions (Häberling et al., 2016; Hund-Georgiadis et al., 2001). In contrast, our fMRI paradigm relied on stimulus-driven linguistic processing of language with minimal additional cognitive effort. Increases in task demands and effort have recently been shown to increase language lateralization (Payne, Gutierrez-Sigut, Subik, Woll, & MacSweeney, 2015), possibly explaining higher LIs in previous studies as compared to the current study.

A second potential reason for relatively small LIs in the current study might be related to the brain regions under investigation. Whereas the current study used ROIs in the temporal lobe, previous studies have frequently used ROIs in frontal brain areas because active language paradigms tend to elicit strong frontal activity (e.g., Hund-Georgiadis et al., 2001) which is more strongly lateralized than activity in the temporal lobe (Lopes et al., 2016). In fact, it has been suggested that the temporal lobe is not consistently lateralized per se but that its lateralization is instead driven in a top-down manner by lateralized frontal areas (Price, 2010). Positive correlations between lateralization in frontal and temporal regions might support this idea (Häberling et al., 2016). Since the passive, low-effort language tasks employed here, did not reliably engage frontal brain areas, as seen in other studies using similar paradigms (e.g., Hagoort, Indefrey, Brown, Herzog, Steinmetz, & Seitz, 1999; Meyer, Friederici, & Von Cramon, 2000; Noesselt, Shah, & Jäncke, 2003), a laterality-enhancing effect from the frontal on the temporal lobe might have been reduced.

A final explanation for comparably small LIs in the current study might be the relatively large variation in individual LIs for different language processes and modalities within subjects. Averaged across conditions, LIs indicated a left language lateralization for the majority of subjects (>90%). However, for all subjects, one or more individual LIs were negative, thus drawing the mean LIs closer to zero when averaging across participants. This finding strongly supports the idea that a reliable assessment of language lateralization requires different language processes and modalities, at least when investigating stimulus-driven, low-effort language processing.

4.5.5 Language lateralization in brain activity and behavioral lateralization

We further investigated the relationship between language lateralization as assessed with fMRI and assessed with well-established behavioral paradigms. Previous studies have found language lateralization as assessed with behavioral paradigms to be positively related to fMRI and fTCD lateralization, although with varying strength, ranging from small to large effect sizes (Bethmann et al., 2007; Hund-Georgiadis et al., 2002; Hunter & Brysbaert, 2008, Krach et al., 2006; Van der Haegen et al., 2011).

The current study assessed behavioral language lateralization with DL (Hugdahl, 1995) and a VHF task (Hirnstein et al., 2008) and found mixed results regarding their relationships with fMRI lateralization. Language lateralization assessed with DL showed a strong positive correlation with fMRI LIs for phonological processing (averaged across modalities) in the temporal lobe. However, DL lateralization was not related to fMRI lateralization during phonological processing in the listening modality alone. This is surprising since listening to pseudowords should share the greatest variance with the DL paradigm compared to reading or repeating pseudowords. It is possible that subtracting activity for auditory processing by using a high-level auditory control condition (i.e., reversed pseudospeech) in the phonological listening fMRI contrast, reduced the similarity between the DL paradigm and the fMRI contrast, explaining the stronger correlation with phonological processing independent of modality. Alternatively, it is possible that the DL paradigm assesses lateralization of phonological processes in the temporal lobe independent of a specific modality. The idea of DL lateralization as an indicator of language lateralization in a broader sense is supported by significant positive correlations between DL lateralization and brain lateralization for visual semantic tasks (Hund-Georgiadis et al., 2002) and speech production tasks (Fernandes & Smith, 2000). In the current study, language lateralization, assessed with an overall fMRI language LI, showed a positive but non-significant correlation with DL lateralization.

Language lateralization as assessed with the VHF task showed positive but non-significant correlations with fMRI LIs for phonological and semantic processing during reading, despite these correlations being moderately strong. Language lateralization as measured with the VHF task revealed a strong positive correlation with fMRI lateralization across the entire brain during reading, averaged across language processes.

4.5.6 Language lateralization and verbal ability

Finally, a further aim of the current study was to investigate the relationship between language lateralization as assessed with fMRI and verbal ability assessed outside the MRI scanner. It was hypothesized that the VCI and verbal fluency, two well-established measures of verbal ability that require predominantly semantic processing, would be positively correlated with brain lateralization, particularly during semantic processing. The results partially supported this hypothesis. All correlations between verbal ability and fMRI LIs of interest were positive, although some of them failed to reach significance. For the VCI, the current study found non-significant but positive correlations with LIs during semantic processing and with an averaged language LI across processes and modalities. For verbal fluency, we found the expected significant positive correlation with fMRI LIs during semantic processing. The correlation of verbal fluency and the averaged language LI was positive but non-significant. While both, verbal fluency and the VCI rely on semantic processing, only the verbal fluency task requires processing on the single word level. In that respect, processing requirements of the verbal fluency task are similar to processing requirements of the semantic part of the fMRI paradigm in the current study. This similarity might partly explain why we found a strong positive correlation of the semantic fMRI LI with verbal fluency but not with the VCI. The VCI on the other hand, requires semantic processing in a broader, more abstract sense, potentially explaining why the VCI correlated more strongly with the averaged language fMRI LI than with the semantic fMRI LI.

The positive relationships between language lateralization and verbal ability are in accordance with previous behavioral studies (Chiarello et al., 2009) and studies on brain lateralization in children (Everts et al., 2009; Groen et al., 2012). In adults, evidence has proven to be more difficult to obtain in the past (Knecht et al., 2001; Powell et al., 2012). Small advantages of a strong left-lateralization during language processing have previously been shown in a group comparison with weakly lateralized subjects (Mellet et al., 2014). However, weakly lateralized subjects did not only perform worse on language tasks than strongly left-lateralized subjects but also than strongly right-lateralized subjects. These results suggest that stronger language lateralization might be beneficial, regardless of the hemisphere that they are lateralized to. The idea that the relationship between language lateralization and verbal ability might not be linear, has also been proposed based on behavioural lateralization data (Hirnstein et al., 2010). In the current study, the sample consisted of right-handers only, who showed a lateralization of language processing to the left hemisphere in over 90% of subjects. Hence, with only two participants showing a (weak) RH language lateralization, our data do not allow any conclusions regarding potential benefits of strong right-hemispheric language lateralization. Future studies comparing correlations between verbal ability and absolute versus directional LIs in a more diverse sample could shed more light on this subject.

It should be noted that, although the level of verbal ability in the student sample of the current study was above the average verbal ability expected in the general population, there is no indication that the sample was not representative with regard to language lateralization. The percentage of left-lateralized participants was comparable to that found in previous studies (Knecht et al., 2000; Hund-Georgiadis et al., 2002). However, future studies should investigate whether the relationship between language lateralization and verbal ability changes in extreme (low/high) verbal ability groups.

The current study illustrates that an appropriate assessment of language lateralization is a prerequisite for investigating the relationship between language lateralization and verbal ability. While the results confirm an overall LH dominance for language processing, they also show distinct differences between language processes with regard to the degree of lateralization. Thus, it is not adequate to treat language lateralization as a unitary concept (Bishop, 2013) and a comprehensive assessment of language lateralization should incorporate different language processes. The positive relationships between language lateralization and verbal ability supports previously hypothesized advantages of pronounced cerebral asymmetries (e.g., Hirnstein et al., 2008; Chiarello et al., 2009).

4.6 References

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Chapter 5

General Discussion

The aim of the current thesis was to develop a suitable fMRI paradigm in order to assess different language processes (i.e., phonological, semantic, and sentence processing) and modalities (i.e., listening, reading, repetition) in a task-independent, stimulus-driven manner, reducing non-linguistic cognitive demands commonly triggered by other language processing paradigms. This paradigm allowed for the systematic investigation of neural correlates of language processing and served as a basis for exploring individual differences in these neural responses, particularly with regard to relationships with verbal ability.

5.1 Brain activity and functional connectivity during sentence comprehension

The first empirical chapter focused on sentence processing and showed that, on the group level, sentence comprehension predominantly activated the left anterior temporal lobe (ATL). This finding supports the combinatorial network proposed by the dual stream model of language processing (Hickok & Poeppel, 2007). While the authors proposed engagement of the left ATL in combinatorial processes involved in sentence comprehension, they also concluded, based on contradictory evidence from patients with ATL anomalies, that the exact role of the ATL in semantic and syntactic integration is still unclear. The current results with respect to separate investigations of semantic and syntactic integration revealed that both of these types of integration drive ATL activations during sentence comprehension. Together with previous research (Brennan, Nir, Hasson, Malach, Heeger, & Pylkkänen, 2012; Humphries, Binder, Medler, & Liebenthal, 2006; Rogalsky & Hickok, 2009; Vandenberghe, Nobre, & Price, 2002), these findings suggest that the role of the left ATL during sentence comprehension is the integration of single words into a meaningful entity, using semantic as well as syntactic integration. This is in contrast to suggestions of separate semantic and syntactic processes, taking place in distinct brain areas with a final step of integration in the posterior temporal lobe (Friederici, 2011; 2012).

The overlap of activations in the left ATL for listening and reading (and also for repetition, as shown in Chapter 3) indicates the existence of a modality-independent processing area, reflecting higher-level cognitive processes involved in sentence comprehension that are independent of lower-level auditory and visual processes (Jobard, Vigneau, Mazoyer, & Tzourio-Mazoyer, 2007; Lindenberg & Scheef, 2007). In fact, modality independence of the ATL does not seem to be restricted to linguistic processing modalities but appears to also be true for processing non-linguistic stimuli such as pictures (Bright, Moss, Stamatakis, & Tyler, 2005; Price, Devlin, Moore, Morton, & Laird, 2005; Visser, Jefferies, & Lambon Ralph, 2010). Accordingly, the role of the ATL has been proposed to be that of an amodal hub where modality-specific information is combined through differential functional connectivity with modality-specific brain areas (Visser et al., 2010). The current results partially confirmed this hypothesis. During auditory sentence comprehension, the left ATL showed increased functional connectivity with the left posterior STG, an area known to be involved in auditory and phonological processing (Rimol, Specht, Weis, Savoy, & Hugdahl, 2005; Specht, Osnes, & Hugdahl, 2009). During sentence reading, the left ATL did not show increased connectivity with the fusiform gyrus as expected, but with the left IFG, possibly reflecting working memory processes necessary to build up a sentence during incremental reading. Connections between the left ATL and left posterior temporal regions and between the left ATL and left IFG have been proposed by the dual stream model of language processing (Hickok & Poeppel, 2007). Structurally, these connections would be expected to be realized through the middle longitudinal fascicle and the extreme capsule, respectively (Friederici, 2011; Saur et al., 2008). Indeed, previous functional connectivity analyses have reported interactions of the left ATL with left posterior temporal regions as well as left inferior frontal regions during sentence comprehension, with the middle longitudinal fascicle and the extreme capsule identified as the most likely pathways for these interactions, respectively (Saur et al., 2010). Although the current study did not involve any analysis of structural connectivity measures, it is conceivable that the functional connectivity found here, was also realized through the pathways found by Sauer and colleagues (Saur et al., 2008, 2010). Thus, the current results provide further evidence for the pathways predicted by the dual stream model (Hickok & Poeppel, 2007) and their involvement in sentence processing.

5.2 Relationship between brain activity and verbal ability

The second empirical chapter of the thesis investigated sentence processing and phonological processing, looking at individual differences in neural responses related to verbal ability. For auditory sentence comprehension as well as phonological processing in repetition, higher verbal ability was associated with increased activity in brain areas engaged by the respective language process on the group level (i.e., the left ATL for auditory sentence comprehension and the left IFG/precentral gyrus for phonological processing). In line with previous research (Van Ettinger-Veenstra, McAllister, Lundberg, Karlsson, & Engström, 2016), this was interpreted as deeper processing of language stimuli in individuals with higher verbal ability.

The direction of a potential causality in the positive relationship between verbal ability and activity can of course not be determined based on correlational data. On the one hand, it is possible that higher verbal ability increases neural responses triggered by language stimuli or situations that involve language processing (Prat, Mason, & Just, 2011). On the other hand, it is possible that higher neural activity during language processing increases performance (Prat & Just, 2010). For natural language processing, increased performance would manifest itself in the form of deeper processing. For active language tasks, on the other hand, increased performance would result in higher scores, for example on verbal ability measurements, explaining positive correlations between activity and verbal ability. These two explanations are not mutually exclusive and could ultimately mean that ability (expressed as behavioral performance) and activity could be viewed as two sides of the same coin, with performance merely being the behavioral equivalent of brain activity and brain activity merely being the neural equivalent of behavioral performance.

The underlying mechanisms of the relationship between verbal ability and brain activity are still unclear. However, research on the neural correlates of learning a foreign (or artificial) language could provide some insight. In contrast to learning a native language during childhood, learning a foreign or artificial language lends itself for the investigation of neural changes associated with language exposure or practice independent of age-related brain maturation and cognitive development in other domains. Learning an artificial language has been shown to increase activity in language-related brain areas such as the left angular gyrus and left inferior frontal gyrus (Kepinska, de Rover, Caspers, & Schiller, 2017; Opitz & Friederici, 2003). Furthermore, pre- versus post-practice comparisons have associated language learning with increases of grey matter and white matter in brain areas associated with language processing (Ilg et al., 2008; Mårtensson et al., 2012; Schlegel, Rudelson, & Peter, 2012; Stein et al., 2012), with evidence of increased activity in these areas after practice (Ilg et al., 2008). Moreover, individual advances in proficiency after practice showed positive relationships with activity (Kepinska et al., 2016) and with grey matter and white matter increases (Mårtensson et al., 2012; Mechelli et al., 2004; Schlegel et al., 2012). These findings indicate that increases in language proficiency result in larger, stronger, and more active cortical networks associated with language processing.

Although evidence is sparse, positive relationships between grey matter density and vocabulary size in one's native language (Lee et al., 2007) suggest that the principles found for foreign language proficiency might also hold true for verbal ability in one's native language. This would mean that "practice" in one's native language, for example in the form of greater exposure (e.g., time spent reading), could result in larger and stronger cortical language processing networks in individuals with more extensive exposure, leading to increased activations during language processing in those individuals. At the same time, measures such as reading frequency have been shown to be positively related to aspects of verbal ability (Cain, & Oakhill, 2011; Braze, Tabor, Shankweiler, & Mencl, 2007;

Sénéchal, Pagan, Lever, & Ouellette, 2008; Stanovich, West, & Harrison, 1995), which would account for positive correlations between verbal ability and brain activity, as found in the current study and others (e.g., Prat et al., 2011; Van Ettinger-Veenstra et al., 2016). Furthermore, it is possible that increased activity in language-related brain areas has a direct positive effect on performance, leading to higher scores in ability measurements.

Previous studies on the relationship between verbal ability and brain activity have also found negative correlations (e.g., Buchweitz, Mason, Tomitch, & Just, 2009; Van Ettinger-Veenstra, Ragnehed, McAllister, Lundberg, & Engström, 2012) that cannot be explained by the mechanisms discussed above. However, negative relationships between ability and brain activity have previously been explained with neural efficiency, that is, performing a cognitive task equally well (or better) with reduced effort and fewer cognitive resources (Prat et al., 2011; Prat, Mason, & Just, 2012). A review on the relationship between ability and brain activity in different cognitive domains has concluded that the principle of neural efficiency applies to fluid aspects of intelligence or task performance, that is, domain-general cognitive processes (Neubauer & Fink, 2009). In contrast, activity associated with domain-specific processes and brain areas was hypothesized to increase with increasing ability, in line with studies described above. This dichotomy might explain the mix of positive and negative relationships between verbal ability and brain activity in previous studies (e.g., Buchweitz et al., 2009; van Ettinger-Veenstra et al., 2012). These studies measured brain activity during language tasks that required linguistic as well as domain-general cognitive processes (e.g., sentence reading which taxes semantic and syntactic processing, and working memory manipulations or sentence judgements which tax general cognitive demands). While linguistic processing would be expected to show positive correlations with ability, domain-general aspects of the paradigm would be expected to show negative correlations with ability. In contrast, the fMRI paradigm used in the current study focused on stimulus-driven linguistic processing with minimal domain-general demands, maybe explaining the consistent positive relationships between verbal ability and activity in brain areas associated with language processing. Future studies that manipulate linguistic and non-linguistic task demands separately, might provide answers to this proposition.

5.3 Brain lateralization in language processing

The third empirical chapter of this thesis further investigated the relationship between verbal ability and brain activity by particularly focusing on lateralization in activity. While left-lateralized brain activity during language processing tasks is a very common finding (Vigneau et al., 2006; 2011), potential differences in the degree of lateralization for different language processes or modalities are often ignored when "language lateralization" is discussed as a unitary concept (Bishop, 2013). The results presented in the current thesis revealed significant differences in the degree of left-lateralization for different language processes, demonstrating the importance of taking into account the multidimensionality of language processing when assessing language lateralization.

Brain lateralization as assessed with fMRI showed concordance with behavioral measurements of language lateralization when the process-specificity of laterality was considered. That is, LIs derived from a dichotic listening and a visual half-field task were only correlated with fMRI LIs of those language processes that were most similar to the processes measured by the two behavioral tasks, respectively (i.e., phonological processing for dichotic listening and reading for the visual half-field task). This specificity further stresses the importance of taking into account different aspects of language lateralization and confirms that different language tasks tap into different "laterality modules" that would not necessarily be expected to be related (Hugdahl, 1995).

Lateralization in brain activity was also positively related to verbal ability. The direction of a potential causality in the relationship is impossible to determine based on the current data. Relationships between verbal ability and language lateralization have usually been discussed in the context of lateralization being adaptive and benefiting task performance (e.g., Chiarello, Welcome, Halderman, & Leonard, 2009; Gotts, Jo, Wallace, Saad, Cox, & Martin, 2013; Hirnstein, Hausmann, & Güntürkün, 2008), a concept that has not always found empirical support (Knecht et al., 2001; Powell, Kemp, & García-Finaña, 2012). The role of lateralization as an effector rather than an effect might have been facilitated by evidence of leftward structural asymmetries in language-related brain areas which are already present shortly after or even before birth (Dubois, Hertz-Pannier, Cachia, Mangin, Le Bihan, & Dehaene-Lambertz, 2008; Kasprian et al., 2010; Witelson & Pallie, 1973). However, recent propositions have also considered the opposite direction of causality, with verbal ability affecting lateralization (Bishop, 2013). The author has described a neuroplasticity model of brain lateralization in which increasing left-lateralization for language processing with children's age (Everts et al., 2009; Holland, Plante, Weber, Byars, Strawsburg, Schmithorst, & Ball, 2001; Lidzba, Schwilling, Grodd, Krägeloh-Mann, & Wilke, 2011) does not purely reflect a genetically determined brain maturation process. Instead, the neuroplasticity model proposes lateralization to be influenced by experience. Increasing exposure to and use of language during childhood is hypothesized to lead to increased functional lateralization of language processing through greater use of the left-hemispheric cortical networks involved. The two accounts (i.e., lateralization affecting ability and ability affecting lateralization) are not mutually exclusive. Instead, there might be a predisposition for a left-lateralized organization of language processing, for example because of structural asymmetries in the brain areas involved, which is strengthened through language use. Individual differences in lateralization could then arise due to genetic predispositions for strong (structural) lateralization and due to more extensive usage of language-related brain areas in some individuals (e.g., time spent reading), explaining positive correlations between lateralization and verbal ability. The findings presented in the second empirical chapter of this thesis did indeed show an increased use of left-hemisphere language networks in higher ability individuals, suggesting that this might be a mechanism that could explain the positive relationship between verbal ability and lateralization.

5.4 The role of the left IFG in language processing

Overall, the results of the current thesis confirmed numerous previous neuroimaging studies (Price, 2010; 2012; Vigneau et al., 2006) and prominent models of language processing, such as the dual stream model (Hickok & Poeppel, 2007), particularly with regard to the localization of different language functions in the brain. In contrast to previous studies, however, the current data set allowed for the systematic investigation and comparison of different language processes and modalities within participants.

One of the most obvious differences between the results of the current study and many other language studies is the limited involvement of the left IFG for most language processes and modalities. Historically, the focus on the left IFG as one of the major language processing areas in the brain has resulted from its dominant role in speech production (Broca, 1861). While the distinction between speech production and speech perception has proven to be too simplistic, the involvement of the left IFG in phonological processing, during production as well as perception, has been confirmed in numerous neuroimaging studies (Vigneau et al., 2006). The results of the current study are fully in line with these findings, showing left IFG activations for phonological processing in all three modalities. However, previous language studies have also found extensive activations in the left IFG for lexical-semantic and sentence processing, investigated in different task contexts, such as synonym judgements or sentence reading (e.g., Devlin, Matthews, & Rushworth, 2003; Fiebach, Schlesewsky, Lohman, Von Cramon, & Friederici, 2005; Gitelman, Nobre, Sonty, Parrish, & Mesulam, 2005). In contrast, semantic and sentence processing in the context of passive tasks (e.g., passive listening or reading), keeping non-linguistic cognitive demands to a minimum, has been shown to result in activations primarily located in the left temporal lobe with minimal or no IFG involvement (e.g., Brennan et al., 2012; Hagoort, Indefrey, Brown, Herzog, Steinmetz, & Seitz, 1999; Humphries et al., 2006; Vandenberghe et al., 2002). Indeed, direct comparisons of language processing under active versus passive task conditions have resulted in left IFG activations (e.g., Noesselt, Shah, & Jäncke, 2003; Plante, Creusere, & Sabin, 2002; Wright, Randall, Marslen-Wilson,

& Tyler, 2011). Thus, in the context of studies using similar paradigms as the one in the current thesis, the lack of or limited involvement of the left IFG in our data is not surprising. Together, these findings suggest that non-linguistic task demands and the active manipulation of language stimuli in some fMRI language paradigms drive IFG activity, rather than the linguistic processes involved. In agreement with this, it has been suggested that the focus of activations for language processing is not primarily determined by the linguistic aspect (i.e., phonology, semantics, syntax), but rather by the mode of processing or type of operation that is performed on the language stimuli (Ben Shalom & Poeppel, 2008). For example, memorizing and retrieving linguistic information, as required in passive listening and reading, was proposed to engage the temporal lobe, with superior temporal regions for phonological information and more inferior temporal for semantic information. On the other hand, the frontal lobe was hypothesized to be engaged in synthesizing operations, i.e., creating relations between linguistic elements. Again, these operations can be performed on different linguistic levels, such as syntactic (e.g., combining single words according to grammatical principles), semantic (e.g., conceptual comparisons in abstract/ concrete judgements), or phonological (e.g., comparisons of elements in phoneme detection or discrimination tasks).

The role of the frontal lobe in creating relations between single elements has also been highlighted for other cognitive domains (Embrick & Poeppel, 2006; Fadiga, Craighero, & D’Ausilio, 2009; Koechlin & Jubault, 2006; Koelsch, 2006; Müller, Kleinhans, Pierce, Kemmotsu, & Courchesne, 2002; Patel, 2003). Taking an even broader approach than the linguistic one adopted by Ben Shalom and Poeppel (2008), these authors have proposed that the IFG is specialized in building (hierarchical) structures, independent of any modality or cognitive domain. Based on the IFG’s involvement in a great variety of non-linguistic cognitive functions, such as musical perception (Levitin & Menon, 2003; Maess, Koelsch, Gunter, & Friederici, 2001), mathematical operations (Kong, Wang, Kwong, Vangel, Chua, & Gollub, 2005; Tang, Ward, & Butterworth, 2008), or action observation and planning (Decety et al., 1997; Johnson-Frey, Maloof, Newman-Norlund, Farrer, Inati, & Grafton, 2003; Molnar-Szakacs, Iacoboni, Koski, & Mazziotta, 2004), it was argued that all of these domains involve sequential processing and concatenation of single elements (e.g., words, tones, numbers, actions). The IFG's specialization in sequential processing has been speculated to arise from its proximity to the (pre-)motor cortex which engages in the planning and execution of action sequences (Fadiga et al., 2009; Müller & Basho, 2004).

The organization of brain areas independently of cognitive domains and rather according to shared processing principles, is likely to be a general mechanism of brain functioning, valid for other regions of the brain as well. For example, the temporal lobe, to which Ben Shalom and Poeppel (2008) ascribed a role in operations associated with memorizing and retrieving linguistic information, is also active when retrieving representations of non-linguistic environmental sounds (Lewis, Wightman, Brefczynski, Phinney, Binder, & DeYoe, 2004; Maeder et al., 2001), voices (Nakamura et al., 2001), faces (Gorno-Tempini & Price, 2001; Leveroni, Seidenberg, Mayer, Mead, Binder, & Rao, 2000), and places (Gorno-Tempini & Price, 2001). The description of brain areas as multifunctional regions contributing to a variety of different domains, instead of being a "language area", is in contrast to the modular view of early neuropsychological work (e.g., Broca's area for language production) and demonstrates the significant contribution of functional neuroimaging to the field.

5.5 Implications of paradigm characteristics in clinical language assessments

When using fMRI to localize cognitive functions, such as language processing, in the brain, the use of passive, stimulus-driven paradigms can be advantageous. In comparison to active, task-driven paradigms, they reflect linguistic processing to a greater degree while keeping domain-general cognitive processes at a minimum. The processing mode in passive paradigms (e.g., passively listening or reading) is also more closely related to natural language processing in everyday communication than is the case for experimental tasks like synonym judgements or rhyme generation. Ecological validity is not only important for research purposes but also in clinical settings, when assessing patients' language processing abilities and the brain areas involved. Furthermore, low-effort passive fMRI paradigms allow even patients with language impairments (or other cognitive deficits) to perform the tasks and will therefore result in more reliable activations (Bookheimer, 2007; Tie et al., 2015). In contrast, active paradigms rely on the patients' ability to understand potentially complicated task instructions and perform complex tasks involving a range of cognitive (and motor) processes, making activations a lot more dependent on individual performance on the task. However, in patients with tumor- or lesion-related language impairments, task performance is not only affected by stable interindividual differences in verbal ability, but also by temporary tumor-/lesion-induced changes in ability. Thus, brain activity for performance-focused paradigms might reflect transient impairment-induced changes in neural responses to language processing, which would not be representative of the patient's normal brain functioning. In contrast, passive language processing paradigms measure neural responses to basic, natural language processing which is more likely to be achievable for patients, and activations are therefore less vulnerable to temporary impairments.

5.6 Implications of the relationship between verbal ability and brain activity

The increasing evidence for variations in extent and intensity of brain activations during language processing related to individual differences in verbal ability might also be an important consideration for clinical assessments because they are, by their nature, conducted on the individual's level. The findings on relationships between verbal ability and brain activity could have implications that are generalizable to cognitive domains other than language. The underlying mechanisms by which verbal ability is linked to the extent, intensity and lateralization of brain activity likely reflect general principles of brain organization and functioning. For example, increases in grey and white matter and a shifting focus of activity from domain-general frontal brain areas to process-specific posterior areas with practice and increasing ability, have been found in a variety of domains, such as music and motor functions (Draganski, Gaser, Busch, Schuierer, Bogdahn, & May, 2004; Fleming, Weil, Nagy, Dolan, & Rees, 2010; Hyde et al., 2009; Shadmehr & Holcomb, 1997). Furthermore, positive relationships between ability and brain activity in process-specific brain areas (e.g., auditory cortex for musical ability) have been shown for experts in different fields (Neumann, Lotze, & Eickhoff, 2016). Likewise, the positive relationship between ability and brain lateralization appears not to be restricted to the language domain. For spatial processing, which engages the right hemisphere relatively more than the left in the majority of people (e.g., Fink, Marshall, Weiss, & Zilles, 2001; Longo, Trippier, Vagnoni, & Lourenco, 2015; Shulman et al., 2010), higher ability has been associated with increased right-lateralization (Everts et al., 2009; Unterrainer, Wranek, Staffen, Gruber, & Ladurner, 2000), thus obeying the same principle as the relationship between verbal ability and left-lateralization.

Research on the relationship between verbal ability and brain activity might also be relevant with regard to language and literacy impairments. Dyslexia, for example, has repeatedly been associated with grey matter reductions (Linkersdörfer, Lonnemann, Lindberg, Hasselhorn, & Fiebach, 2012; Richlan, Kronbichler, & Wimmer, 2013) and white matter reductions (Deutsch, Dougherty, Bammer, Siok, Gabrieli, & Wandell, 2005; Klingberg et al., 2000; Rimrodt, Peterson, Denckla, Kaufmann, & Cutting, 2010) in brain areas associated with language processing, compared to non-impaired readers. Dyslexics also show reduced activity in these brain areas (Linkersdörfer et al., 2012; Richlan, Kronbichler, & Wimmer, 2009) and reduced functional connectivity within the cortical language network (Finn et al., 2014; van der Mark et al., 2011). In addition, typical leftward structural and functional asymmetries in the language network are less pronounced in dyslexics (Illingworth & Bishop, 2009; Maisog, Einbinder, Flowers, Turkeltaub, & Eden, 2008). All of these findings mirror the neural differences found between subjects with lower versus higher ability, and comparisons before and after practice in language and other cognitive domains, as described above. The similarities in the results raise the question of whether diagnosable language/literacy impairments can be viewed as the extreme end of an ability spectrum. If this is the case, research into the relationship between verbal ability and brain activity could have important implications for prevention and training opportunities regarding these impairments.

5.7 Limitations of the thesis

A general limitation of the current study is the relatively small sample size (n=22). Due to the extensive resource requirements imposed by fMRI studies in particular, samples of around twenty or fewer subjects are very common in neuroimaging research (Carp, 2012). However, the appropriateness of sample sizes in fMRI studies and potential risks associated with small samples have been a matter of extensive debate in recent years (Carp, 2012; Cremers, Wagner, & Yarkoni, 2017; David et al., 2013; Forstmeier, Wagenmakers, & Parker, 2017).

In short, there are two main risks associated with drawing conclusions based on results from an insufficiently large sample. First, a lack of a significant effect is more likely to be caused by a lack of sufficient statistical power than in studies with larger sample sizes. Consequently, it is difficult to draw conclusions about the absence of an effect. Second, extreme values of single subjects are less likely to be balanced out across a small sample, skewing the sample mean away from the population mean. Therefore, results might be influenced by characteristics that are specific to the sample, leading to spurious effects that are not representative of the population that one aims to draw conclusions about. The first problem can result in false negative findings (type II errors), whereas the second problem can result in false positive findings (type I errors).

Estimating the ideal or sufficient number of subjects in a power calculation is difficult in the case of fMRI studies because it does not only depend on the effect size that one aims to measure but also on the scanning parameters, thus requiring pilot data collected with the same setup (Poldrack, Mumford, & Nichols, 2011; Suckling et al., 2014). The large number of parameters affecting statistical power in fMRI studies might also explain the varying results of studies that have investigated the appropriateness of fMRI sample sizes. While some authors have argued that typical sample sizes of approximately twenty subjects have insufficient power and can lead to unreplicable results (Carp, 2012; Cremers et al., 2017), other studies have found the opposite (Desmond & Glover, 2002; Hayasaka, Peiffer, Hugenschmidt, & Laurienti, 2007; Seghier, Lazeyras, Pegna, Annoni, & Khateb, 2007). Yet another study found poor statistical power for a sample of twenty subjects as measured by false negative rates but not false positive rates (Murphy & Garavan, 2004). That is, voxels that were active in a "gold standard" map based on a large sample were often not significantly activated in the sample of n=20. However, activations found in n=20 were likely to be present in the gold standard, with a high degree of overlap in the activations' centres of mass.

These findings should be borne in mind when interpreting the results of the current study since it is possible that the relatively small sample resulted in occasional false positive or false negative findings. For example, contrary to our hypothesis, there was no significant difference in brain activity during word and pseudoword processing in the listening modality despite obvious differences between the two stimulus types with regard to semantic content. This finding is consistent with results from a passive listening task with the same types of stimuli in a sample of similar size (n=28) (Binder et al., 2000). Binder et al. suggested that pseudowords activate lexical representations to a certain degree due to common processing steps on the phonological level. Hence, the effect size of such a comparison might be relatively small and would require a large sample to be detected. The absence of a significant effect in the current study might then have to be ascribed to a lack of statistical power rather than a real absence of difference between the clearly distinct stimulus types.

On the other hand, the current study revealed activations in brain areas that were not expected and cannot easily be explained based on prior research. While those findings were reported for reasons of completeness, it was clearly stated that any post-hoc explanations were speculative and will need further research.

It should be noted that sample size issues can be of particular relevance when studying relationships between neuroimaging data and behavioural data, with poor statistical power for small correlations that are distributed across a large set of brain regions (Cremers et al., 2017). The inconsistencies in the relationships between verbal ability and brain lateralization found in chapter 4 might be an example for such a scenario and should be interpreted cautiously.

Despite speculations about occasional false negative or false positive findings in the current study, it should be noted that the majority of results were highly reliable with respect to within-study comparisons (e.g. activations were consistent across modalities, activity relationships with verbal ability were consistent across ability measures) as well as with respect to comparisons with previous studies (as discussed in the empirical chapters). Nevertheless, the small sample size should be borne in mind when interpreting the more novel results of the study, such as relationships between brain activity and verbal ability. Independent replications and meta-analyses will be needed to confirm the results or reveal any potential spurious effects of single small-sample studies (Forstmeier et al., 2017; Lieberman & Cunningham, 2017).

5.8 Conclusion

In the current Ph.D. project, a comprehensive fMRI paradigm for the localization of different language functions in the brain was developed and validated in healthy subjects. The passive, undemanding nature of the paradigm, along with its focus on basic, natural language processing, makes it a promising tool to evaluate in the preoperative mapping of language functions. Furthermore, as this paradigm involves minimal non-linguistic task demands, the results obtained in the current study highlight the underestimation of task effects in parts of the existing literature (Hickok & Poeppel, 2007). For example, the involvement of the left IFG in semantic and sentence processing seems to vary with task requirements and operations performed on (language) stimuli, with limited IFG activations for passive, natural language comprehension. Thus, passive language processing paradigms, such as the one presented in the current thesis, can provide a valuable contribution when localizing language functions in the brain. Moreover, minimizing non-linguistic task effects on language activations in the current study also allowed for the systematic comparison of different language processes and modalities, for example with respect to lateralization of brain activity. Avoiding confounding effects of task-specific cognitive demands that occurred in previous studies, we showed that brain lateralization during language processing is modality-independent but process-specific, with the degree of left-lateralization as well as relationships with behavioral laterality measures and verbal ability being highly dependent on the particular language process under investigation. This process-specificity might explain some of the inconsistencies in previous studies and demonstrates that language lateralization should not be treated as a unitary concept (Bishop, 2013). Finally, the activations obtained with the current passive, linguistic paradigm showed consistent and strong positive correlations with verbal ability, a sharp contrast to the highly mixed results from previous studies that confounded linguistic and non-linguistic task demands when assessing language-related brain activity. Altogether, the results of the current thesis emphasize the need to consider both, task effects and different language processes in the investigation of the neural correlates of language processing.

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