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The relation between neurofunctional and neurostructural determinants of phonological processing in pre-readers

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ABSTRACT

Phonological processing skills are known as the most robust cognitive predictor of reading ability. Therefore, the neural determinants of phonological processing have been extensively investigated by means of either neurofunctional or neurostructural techniques. However, to fully understand how the brain represents and processes phonological information, there is need for studies that combine both methods. The present study applies such a multimodal approach with the aim of investigating the pre-reading relation between neural measures of auditory temporal processing, white matter properties of the reading network and phonological processing skills. We administered auditory steady-state responses, diffusion-weighted MRI scans and phonological awareness tasks in 59 pre-readers. Our results demonstrate that a stronger rightward lateralization of syllable-rate (4 Hz) processing coheres with higher fractional anisotropy in the left fronto-temporoparietal arcuate fasciculus. Both neural features each in turn relate to better phonological processing skills. As such, the current study provides novel evidence for the existence of a pre-reading relation between functional measures of syllable-rate processing, structural organization of the arcuate fasciculus and cognitive precursors of reading development. Moreover, our findings demonstrate the value of combining different neural techniques to gain insight in the underlying neural systems for reading (dis)ability.

1. Introduction

The cognitive precursors of reading have been extensively investigated over the past decades. Amongst other pre-reading factors, phonological processing skills in particular demonstrate to be closely related to later reading development. Phonological processing skills include a child's ability to access, reflect upon and manipulate the sound structure of spoken language. Traditionally, phonological processing skills are quantified by means of three measurable subskills, i.e., phonological awareness, rapid automatized naming and verbal short-term memory (Wagner and Torgesen, 1987). Each of these subskills has to some extent been linked to reading (e.g., Castles and Coltheart, 2004; Norton and Wolf, 2012; Savage et al., 2007), although the strongest predictive relations in early stages of reading development are generally found with measures of phonological awareness (Boets et al., 2010; Dandache et al., 2014; Hulme and Snowling, 2013; Vaessen and Blomert, 2010; Ziegler et al., 2010). The importance of phonological processing for reading is also evident from studies in developmental dyslexia, a specific learning disability characterized by severe and persistent difficulties with reading and / or spelling (Peterson and Pennington, 2012). Indeed, children with dyslexia exhibit difficulties with cognitive tasks involving phonological processing skills, already prior to the onset of reading acquisition (e.g., Boets et al., 2010; Elbro et al., 1998; Pennington and Lefly, 2001; Puolakanaho et al., 2004; Snowling et al., 2003).

A common feature of phonological processing skills is that they rely on phonological representations, i.e., mental representations of the phonological structure of spoken language. Therefore, the relation

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between phonological processing skills and reading is presumed to be determined by the quality of the underlying phonological representations (Fowler, 1991; Goswami, 2000; Swan and Goswami, 1997). Along the same lines, it has been suggested that dyslexic's phonological processing problems are rooted in a deficiency in (the access to) these phonological representations (Boada and Pennington, 2006; Boets et al., 2013; Ramus and Szenkovits, 2008; Vandermosten et al., 2020; Vellutino et al., 2004).

Given the importance of phonological processing skills for reading, more recent studies have strived to identify the neural determinants of phonological representations. One point of view is that the construction of phonological representations depends to a large extent on the temporal precision with which the auditory system processes speech. In particular, the ability to extract slowly varying acoustic cues fluctuating between 4 Hz ($\pm$250 ms) and 20 Hz ($\pm$50 ms) is considered to be important because these temporal modulations correspond to the rates at which important phonological units, syllables and phonemes respectively, occur in speech (Chait et al., 2015; Drullman et al., 1994; Greenberg et al., 2003; Rimmele et al., 2015). Functionally, these low-level acoustic processes are presumed to be sustained by specific cortical oscillation bands that synchronize their activity to temporal information in speech (Buzsáki and Draguhn, 2004; Giraud et al., 2007; Luo and Poeppel, 2012). This process allows the incoming speech signal to be processed at multiple timescales. More specifically, it is suggested that delta- (1–3 Hz) and / or theta-range (4–8 Hz) synchronization networks contribute to the neural encoding of syllable-rate information, while beta- (14–30 Hz) and / or gamma-range (30–60 Hz) synchronization networks are presumed to determine phoneme-rate representations (Goswami, 2011; Luo and Poeppel, 2012; Peelle and Davis, 2012).

An interesting characteristic of these auditory synchronization networks is their hemispheric specialization. Although there is an ongoing debate as to which acoustical features drive the observed hemispheric differences (see Scott and McGettigan (2013) for a critical review), it is evident that hemispheric specializations during auditory temporal processing are essential for higher cognitive functions. The latter is endorsed by studies that demonstrate a relation between hemispheric lateralization of neural synchronization and phonological or reading skills. Hereby, a stronger rightward lateralization of cortical activity in response to syllable-rate information is found to be positively correlated with phonological processing skills (Abrams et al., 2009; Molinaro et al., 2016; Power et al., 2016) and reading (Lizarazu et al., 2015; Soltész et al., 2013), both in children and adults. Accordingly, in dyslexia, deficits with respect to delta-theta synchronization appear to be situated primarily in the right hemisphere (Cutini et al., 2016; Di Liberto et al., 2018; Hämäläinen et al., 2012; Molinaro et al., 2016) or in reduced rightward lateralization (Abrams et al., 2009; Lizarazu et al., 2015). Regarding neural activity in response to phoneme-rate information, stronger lateralization towards the left hemisphere appears to correlate positively with phonological skills in adults (Lehongre et al., 2011; Lizarazu et al., 2015; Poelmans et al., 2012a). Abnormalities in dyslexia have also been reported, including reduced beta-gamma synchronization in the left hemisphere (Lehongre et al., 2011; Poelmans et al., 2012a), enhanced beta-gamma synchronization in the right hemisphere (Lehongre et al., 2011; Lizarazu et al., 2015) and bilaterally enhanced beta synchronization (De Vos et al., 2017a, 2017b).

Another point of view is that the access to, rather than the quality of, phonological representations is of crucial importance (Boets et al., 2013). To this end, white matter pathways connecting distant regions of the reading network have been studied with particular interest (see Wandell and Yeatman (2013) for a review). White matter tracts can be examined in vivo by means of diffusion-weighted magnetic resonance imaging (DW-MRI) and are most frequently quantified by the fractional anisotropy index. Fractional anisotropy is an indirect measure of white matter organization characterized by microstructural and macrostructural properties (Beaulieu 2009).

The white matter pathway sustaining access to the region considered to host phonological representations, is a segment of the arcuate fasciculus (AF), a left-lateralized tract that connects inferior frontal to temporoparietal regions such as the planum temporale (Price, 2012), referred to as the AF$_{FTP}$. Indeed, relations have been reported between fractional anisotropy of the left arcuate fasciculus, both in the AF$_{FTP}$ and the temporoparietal (AF$_{TP}$) segment and phonological processing in adults (Vandermosten et al., 2012) and in school-aged children and pre-readers (Dodson et al., 2018; Saygin et al., 2013; Travis et al., 2017; Vanderauwera et al., 2015; Vandermosten et al., 2015; Wang et al., 2016; Yeatman et al., 2011). Moreover, fractional anisotropy of different segments of the left arcuate fasciculus is shown to be predictive of reading development in children (Borchers et al., 2019; Gullick and Booth, 2015) and decreased fractional anisotropy in this pathway has been related to dyslexia (Rauschecker et al., 2009; Rimrodt et al., 2010; Vandermosten et al., 2012) even prior to reading onset (Vanderauwera et al., 2017). With regard to hemispheric specialization, fractional anisotropy of the AF$_{FTP}$ and the AF$_{TP}$ demonstrates to be left lateralized in typical readers and pre-readers without a family risk for dyslexia, while symmetrical lateralization is found in adults with dyslexia (Vandermosten et al., 2013) and rightward lateralization in pre-readers with a family risk for dyslexia (Wang et al., 2016).

Altogether, both functional and structural neural components have been associated with phonological processing and reading. Neurofunctional components include low-level acoustic analyses of temporal features, sustained by synchronized oscillations in auditory regions, and neurostructural components include a network of frontal and temporoparietal regions, connected by the arcuate fasciculus. Interestingly, both neural components occur in anatomical proximity, since the fibers that compose the arcuate fasciculus depart from the posterior part of the superior temporal gyrus, close to the regions where auditory temporal processing occurs. In addition, both neural components are characterized by hemispheric differences, suggesting that hemispheric specializations are a common and essential feature of the neural system supporting phonological processing. Furthermore, abnormalities in both components have been found in individuals with dyslexia.

Based on these similarities, a link between acoustic temporal analyses and white matter connections sustaining phonological processes is often assumed, but rarely explicitly and systematically investigated. Vandermosten et al. (2013) found that interhemispheric coherence to phoneme-rate modulations relates to white matter lateralization in the posterior superior temporal gyrus and white matter organization in the splenium of the corpus callosum. Additionally, Molinaro et al. (2016) provided evidence for a relation between atypical auditory sampling and subsequent phonological processing steps in higher-level areas such as the inferior frontal gyrus. Although no neuroanatomical measures were assessed, the arcuate fasciculus was suggested as the anatomical counterpart of this feedforward connection.

The aim of the present study is to examine the relations between auditory processing of temporal information and white matter properties of the arcuate fasciculus in a group of pre-readers with a wide range of cognitive reading-related skills. We focus on pre-reading stages of development, since learning to read is associated with considerable structural as well as functional changes in the corresponding brain regions (e.g., Brem et al., 2010; Dehaene et al., 2010; see Black et al. (2017) for a review). The following research questions will be addressed:

(1) Is there evidence for a pre-reading "neural system" of functional and structural measures that relate neurophysiological auditory temporal processing to neuroanatomical phonological correlates?
(2) In what way and to what extent does this "neural system" contribute to the prediction of behavioral variance observed in cognitive precursors of reading, such as phonological awareness?

Both research questions will be addressed in terms of neural measures per hemisphere as well as hemispheric lateralization measures.

Table 1
Participant characteristics.

	Mean (SD)	Range
Descriptive variables		
Age pre-reading ASSR (years)	5.1 (0.3)	4.6−5.8
Age pre-reading MRI (years)	6.2 (0.3)	5.7−6.8
Gender (male / female)	37 / 22	
Non-verbal IQ: Coloured Progressive Matrices	110.5 (12.0)	87−131
Cognitive measures		
Last year of kindergarten		
Productive letter knowledge (/16) [a]	0 (1)	0−13
Start of first grade		
Receptive letter knowledge (/16)	10.4 (3.7)	3−16
Productive letter knowledge (/16)	9.7 (4.0)	0−16

[a]Non-normally distributed data, described in terms of median (interquartile range) instead of mean (SD).

2. Materials and methods

This study is part of an ongoing longitudinal research project including the collection of multiple EEG, MRI and behavioral measures in young children at different time points during reading development. In the context of this longitudinal research project, we have formerly reported on pre-reading (Vanvooren et al., 2014; N = 75) and longitudinal EEG data (De Vos et al., 2017a; N = 68), as well as pre-reading (Vanderauwera et al., 2015; Vandermosten et al., 2015; N = 71) and longitudinal DW-MRI data (Vanderauwera et al., 2018, 2017; N = 61). The data presented here pertain to a subsample of children in which we were able to successfully acquire both EEG measurements and MRI scans at the pre-reading stage (N = 59, cf. 2.1).

This study was approved by the Medical Ethics Committee of UZ KU Leuven (Research). Informed consent was obtained from the parents of all participating children included in the study.

2.1. Participants

The original sample consisted of 87 children that were recruited in the course of the second year of kindergarten (Vanvooren et al., 2014). All children were native Dutch speakers with no history of long-term hearing loss, visual problems, brain injury, or neurological disorders. In addition, all participants had a normal non-verbal IQ, verified by means of the Coloured Progressive Matrices (Raven et al., 1984; standardized score ≥ 80) at the time of recruitment.

At the end of the second year of kindergarten (age 4–5 years), EEG measurements were administered in all children. One year later, at the end of the last year of kindergarten (age 5–6 years), 75 children were willing to undergo an MRI scan. EEG data from five children and MRI data from four children were found to be unusable for further processing because of motion artefacts or unsuccessful acquisitions. We also excluded data from nine left handed children based on a score below -40 on the Edinburgh Handedness Inventory (Oldfield, 1971), given that the purpose of the present study is to investigate hemispheric lateralization patterns of the brain regions and connections of the language network. The subsample included in the present study thus consists of 59 children. Participant characteristics are presented in Table 1.

At the time of neural data collection, none of the children received formal reading and writing instructions, as determined by the Flemish government (https://onderwijs.vlaanderen.be/). The lack of substantial reading experience of the children was confirmed by means of a productive letter knowledge task conducted at the start of the last year of kindergarten and a productive and a receptive letter knowledge task conducted at the start of first grade of elementary school. Sixteen frequent Dutch letters were visually presented in each subtest (Boets et al., 2008). The test score was defined as the number of correctly identified letters. As can be deduced from Table 1, the median test score for the productive subtest conducted at the start of the last year of kindergarten was 0 out of 16. The minimum score of 0 was obtained by 41 children and the maximum score of 13 was obtained by two children. None of the children correctly identified all test items. At the start of first grade of elementary school, when grapheme-phoneme coupling is intensively trained, the mean score for the productive subtest was 9.7 out of 16 and the mean score for the receptive subtest was 10.4 out of 16. Only four children correctly identified all test items. Please note that all of the neural measures were conducted prior to the onset of first grade, when letter knowledge was not sufficient to result into reading ability.

Twenty-seven children of the present subsample presented a family risk for dyslexia, meaning that they have at least one first degree relative with a formal dyslexia diagnosis. The remaining 32 children had no family risk for dyslexia. Ten children of the present subsample would retrospectively qualify as dyslexic readers because of severe and persistent literacy difficulties, as evidenced by test scores below the 10th percentile on word reading, pseudo-word reading and / or spelling tasks that were administered at the start of second and third grade (De Vos et al., 2017a, Vanderauwera et al., 2017). Eight out of these children have a family risk for dyslexia. Hence, 30 % of the children with a family risk developed dyslexia themselves, which is in line with the literature (Gilger et al., 1991).
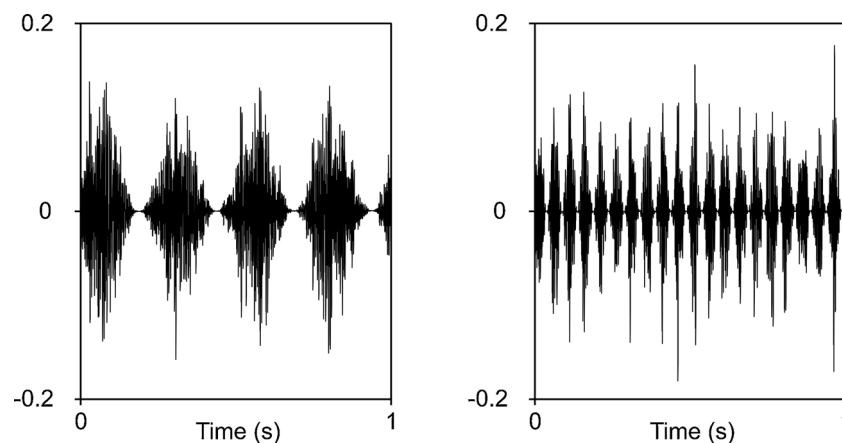

Fig. 1. Time domain representations of a 1 s extract from the ASSR stimuli: A speech-weighted noise carrier wave was 100 % amplitude modulated at 4 Hz syllable rate (left panel) and 20 Hz phoneme rate (right panel).

2.2. Neurophysiological assessments

As a measure for auditory temporal processing, we used auditory steady-state responses (ASSRs). ASSRs are evoked by periodically varying stimuli, typically a carrier wave to which some sort of modulation is applied. The neural response is a complex waveform with the same periodicity as the stimulus, that is, the response reflects the synchronized firing of neurons to the modulation rate (Rickards, 2008). Different modulation rates result in stimulation of different stages of the auditory pathway. It appears that ASSRs elicited by lower modulation rates (< 40 Hz) reflect activity of cortical generators, while ASSRs evoked by higher modulation rates (> 60 Hz) reflect activity from the brainstem (e.g., Herdman et al., 2002; Luke et al., 2017). By carefully choosing the parameters of the stimulus, ASSRs can thus be used to quantify the ability of the auditory cortex to encode the different timescales represented in speech (Miyazaki et al., 2013; Tang et al., 2016a, 2016b).

2.2.1. ASSR acquisition

The stimuli used in the present study consist of a continuous, stationary speech-weighted noise carrier wave, which was 100 % amplitude modulated at approximately 4 Hz and 20 Hz (Fig. 1). The speech-weighted noise carrier wave was adopted from the Leuven Intelligibility Sentence Test (LIST) and has a frequency spectrum that is identical to the long-term average speech spectrum of 730 sentences of a female speaker (van Wieringen and Wouters, 2008v). Modulation rates of ±4 Hz and ±20 Hz were chosen to measure neural synchronization in the auditory cortex to syllable- and phoneme-rate modulations, respectively. Note that the exact modulation frequencies were set at 3.91 Hz and 19.53 Hz in order to prevent electromagnetic effects from affecting ASSR detection. Given that our stimuli share specific acoustic features (spectral as well as temporal) with realistic speech, we presume that they activate the spectrotemporal computations in the superior

temporal gyrus in a way analogous to the early stages of cortical speech processing (Hickok and Poeppel, 2015, 2007). Each stimulus was presented to the right ear at 70 dB SPL through an insert earphone during 10 min (600 s). Right ear stimulation was chosen to allow for comparison with our previous work in adults (Poelmans et al., 2012a; Vandermosten et al., 2013). We do not expect our results to change drastically when using a bilateral stimulation modality, as hemispheric lateralization was found to be similar for right ear and bilateral stimulation (Poelmans et al., 2012b).

EEG recordings were made in a double-walled soundproof booth with a Faraday cage using the BioSemi ActiveTwo system with 64 active Ag/AgCl electrodes mounted in head caps according to the 10−10 electrode system. Recordings were digitized by an A/D box at a sampling rate of 8192 Hz with a gain of 32.25 nV/bit. Electrode offsets were kept between −30 mV and +30 mV. A passive listening paradigm was adopted, whereby participants were instructed to lie down on a bed and watch a soundless movie while auditory stimulation was provided. The implicit nature of this procedure is beneficial when testing young children, as (1) it does not require any response from the participant and (2) it does not necessitate the participant to pay attention to the auditory stimuli. Although the use of a more explicit task based on attentive listening might have resulted in stronger ASSRs, as has previously been observed in adults (Ross et al., 2004), it was not the aim of this study to investigate effects of attentional state. Alertness and movement were continuously monitored by an experienced test leader who was present in the EEG cabin.

2.2.2. ASSR processing

All pre-processing was done in Matlab R2013a. Each 10 min EEG recording was divided into epochs of 1.024 s, resulting in 585 epochs per electrode. We implemented a zero phase high-pass filter with a cut-off frequency of 2 Hz and a slope of 12 dB per octave to remove any DC component in the recordings. The amplitude rejection level for artefact
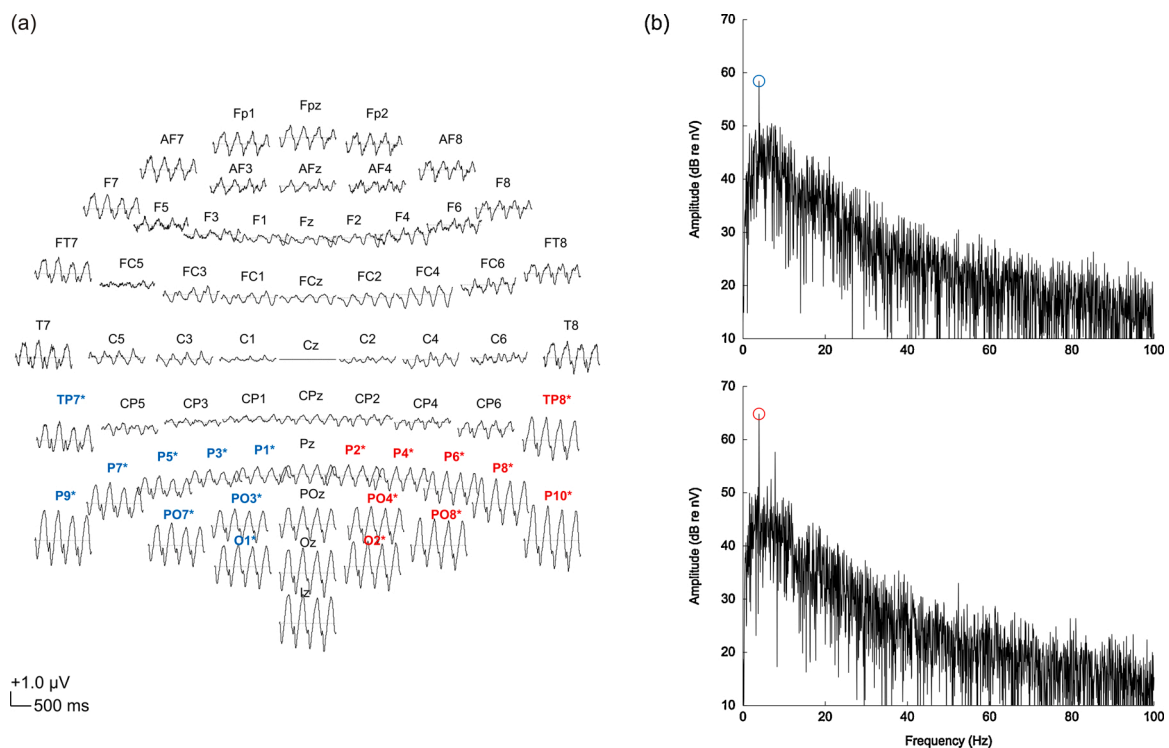

Fig. 2. Characteristics of a 4 Hz ASSR in time and frequency domain: (a) Grand mean averaged response waveforms for all 64 electrodes. Asterisks indicate the pre-selected electrode configuration. (b) FFT spectra of EEG signals recorded over the left and right temporal, parietal and occipital regions for a randomly selected subject after pre-processing. Circles mark the response amplitude, which was converted to dB using a logarithmic transformation with reference to 1 nV for graphical reasons.

rejection was set on an individual basis, until exactly 448 epochs per electrode (~ 77 %) were retained. EEG recordings were considered as too noisy for further analysis if less than 448 epochs were retained at the maximum amplitude rejection level, which was set at 200 μV. All artifact-free epochs were referenced to electrode Cz and clustered into sweeps of 64 consecutive epochs. This resulted in seven sweeps per electrode, which were subsequently averaged into one sweep per electrode. Next, sweeps were averaged across a pre-selected electrode configuration, which was described by Vanvooren et al. (2015, 2014). Nine electrodes in the left hemisphere (TP7, P1, P3, P5, P7, P9, PO3, PO7 and O1) and nine electrodes in the right hemisphere (TP8, P2, P4, P6, P8, P10, PO4, PO8 and O2) were included in the electrode configuration, resulting in the construction of two artificial "channels" representing the averaged time signal recorded over the left and right temporoparietal and occipital regions. A Fast Fourier Transformation (FFT) algorithm was used to convert the time signals of the two artificial channels into a set of complex values that vary with frequency. Finally, the inverse gain of the high-pass filter was added to the spectral power to compensate for the filter attenuation.

The ASSR appears in the FFT spectrum as a peak in the frequency bin corresponding to the modulation frequency f (Fig. 2). We quantified the ASSRs in terms of response amplitude and hemispheric lateralization. The response amplitude (μV) was defined as $\sqrt{P_f}$, that is, the root of the power of the Fourier component in frequency bin f. It provides a measure for the strength of auditory neural synchronization by reflecting the degree to which neural oscillations in the auditory cortex synchronize their activity to the modulation frequency. For results in terms of response amplitudes in an overlapping set of participants, see De Vos et al. (2017a). Hemispheric synchronization asymmetry was determined by means of the laterality index. In accordance with Poelmans et al. (2012b), the laterality index was calculated as follows:

laterality index $_{ASSR}$ = ($\sqrt{P_f}$ right - $\sqrt{P_f}$ left) / ($\sqrt{P_f}$ right + $\sqrt{P_f}$ left)

Values of the laterality index vary between -1 and +1. Negative values indicate a left hemisphere dominance for auditory temporal processing, while positive values indicate a right hemisphere dominance.

2.3. Neuroanatomical assessments

2.3.1. DWI acquisition

Diffusion-weighted images (DWI) were acquired on a 3.0 T MRI scanner (Philips, Best, The Netherlands) using a 32-channel head coil and a single shot EPI with SENSE (parallel) acquisition. Sagittal diffusion slices were obtained using the following parameters: bvalue 1300s/mm^2, repetition time 7600 ms, echo time 65 ms, isotropic voxel size $2.5 \times 2.5 \times 2.5$ mm, 60 non-collinear directions and 6 non-diffusion-weighted images. The scan acquisition time was 10:32 min.
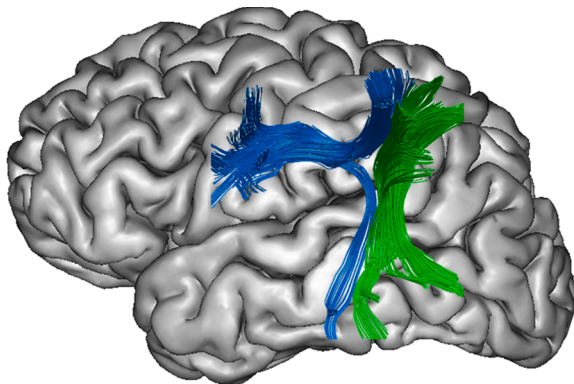

Fig. 3. Left hemispheric tracts of interest: The AF$_{FTP}$, depicted in blue, and the posterior AF$_{TP}$, depicted in green. Right homologues are not presented in the figure, but were also delineated and included in the analyses.

2.3.2. DWI processing

All data were pre-processed using ExploreDTI (version 4.8.3; (Leemans and Jones, 2009). Diffusion images were corrected for eddy current-induced distortions and subject motion. The diffusion tensor model was fitted to the data and whole-brain tractography was conducted using the following parameters: Fractional anisotropy threshold 0.20, maximum turning angle between voxels 40°, step length between calculations 1 mm. TrackVis (http://www.trackvis.org/) was used to perform virtual in vivo dissections of the arcuate fasciculus. Two segments were manually dissected in the left and right hemisphere of each subject (Fig. 3), overarchingly referred to as the arcuate fasciculus (AF) in the current study. The first segment contains fibers that connect the inferior frontal region to posterior temporal and inferior parietal regions, here referred to as the AF$_{FTP}$. The second segment contains fibers that connect posterior temporal and inferior parietal regions, here referred to as the AF$_{TP}$. Both segments of the arcuate fasciculus contain fibers that depart from the superior temporal gyrus, the region where spectrotemporal processing is presumed to take place. We decided to keep the posterior AF$_{TP}$ separate from the AF$_{FTP}$ since tractography atlases are inconsistent in considering this tract as part of the arcuate fasciculus (Catani and Thiebaut de Schotten, 2008) or as a distinct tract (Glasser and Rilling, 2008; Wakana et al., 2004). In order to manually dissect the AF$_{FTP}$ and the AF$_{TP}$, two mandatory passages were defined for each segment on a coronal and an axial slide for the AF$_{FTP}$ and on two axial slices for the AF$_{TP}$, as described by Catani and Thiebaut de Schotten (2008) and Wakana et al. (2007). All manual dissections were performed by one of the first authors, J.V. Inter-rater reliability for white matter segmentations between J.V. and M.V. has been reported in Vandermosten et al. (2015) and was high (> .96). Moreover, intra-rater reliability of J.V. is also high (.98), as reported in Vanderauwera et al. (2017). Tractspecific measurements, quantified by the mean fractional anisotropy index were extracted for statistical analysis. For results in terms of fractional anisotropy in an overlapping set of participants, see Vanderauwera et al. (2017). Here, we additionally determined structural asymmetry in white matter by means of a laterality index. In accordance with Niogi and Mccandliss (2006) and Vandermosten et al. (2013), the laterality index was calculated as follows:

laterality index $_{AF}$ = (FA $_{right}$ - FA $_{left}$) / (FA $_{right}$ + FA $_{left}$)

These laterality indices are interpreted in the same way as described above for ASSRs, that is, negative values represent a leftward lateralization of the arcuate fasciculus, while positive values indicate a rightward lateralization. For each individual, a value for head motion during the MRI scan was calculated as the root mean square (RMS) of the relative motion in all three directions. Relative motion is calculated as the average motion between subsequent volumes. The motion parameters for the participants of the present study have been described by Theys et al. (2014) and indicate that the applied scanning procedure sufficiently avoided excessive subject motion in the scanner. The median RMS of motion for this sample is 0.08 mm (IQR = 0.06 mm). Adding head motion in the scanner as a covariate did not change any of the reported results.

2.4. Cognitive assessments

At the start of last year of kindergarten, phonological awareness was assessed by an end-rhyme and an end-phoneme identification task (de Jong et al., 2000d, adapted by van Otterloo and Regtvoort; Boets et al., 2006). In both tasks, each item consisted of a row of five pictures. The first picture was separated from the other four pictures by a vertical line to indicate the given word and the answer alternatives. The test leader named all items for the child. The child had to select the answer alternative that respectively had the same end-rhyme or end-phoneme as the given word by naming or by pointing to the corresponding picture. Both tests were preceded by two practice items. The test score was calculated

as the number of correctly identified items, with a maximum score of 12 for the end-rhyme task and 10 for the end-phoneme task. To form a composite score, the test scores of both subtests were converted to *z* scores and averaged.

2.5. Statistical analyses

Data were statistically analyzed using IBM SPSS Statistics 24.0 software. Normality of the data was controlled for by means of Shapiro-Wilk tests. There were no univariate or multivariate outliers (Cook's distance < 1, Mahalanobis distance $p > .001$) and there was no collinearity in the data (variance inflation factor (VIF) ≈ 1, tolerance > 0.2). Residuals of variables used in the regression models were normally distributed (normal probability plot) and independent (Durbin-Watson statistic ≈ 2) with no heteroscedasticity (standardized residuals vs. standardized predicted values plot). All analyses were two-tailed ($\alpha = 0.05$).

Prior to the investigation of our research questions, we determined the degree of hemispheric lateralization for 4 Hz and 20 Hz ASSRs and for the AF_{FTP} and posterior A_{FTP} segments by means of a one-sample *t*-test of the laterality index relative to zero ($H_0: \mu = 0$). If the laterality index is found to differ significantly from zero, the value of the laterality index can be interpreted in terms of (leftward or rightward) hemispheric lateralization.

To investigate the relations between neural measures (research question 1), four regression analyses with backward elimination were performed. All models included the neurophysiological measures as predictor variables, i.e., the response amplitudes of the left and right hemispheric 4 Hz and 20 Hz ASSRs. The dependent variables were fractional anisotropy in the left AF_{FTP}, the right AF_{FTP}, the left posterior AF_{TP} and the right posterior AF_{TP}.

To investigate the relations between neural and behavioral measures (research question 2), analyses proceeded in three steps. The first step concerned an investigation of the relation between the ASSR measures and phonological awareness. Therefore, a backward regression analysis was performed, including phonological awareness composite scores as the dependent variable and left and right hemispheric 4 Hz and 20 Hz response amplitudes as predictor variables. In addition, the relation with hemispheric lateralization of 4 Hz and 20 Hz ASSRs was investigated by including the laterality indices as predictor variables instead. The second step aimed at investigating the relation between phonological awareness and fractional anisotropy of the left and right AF_{FTP} and AF_{TP}, by means of two similar backward regression models. In the third step, the relative contribution of neurophysiological and neuroanatomical measures to the behavioral variance in phonological awareness skills was determined. A hierarchical regression analysis was performed with the phonological awareness composite score as the dependent variable. In a first block, the white matter properties for which the previous steps revealed significant relations with phonological awareness were entered. In the second block, neural synchronization measures for which the previous steps revealed significant relations with phonological awareness were added. This sequence was chosen as such, because our neural synchronization measures are considered as novel predictors for pre-reading phonological awareness skills, while there is existing literature in pre-readers regarding the neuroanatomical measures.

For each significant regression model, a table with the model parameters is provided. Beta values (*b*) indicate the contribution of a predictor to the model while the effects of all other predictors are held constant. The standardized beta values (β) hold the same information, but can be interpreted independently of the units of measurement, and so are directly comparable between variables. The associated standard error (SE) for *b* specifies to what extent *b* values would vary across different samples. Based on the SE for *b*, *t*-statistics and *p* values are derived to test whether *b* values differ significantly from zero, that is, to test whether a predictor is making a significant contribution to the model. The 95 % confidence intervals (CI) for *b* aid in the interpretation, by providing the boundaries within which the true value of *b* will fall in

Table 2

Descriptive results. For the whole sample of pre-readers, we present the mean, standard deviation (SD) and range for the neurophysiological responses (ASSR amplitude), the neuroanatomical measures (white matter fractional anisotropy) and cognitive assessments (phonological awareness).

	Mean (SD)	Range
4 Hz ASSR amplitude (µV)		
Left	1.06 (0.55)	0.15−2.54
Right	1.29 (0.55)	0.33−2.76
Laterality index	0.11 *** (0.19)	−0.26 - 0.66
20 Hz ASSR amplitude (µV)		
Left [a]	0.28 (0.24)	0.04−0.85
Right [a]	0.31 (0.25)	0.04−0.96
Laterality index	0.07 * (0.24)	−0.79−0.63
AF_{FTP} fractional anisotropy		
Left	0.47 (0.02)	0.42−0.53
Right	0.44 (0.02)	0.39−0.49
Laterality index	−0.03 *** (0.02)	−0.09−0.02
Posterior AF_{TP} fractional anisotropy		
Left	0.47 (0.02)	0.42−0.51
Right	0.45 (0.02)	0.39−0.49
Laterality index	−0.02 *** (0.02)	−0.07−0.02
Phonological awareness		
End rhyme [a]	9.0 (4.0)	2−12
End phoneme	4.1 (2.4)	0−10
Composite	0.0 (0.8)	−1.8−1.7

* $p < .05$, *** $p < .001$ (one-sample t-tests with $H_0: \mu = 0$).
[a] Non-normally distributed data, described in terms of median (interquartile range) instead of mean (SD).

95 % of the samples. Good models will have small confidence intervals, indicating that the value of *b* in our sample is close to the true value of *b* in the population, and confidence intervals that do not cross zero, indicating that the direction of the relationship between the predictor and the outcome would be the same (either negative of positive) in different samples. In addition to the model parameters, partial correlations between dependent and predictor variables were also examined for each significant regression model.

3. Results

3.1. Descriptive statistics for neural and behavioral measures

Descriptive results from neurophysiological, neuroanatomical and cognitive assessments are presented in Table 2.

For syllable-rate (4 Hz) ASSRs, mean response amplitudes were 1.06 µV in the left hemisphere and 1.29 µV in the right hemisphere. The mean laterality index was equal to 0.11. For phoneme-rate (20 Hz) ASSRs, the median response amplitudes were 0.28 µV and 0.31 µV in the left and right hemisphere, respectively, and the mean laterality index was equal to 0.07. For the AF_{FTP} segment, mean fractional anisotropy indices were 0.47 in the left hemisphere and 0.44 in the right hemisphere. The mean laterality index was equal to -0.03. For the posterior AF_{TP} segment, the mean fractional anisotropy indices were 0.47 and 0.45 in the left and right hemisphere, respectively, and the mean laterality index was equal to -0.02. Note that all neural measures demonstrated significant hemispheric asymmetry, that is, a laterality index that differs significantly from 0. Lateralization towards the right hemisphere was found for both syllable-rate (4 Hz) and phoneme-rate (20 Hz) processing ($t_{(58)} = 4.50$, $p < .001$; $t_{(58)} = 2.31$, $p = .024$), while lateralization towards the left hemisphere was found for fractional anisotropy of the AF_{FTP} and the posterior AF_{TP} segment ($t_{(58)} = -9.84$, $p < .001$; $t_{(58)} = -8.80$, $p < .001$).

For phonological awareness, the median score was 9.0 out of 12 on the end-rhyme task and the mean score was 4.1 out of 10 on the end-phoneme task.

Table 3
Parameters of the regression models describing the relations between neural measures. Significant regression models were found for the left AF_{FTP} segment (top) and for the left posterior AF_{TP} segment (bottom).

AF_{FTP} Left [a]							
	b	SE for b	β	t	p	95 % CI for b	
4 Hz ASSR Left	−0.023	0.008	−.502	−2.748	.008	−0.039	−0.006
4 Hz ASSR Right	0.015	0.008	.322	1.764	.083	−0.002	0.031
Posterior AF_{TP} Left [b]							
	b	SE for b	β	t	p	95 % CI for b	
4 Hz ASSR Left	−0.020	0.007	−.498	−2.720	.009	−0.034	−0.005
4 Hz ASSR Right	0.015	0.007	.362	1.979	.053	0.000	0.029

[a]Predictor variables that were excluded from the model during the backward elimination procedure: 20 Hz ASSR Left ($b = 0.061$, $t = 0.462$, $p = .646$) and 20 Hz ASSR Right ($b = 0.017$, $t = 0.132$, $p = .896$).

[b]Predictor variables that were excluded from the model during the backward elimination procedure: 20 Hz ASSR Left ($b = -0.002$, $t = 0.138$, $p = .891$) and 20 Hz ASSR Right ($b = 0.018$, $t = 0.138$, $p = .891$).

3.2. Relations between neural measures

With the aim of investigating the first research question, we examined the relations between neural measures, i.e., the relations between neural synchronization to syllable- and phoneme-rate information and white matter properties of the arcuate fasciculus. Therefore, four regression analyses with backward elimination were performed. The dependent variables were fractional anisotropy of (1) the left AF_{FTP}, (2) the right AF_{FTP}, (3) the left posterior AF_{TP} and (4) the right posterior AF_{TP} segments. The predictor variables were the same for each of the regression analyses, namely the response amplitudes of left and right hemispheric 4 Hz and 20 Hz ASSRs.

A significant regression model was found for the left AF_{FTP} segment

($F_{(2, 56)} = 3.83$, $p = .028$, $R^2 = .12$), which retained left and right hemispheric 4 Hz ASSRs as predictors (Table 3, top). Partial correlation analyses revealed that white matter properties of the left AF_{FTP} segment correlated negatively with left hemispheric 4 Hz ASSRs ($r = -.34$, $p = .008$), indicating that higher fractional anisotropy in the left AF_{FTP} segment was related to lower left hemispheric 4 Hz ASSRs. The positive correlation with right hemispheric 4 Hz ASSRs did not reach significance ($r = .23$, $p = .083$). A similar regression model was found for the left posterior AF_{TP} segment ($F_{(2, 56)} = 3.70$, $p = .031$, $R^2 = .12$), again retaining left and right hemispheric 4 Hz ASSRs as predictors (Table 3, bottom). Partial correlations confirmed a negative relation with left hemispheric 4 Hz ASSRs ($r = -.34$, $p = .009$), indicating that higher fractional anisotropy in the left AF_{TP} segment was related to lower left
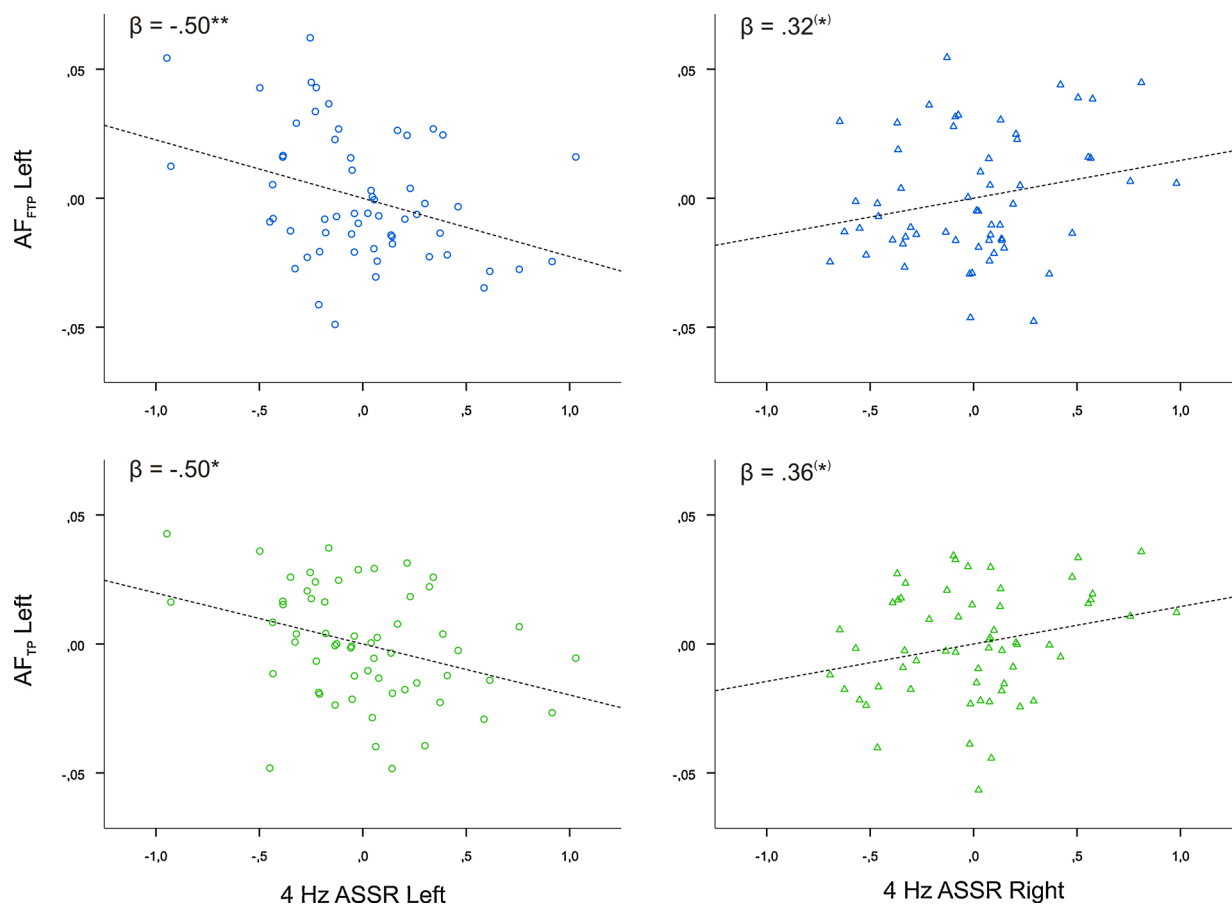

Fig. 4. Relations between neural measures: Partial regression plots depict the relation between neural synchronization to syllable-rate information (4 Hz ASSRs) in the left (○) and right (△) hemisphere and fractional anisotropy of the left AF_{FTP} (blue) and the left AF_{TP} (green) with [(*)]$p < .10$, * $p < .05$, ** $p < .01$. The dotted lines represent the obtained regression equations.

Table 4

Parameters of the regression models describing the relations between neural measures in terms of hemispheric lateralization, i.e., based on the laterality index (LI) of each neural measure. Significant regression models were found for the AF_{FTP} segment (top) and for the posterior AF_{TP} segment (bottom).

AF_{FTP} LI [a]							
	b	SE for b	β	t	p	95 % CI for b	
4 Hz ASSR LI	−0.036	0.016	−.293	−2.311	.024	−0.067	−0.005
Posterior AF_{TP} LI [b]							
	b	SE for b	β	t	p	95 % CI for b	
4 Hz ASSR LI	−0.032	0.014	−.295	−2.328	.024	−0.059	−0.004

[a]Predictor variables that were excluded from the model during the backward elimination procedure: 20 Hz ASSR LI ($b = 0.149$, $t = 1.092$, $p = .280$).
[b]Predictor variables that were excluded from the model during the backward elimination procedure: 20 Hz ASSR LI ($b = 0.120$, $t = 0.880$, $p = .383$).

hemispheric 4 Hz ASSRs. The positive correlation with right hemispheric 4 Hz ASSRs did not reach significance ($r = .26$, $p = .053$). The regression plots for both regression models are depicted in Fig. 4.

We re-investigated the relations between neural measures in terms of hemispheric lateralization by means of two additional regression analyses. The dependent variables were the laterality index of (1) the AF_{FTP} and (2) the posterior AF_{TP}. The predictor variables were the same for both regression analyses, namely the laterality index of 4 Hz and 20 Hz ASSRs.

Significant regression models were found for the laterality index of the left AF_{FTP} segment ($F_{(1, 57)} = 5.34$, $p = .024$, $R^2 = .09$) and the left posterior AF_{TP} segment ($F_{(1, 57)} = 5.42$, $p = .024$, $R^2 = .09$), both retaining the laterality index of 4 Hz ASSRs as a predictor (Table 4). Partial correlation analyses demonstrated a negative correlation between the laterality index of 4 Hz ASSRs and the laterality index of the AF_{FTP} ($r = -.29$, $p = .024$) and the posterior AF_{TP} segment ($r = -.29$, $p = .024$). Hence, the stronger 4 Hz ASSRs are lateralized towards the right hemisphere, the stronger the AF_{FTP} and the AF_{TP} are lateralized towards the left hemisphere.

Note that measures of phoneme-rate (20 Hz) processing were not retained in any of the regression models. Also, no significant regression equations were found for the right arcuate fasciculus (all $p > .10$).

3.3. Relations between neural and behavioral measures

To investigate our second research question, we examined the relations between neural and behavioral measures, for which we proceeded the analyses in three steps.

3.3.1. Relations between neurofunctional and cognitive reading-related measures

In the first step, we examined the relations between neural synchronization to syllable- and phoneme-rate information and phonological awareness skills. The corresponding backward regression analysis included phonological awareness scores as the dependent variable and left and right hemispheric 4 Hz and 20 Hz ASSRs as predictor variables.

A significant regression model was found ($F_{(2, 56)} = 4.41$, $p = .017$, $R^2 = .14$), which retained left and right hemispheric 4 Hz ASSRs as predictors (Table 5). Partial correlation analyses revealed that phonological awareness correlated negatively with left hemispheric 4 Hz ASSRs ($r = -.36$, $p = .005$) and positively with right hemispheric 4 Hz ASSRs ($r = .32$, $p = .015$). Hence, higher phonological awareness scores

were related to lower left and higher right hemispheric 4 Hz ASSRs. The regression plots are depicted in Fig. 5.

We re-investigated this relation in terms of hemispheric lateralization by means of an additional regression analysis. The dependent variable was phonological awareness and the predictor variables were the laterality indices of 4 Hz and 20 Hz ASSRs.

A significant regression model was found ($F_{(1, 57)} = 5.11$, $p = .028$, $R^2 = .08$), in which the laterality index of 4 Hz ASSRs was retained as a predictor (Table 6). Partial correlation analyses demonstrated a positive correlation between the laterality index of 4 Hz ASSRs and phonological awareness ($r = .29$, $p = .028$). This result indicates that a stronger lateralization of 4 Hz ASSRs towards the right hemisphere relates to better phonological awareness skills.

Note that measures of phoneme-rate (20 Hz) processing were not retained in any of the regression models (all $p > .10$).

3.3.2. Relations between neuroanatomical and cognitive reading-related measures

In the second step, we examined the relations between white matter properties of the arcuate fasciculus and phonological awareness skills. The corresponding backward regression analysis included phonological awareness scores as the dependent variable and left and right hemispheric AF_{FTP} and posterior AF_{TP} as predictor variables.

A significant regression model was found ($F_{(1, 57)} = 5.12$, $p = .027$, $R^2 = .08$), including the left AF_{FTP} segment as a significant predictor (Table 7). Partial correlation analyses revealed a positive correlation between fractional anisotropy in the left AF_{FTP} segment and phonological awareness ($r = .29$, $p = .027$), indicating that higher fractional anisotropy values in the left AF_{FTP} relate to better phonological awareness scores. The regression plot is depicted in Fig. 6. Note that fractional anisotropy in the right AF_{FTP} segment and fractional anisotropy in the left and right posterior AF_{TP} segment were not retained in the model (all $p > .05$).

When re-investigating the relation between phonological awareness and structural neural measures in terms of hemispheric lateralization, no significant regression models were found (all $p > .10$).

3.3.3. Relative contributions to cognitive reading-related measures

In the third step, we examined the relative contributions of both neural measures to phonological awareness skills. Therefore, a hierarchical regression analysis with two blocks was performed. The dependent variable was phonological awareness. As predictor variables, we
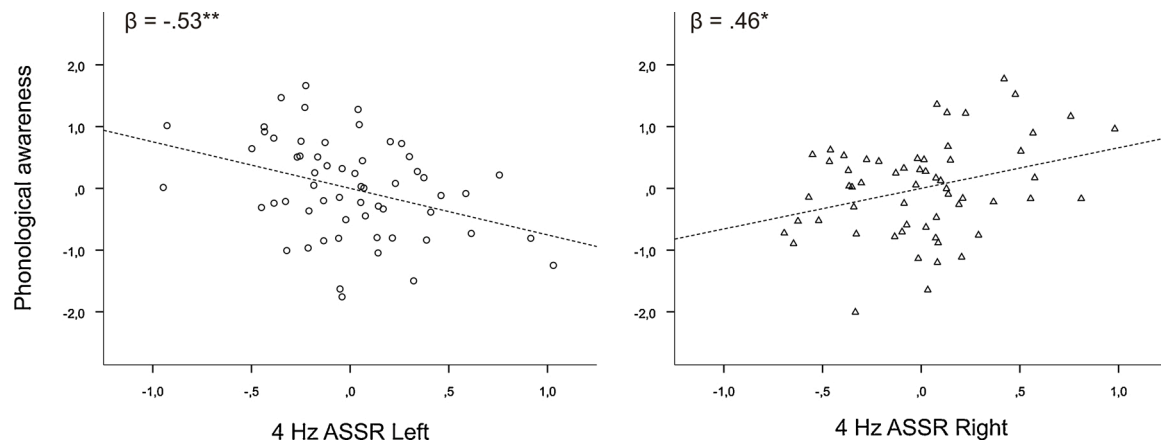
Table 5

Parameters of the regression model describing the relation between neurofunctional measures and phonological awareness.

Phonological awareness [a]							
	b	SE for b	β	t	p	95 % CI for b	
4 Hz ASSR Left	−0.753	0.259	−.527	−2.912	.005	−1.271	−0.235
4 Hz ASSR Right	0.657	0.261	.456	2.519	.015	0.135	1.180

[a]Predictor variables that were excluded from the model during the backward elimination procedure: 20 Hz ASSR Left ($b = -0.004$, $t = 0.033$, $p = .973$) and 20 Hz ASSR Right ($b = -0.052$, $t = -.396$, $p = .694$).

Fig. 5. Relations between neurofunctional and cognitive measures. Partial regression plots depict the relation between phonological awareness and neural synchronization to syllable-rate information (4 Hz ASSRs) in the left (○) and right (△) hemisphere with * $p < .05$, ** $p < .01$. The dotted lines represent the obtained regression equations.

Table 6
Parameters of the regression model describing the relation between neurofunctional measures and phonological awareness in terms of hemispheric lateralization, i.e., based on the laterality index (LI) of each neurofunctional measure.

Phonological awareness [a]							
	b	SE for *b*	*β*	*t*	*p*	95 % CI for *b*	
4 Hz ASSR LI	1.163	0.515	.287	2.260	**.028**	0.133	2.193

[a]Predictor variables that were excluded from the model during the backward elimination procedure: 20 Hz ASSR LI ($b = -0.171$, $t = -1.255$, $p = .215$).

Table 7
Parameters of the regression model describing the relation between neuroanatomical measures and phonological awareness. No significant models were found when the relations were re-investigated in terms of hemispheric lateralization.

Phonological awareness [a]							
	b	SE for *b*	*β*	*t*	*p*	95 % CI for *b*	
AF$_{FTP}$ Left	9.110	4.025	.287	2.263	**.027**	1.050	17.171

[a]Predictor variables that were excluded from the model during the backward elimination procedure: AF$_{FTP}$ Right ($b = 0.125$, $t = .826$, $p = .412$), AF$_{TP}$ Left ($b = 0.064$, $t = .412$, $p = .682$) and AF$_{TP}$ Right ($b = 0.093$, $t = .685$, $p = .496$).

successively included those variables for which significant relations with phonological awareness were found in the previous steps. Based on knowledge from previous neuroanatomical studies in pre-readers (Saygin et al., 2013; Vanderauwera et al., 2015; Vandermosten et al., 2015; Wang et al., 2016), white matter properties of the arcuate fasciculus were prevised to be entered in the first block. Neural synchronization measures were entered in the second block, as novel predictors.

In the first block ($F_{(1, 57)} = 5.12$, $p = .027$, $R^2 = .08$), fractional anisotropy in the left AF$_{FTP}$ segment was identified as a significant predictor for phonological awareness. After adding 4 Hz ASSRs in the second block ($F_{(3, 55)} = 3.68$, $p = .017$, $R^2 = .17$), both left and right hemispheric ASSRs were found to contribute significantly, but in an opposite direction. However, due to the addition of left and right hemispheric 4 Hz ASSRs to the model, the contribution of the left AF$_{FTP}$ segment was no longer significant (Table 8).
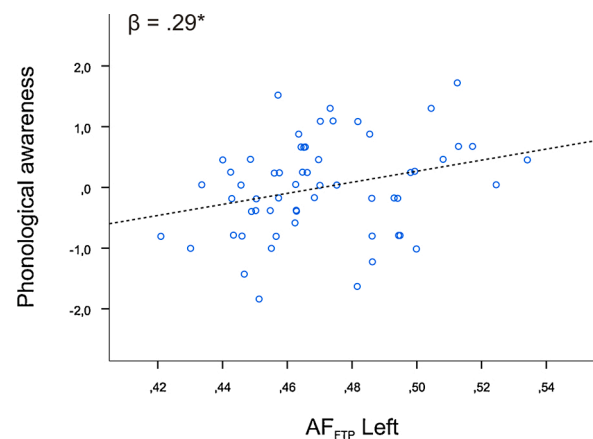

Fig. 6. Relations between the neuroanatomical and cognitive measures. The regression plot depicts the relation between phonological awareness and fractional anisotropy of the left AF$_{FTP}$ with * $p < .05$. The dotted line represents the obtained regression equation.

4. Discussion

At the neural level, processing of phonological information is assumed to depend on (1) acoustically-based processes in the posterior temporal cortex, sustained bilaterally (yet asymmetrically) by synchronized oscillations, and (2) a left lateralized dorsal interaction with inferior frontal regions and parietal regions, connected via the arcuate fasciculus. Given that phonological processing is an important precursor of reading (dis)ability, it is of particular interest to understand the role of both neural subcomponents and their interactions. However, most studies have merely considered the role of either neurofunctional or neuroanatomical correlates of phonological processing. In addition, neuroimaging studies are usually conducted in school-aged children or adults. Despite its relevance, the pre-reading link between both neural components as well as its effects on phonological processing thus remains unexplored. The present study provides a first attempt to fill this gap in research by systematically investigating the relations between auditory neural synchronization to syllable- and phoneme-rate information, white matter properties of the arcuate fasciculus and cognitive phonological processing skills in a group of 59 pre-reading children with a wide range of pre-reading cognitive abilities. Our results reveal significant relations between a specific triad of neurofunctional, neuroanatomical and cognitive measures, including syllable-rate (4 Hz)

Table 8
Parameters of the two-block hierarchical regression model describing the relative contribution of each neural measure to phonological awareness. In block 1, fractional anisotropy of the left AF_{FTP} was entered in the model ($R^2 = .08$). In block 2, left and right hemispheric 4 Hz ASSRs were added to the model ($\Delta R^2 = .08$).

Phonological awareness							
	b	SE for *b*	*β*	*t*	*p*	95 % CI for *b*	
Block 1							
AF_{FTP} Left	9.110	4.025	.287	2.263	**.027**	1.050	17.171
Block 2							
AF_{FTP} Left	5.978	4.162	.188	1.436	.157	−2.363	14.319
4 Hz ASSR Left	−0.618	0.273	−.432	−2.264	**.028**	−1.165	−0.071
4 Hz ASSR Right	0.570	0.266	.395	2.146	**.036**	0.038	1.102

processing in both hemispheres, white matter properties of the left arcuate fasciculus and phonological awareness (Fig. 7).

4.1. A pre-reading "neural system"

Our first aim was to investigate the relation between neural measures, i.e., between neural synchronization to syllable and phoneme rates and fractional anisotropy properties of the arcuate fasciculus. We assessed neural synchronization by means of ASSRs evoked by speech-weighted noise stimuli modulated at syllable (4 Hz) and phoneme (20 Hz) rate. In the context of the present study, 4 Hz and 20 Hz ASSRs were of particular interest, since these neural responses reflect the processing of specific, phonologically relevant, temporal modulation rates. As such, we are tapping into the first steps of cortical speech processing, i.e., the spectrotemporal computations in the superior temporal gyrus.

Our results revealed significant correlations between the strength of neural synchronization to 4 Hz syllable-rate modulations and white matter integrity of the left arcuate fasciculus (both AF_{FTP} and AF_{TP}). Interestingly, the stronger 4 Hz ASSRs were lateralized to the right hemisphere, the stronger the arcuate fasciculus was lateralized to the left hemisphere. Hence, this structural-functional relation was driven by opposite hemispheric effects. These findings provide evidence for the existence of a relation between the functional specialization for processing syllable-rate modulations and structural white matter properties in regions and connections responsible for processing this information.

Notably, we found no correlations between neural synchronization to phoneme-rate modulations and white matter properties of the arcuate fasciculus. These results might suggest that phoneme-rate processing is not (yet) fully established at the neural level in pre-readers. Given that phoneme awareness is presumed to develop in interaction with reading acquisition (Ziegler and Goswami, 2005), the pre-reading children included in the present study possibly still reflect on and manipulate speech predominantly at the syllable level. This hypothesis is supported

by our previous study, which disclosed emerging developmental effects with regard to phoneme-rate synchronization in beginning readers around the age of 7 (De Vos et al., 2017a). Similarly, the association between neural synchronization to phoneme-rate modulations and white matter properties of the arcuate fasciculus might only be substantiated after the onset of reading acquisition. In adults, a significant relation between 20 Hz phoneme-rate processing and white matter lateralization has indeed been established (Vandermosten et al., 2013). However, Vandermosten et al. (2013) applied different metrics to quantify both neural components. Therefore, we alternatively acknowledge the possibility that other metrics than the ones used in the current study could be more sensitive to detect the suggested association.

4.2. Complementary predictors for phonological awareness

The premise of this study was that both neural measures, i.e., auditory processing of phonologically relevant temporal modulations and white matter properties of the arcuate fasciculus, support the phonological processing of speech. This premise was based on the model proposed by Hickok and Poeppel (2007), in which temporal processing of specific speech rates determines the quality of phonological representations and provides input to the phonological network, but also on evidence from previous studies in school-aged children and adults that have identified neural processing of syllable and phoneme rates (Lehongre et al., 2011; Lizarazu et al., 2015; Poelmans et al., 2012a) as well as the arcuate fasciculus (Vandermosten et al., 2012; Yeatman et al., 2011) as neural correlates of phonological processing.

With regard to neural synchronization to syllable- and phoneme-rate information, our study established the presumed relation between auditory processing of temporal modulations and phonological processing skills in pre-readers. The relation was specific to syllable-rate processing and revealed an opposite association with phonological awareness in both hemispheres, that is, higher neural synchronization in
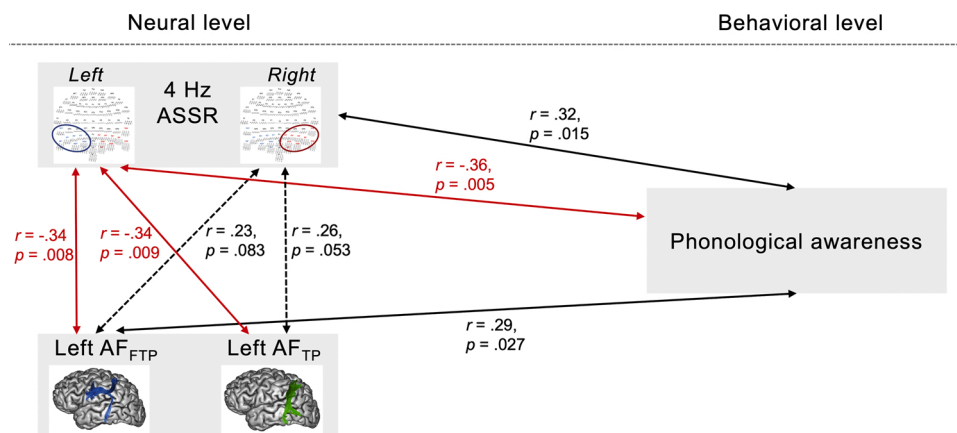

Fig. 7. Overview of the main relations between neural and behavioral measures. Positive relations are presented in black and negative relations in red. Note that the dotted line refers to a non-significant relation.

the right hemisphere related to better phonological awareness skills, whereas higher neural synchronization in the left hemisphere related to poorer phonological processing skills. This effect also emerged as a significant correlation between phonological awareness skills and the hemispheric lateralization of syllable-rate processing. Again, it seems to be the inverse hemispheric interaction of neural synchronization that determines the relation with phonological awareness. As such, our results are in line with the findings of Abrams et al. (2009) and Lizarazu et al. (2015), but extend the observed relations to pre-readers.

Also with regard to the arcuate fasciculus, a significant relation was found with phonological processing skills. This relation was specific to white matter properties of the left AF_{FTP} and revealed a positive association with phonological awareness, that is, higher fractional anisotropy relates to better phonological awareness skills. Although the right AF_{FTP} was not identified as a significant predictor for phonological awareness, the partial correlation coefficient revealed a similar trend ($r = .24$, $p = .064$) as for the left AF_{FTP}. This might explain why the hemispheric lateralization of the arcuate fasciculus was not significantly related to phonological awareness. Despite a clear leftward dominance of the AF_{FTP}, it turns out that the interaction (or the difference) between both hemispheres is of less importance. In contrast to the results regarding neural synchronization, it rather seems that the relation with phonological awareness is similar in both hemispheres, but stronger in the left than in the right hemisphere. Hence, our results are in line with recent studies in pre-readers (Saygin et al., 2013; Wang et al., 2016), including our own reports in an overlapping set of participants (Vanderauwera et al., 2015; Vandermosten et al., 2015). Unlike the AF_{FTP}, the posterior AF_{TP} was not significantly related to phonological processing. Yet, note that our results did show that the posterior AF_{TP} is significantly related to the neural processing of syllable-rate (4 Hz) modulations. Therefore, an alternative hypothesis is that the posterior AF_{TP} segment is related to a different behavioral correlate which was not assessed in the present study. In adults for example, the posterior AF_{TP} has been shown to be related to speech-in-noise perception (Vandermosten et al., 2012).

An ensuing question is in what way and to what extent the neural aspects captured by this "neural system" are able to explain the observed variance in pre-reading phonological skills. Our final analysis therefore investigated the relative contribution of both neural measures, when taking into account the influence of the other factor. Both neural features might, to some extent, explain the same variance in phonological awareness. Alternatively, the variance explained by the neural features might be additive. Our results demonstrated that there is an overlap in the variance explained by both features. In a model including only the white matter properties of the arcuate fasciculus, the left AF_{FTP} significantly predicted phonological awareness. However, after taking auditory processing into account, white matter properties of the left AF_{FTP} did not significantly contribute to the prediction of phonological awareness on top of left and right hemispheric 4 Hz ASSRs. Although this might seem contradictory to what was found earlier, namely that white matter properties are significantly related to phonological awareness, this result implicates that white matter properties do not explain any additional variability in phonological awareness that is not already explained by auditory temporal processing measures. These results suggest that both neural components should be regarded as complementary predictors, which do not appear to explain any unique variance in phonological processing skills.

4.3. Implications for developmental dyslexia

The results of the present study suggest that phonological processing of speech is sustained by a rightward processing of syllable-rate modulations and a left dorsal phonological network, which in turn are also interrelated to each other. With regard to dyslexia, we speculate that our results might implicate that syllable-rate information is less well processed and therefore less well integrated in the dorsal phonological

system. If a disturbance in hemispheric lateralization of syllable-rate modulations is present at young age, this might reduce the quality of information that is submitted to the phonological system. Alternatively, we speculate that the connection of the right lateralized auditory system for syllable-rate processing with the left lateralized phonological system, which is presumably sustained by the corpus callosum, is not optimal in dyslexia. However, further research is required to investigate the implications of the present research findings for individuals with dyslexia.

5. Conclusions

Our study presents a first attempt to combine functional and structural neural correlates of phonological processing of speech in the same sample of pre-reading children. The results provide evidence for the existence of a pre-reading "neural system", which includes a combination of interrelated functional (i.e., bilateral syllable-rate processing) and structural measures (i.e., white matter in the left AF_{FTP}) that are both associated with phonological processing in a complementary way. In the light of existing models on speech processing and reading, we suggest that syllable-rate processing might influence the quality of the information that is integrated in the phonological system as phonological representations, thereby predetermining phonological (and reading) development. According to our findings, this might occur through an influence on the arcuate fasciculus. To fully grasp the neural underpinnings of reading and developmental dyslexia, further investigation of the brain structure - function relations by directly combining different advanced structural and functional neuroimaging techniques is necessary, which can lead to larger effect sizes.

Declaration of Competing Interest

The author declare to have no conflicts of interest.

Acknowledgments

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