



Pulsatile modulation greatly enhances neural synchronization at syllable rate in children

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ARTICLE INFO

Keywords:

Neural synchronization
Auditory steady state response
Amplitude modulation
Development

ABSTRACT

Neural processing of the speech envelope is of crucial importance for speech perception and comprehension. This envelope processing is often investigated by measuring neural synchronization to sinusoidal amplitude-modulated stimuli at different modulation frequencies. However, it has been argued that these stimuli lack ecological validity. Pulsatile amplitude-modulated stimuli, on the other hand, are suggested to be more ecologically valid and efficient, and have increased potential to uncover the neural mechanisms behind some developmental disorders such as dyslexia. Nonetheless, pulsatile stimuli have not yet been investigated in pre-reading and beginning reading children, which is a crucial age for developmental reading research. We performed a longitudinal study to examine the potential of pulsatile stimuli in this age range. Fifty-two typically reading children were tested at three time points from the middle of their last year of kindergarten (5 years old) to the end of first grade (7 years old). Using electroencephalography, we measured neural synchronization to syllable rate and phoneme rate sinusoidal and pulsatile amplitude-modulated stimuli. Our results revealed that the pulsatile stimuli significantly enhance neural synchronization at syllable rate, compared to the sinusoidal stimuli. Additionally, the pulsatile stimuli at syllable rate elicited a different hemispheric specialization, more closely resembling natural speech envelope tracking. We postulate that using the pulsatile stimuli greatly increases EEG data acquisition efficiency compared to the common sinusoidal amplitude-modulated stimuli in research in younger children and in developmental reading research.

1. Introduction

Speech perception and comprehension are skills that people often take for granted. Nevertheless, the auditory perception of a complex and dynamic signal such as natural speech depends on several processes. It is generally agreed upon that the ability of the auditory system to process the speech envelope, which contains temporal modulations in the speech signal below 50 Hz (Rosen, 1992), is crucial for speech perception (Drullman et al., 1994; Shannon et al., 1995). Amplitude modulation rates in the speech envelope coincide with linguistically meaningful units such as phonemes (gamma and beta range; > 30 Hz and 12–30 Hz respectively), syllables (theta and delta range; 4–8 Hz and < 4 Hz respectively) and intonational phrase boundaries (delta range; < 4 Hz) (Ghitza, 2011; Ghitza and Greenberg, 2009; Meyer, 2018; Poeppel, 2003). The neural mechanism proposed to underlie their perception is neural synchronization, which refers to the phase-locking of neural oscillations to temporal modulations in the speech envelope (Peelle and Davis, 2012). Successful neural synchronization

is indeed strongly associated with speech perception and intelligibility (Ghitza and Greenberg, 2009; Giraud and Poeppel, 2012; Luo and Poeppel, 2007; Peelle and Davis, 2012; Riecke et al., 2018). Furthermore, influential speech perception theories such as the ‘asymmetric sampling in time’ or AST theory suggest a hemispheric specialization in which slow temporal rates are preferentially processed in the left hemisphere, whereas fast temporal rates are preferentially processed in the right hemisphere or bilaterally (Poeppel, 2003).

Over the past decades, several electrophysiological paradigms have been developed in order to investigate the neural processing of the speech envelope. One such paradigm involves measuring the brain’s response to natural speech (Aiken and Picton, 2008; Vanthornhout et al., 2018). Although ecologically relevant, using real speech poses a few challenges such as disentangling aspects of the neural response that are associated with comprehension from those associated with actual envelope processing (Gransier and Wouters, 2021). Gransier and Wouters (2021) argue that despite the importance of using real speech for understanding how it is processed by the brain, this stimulus is sub-

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optimal to investigate (deficits in) envelope processing. A paradigm that allows to investigate envelope processing without having to face these challenges involves sinusoidally amplitude-modulated (SAM) sounds (Alaerts et al., 2009; Rees et al., 1986; Wang et al., 2012). Such stimuli evoke Auditory Steady-State Responses (ASSRs), which measure how well the auditory system phase-locks or synchronizes to a stimulus rhythm (Picton et al., 2003). Measuring ASSRs to multiple frequencies provides insight into how the auditory system processes the temporal modulations relevant to speech perception. However, it has been argued that SAM stimuli do not accurately represent the features of our acoustic world and are suboptimal for investigating speech processing (Prendergast et al., 2010). Prendergast et al. (2010) stated that the speech envelope mainly consists of short pulsatile bursts of energy rather than gradual transitions such as those in SAM stimuli. These sharper edges or rise times in speech are specifically important for neural synchronization to the speech envelope. Rise times trigger neural oscillations to accurately synchronize to the temporal modulations in the speech signal (Gross et al., 2013) and it is specifically their sharpness that facilitates synchronization (Doelling et al., 2014). In this respect, more pulsatile stimuli with sharper rise times might better represent the features of our acoustic world and are hence more ecologically valid and suitable to investigate speech processing (Prendergast et al., 2010).

Aforementioned pulsatile stimuli have already been developed and implemented in a few studies (John et al., 2002, 2003, 2004; Prendergast et al., 2010; Van Hirtum et al., 2019a). In these studies, the envelope shape of SAM sounds was varied (semi-)exponentially, leading to a rise time reduction of the stimuli without affecting the rate at which the envelope is amplitude-modulated. Exponentially-modulated tonal stimuli significantly increase steady-state responses compared to SAM stimuli with the same modulation frequencies in both adults (John et al., 2002; Prendergast et al., 2010) and young infants (John et al., 2004). It is argued that stronger responses such as the ones obtained by the pulsatile stimuli allow for more rapid and accurate detection of responses (John et al., 2002, 2004) and are more suitable for investigations of neural synchronization (Prendergast et al., 2010). A study by Van Hirtum et al. (2019a) confirmed stronger responses to pulsatile, in their case modulated noise stimuli, at least in typically reading adults and at modulation frequencies of 4, 10 and 40 Hz. Additionally, the authors demonstrated an atypical neural synchronization in people with dyslexia, a developmental reading disorder, only when using the pulsatile stimuli, and not when using the SAM stimuli. Atypical neural synchronization is suggested to contribute to the development of dyslexia (Goswami, 2011), and by using the pulsatile stimuli, Van Hirtum et al. (2019a) now allocated this to a deficit with neural synchronization to sharper rise times specifically. Hence, using pulsatile stimuli instead of SAM stimuli is also beneficial for uncovering the neural mechanisms behind developmental disorders such as dyslexia.

Researchers aiming to uncover these neural mechanisms often focus on the pre-reading to beginning reading age range, considering that there is a natural plasticity window for reading in this period (Phan et al., 2021) and that research during this period allows to uncover the causal mechanisms behind the disorder. The pulsatile stimuli could prove invaluable for such investigations. Not only are these stimuli suggested to make detection of responses more efficient (John et al., 2002, 2004), which is of particular interest in pediatric populations in which acquiring extensive electrophysiological (EEG) data can be challenging. As Prendergast et al. (2010) suggested, they are also more suitable for representing our real acoustic world. Despite these clear advantages of the pulsatile stimuli over SAM stimuli with respect to ecological validity and efficiency, only very few studies in children have included these kinds of stimuli. Most studies investigating neural synchronization to the speech envelope in children included only regular SAM stimuli (De Vos et al., 2017a, 2020; Lizarazu et al., 2015; Vanvooren et al., 2014, 2015). To the best of our knowledge, only the study of John et al. (2004) investigated the application of pulsatile stimuli in young children, and confirmed stronger responses to these stim-

uli in newborn infants. However, a thorough investigation of pulsatile stimuli in pre-reading to beginning reading age still remains to be performed before their application in research in younger children and developmental reading research aiming to uncover neural precursors of dyslexia.

To this end, we designed a longitudinal study that investigated responses to pulsatile stimuli in Dutch-speaking pre-reading to beginning reading children with typical reading skills. We longitudinally investigated ASSRs to SAM stimuli and pulsatile (PULS) stimuli with envelope shapes in which the rise times were fixed to 30 ms. Measurements took place in the middle (T0) and at the end (T1) of the last year of kindergarten, and at the end of first grade (T2), after approximately one year of formal reading instruction. We included 4 Hz (syllable rate) and 20 Hz (phoneme rate) modulations considering their frequent application in reading research and direct links to linguistically meaningful units (De Vos et al., 2017a, 2017b; Poelmans et al., 2012; Van Hirtum et al., 2019a; Vanvooren et al., 2014). In line with the study of Van Hirtum et al. (2019a), we hypothesized to find stronger ASSR responses to the PULS stimuli compared to the SAM stimuli. We suggest that the physiological basis for these hypothesized stronger responses lies in the enhancement of the probability of discharge at the synapse to the auditory nerve fiber at the onset of a stimulus, which is more prominent for steeper stimulus onset slopes (Delgutte, 1980, 1997; Geurts and Wouters, 1999). Furthermore, we hypothesize stronger responses to the PULS stimuli to be more marked at 4 Hz, considering that the difference between the rise times of the SAM and PULS stimuli is much greater at 4 Hz than at 20 Hz. Based on Van Hirtum et al. (2019a), we did not expect stimulus type to impact hemispheric specialization. Furthermore, we hypothesized that the PULS stimuli, because of their stronger responses, might reveal more subtle maturational effects that are possibly not revealed by the SAM stimuli. Investigating maturation in neural synchronization is not a primary goal in the current study, but examining the suitability of the PULS stimuli across pre-reading and beginning reading stages is an important prerequisite for future longitudinal developmental reading research, where investigating maturation of neural synchronization is a primary goal.

2. Materials and methods

2.1. Participants

Fifty-two children (31 male) participated in the current study. The children were recruited from a large preventive reading intervention study in children at cognitive risk for developing dyslexia in which EEG measurements were collected ($N = 91$) (see Economou et al., 2022; Van Herck et al., 2022; Vanden Bempt et al., 2021, 2022). All children in the current study were retrospectively classified as typical readers based on third grade reading data. Typical readers did not score low on standardized word reading (Brus and Voeten, 1973; Verhoeven, 1995) and pseudoword reading tasks (van den Bos et al., 1994), and a standardized spelling task (DeLoof, 2006) at the start of third grade. Children who were classified as dyslexic readers by scoring below the 10th percentile on at least one of the reading or spelling tasks, and below the 25th percentile on all other reading and spelling tasks, were not included in the current study. In total, third grade reading data were obtained for 78 of the children that participated in the intervention study with EEG measurements, of which 26 were classified as dyslexic readers. All remaining children ($n = 52$) were classified as typical readers and included in the current study. In the course of the intervention study, all children received some kind of (reading) intervention between T0 and T1, which is outside the scope of the current study, but which is thoroughly described Economou et al. (2022), Van Herck et al. (2022), Vanden Bempt et al. (2021, 2022). Of the sample included in the current study, 17 children belonged to a group receiving a phonics-based training and an auditory training included in a story-listening game, 22 children received a phonics-based training and a story-listening game without au-

Table 1
Participant characteristics.

Characteristic	Levels	(N = 52)	
		M	SD
Age T0 (months)		65	3
Non-verbal IQ ^a		101	14
Sex	Male/Female	31/21	
SES ^b	Low/Middle/High	14/16/22	
Handedness	Left/Ambidextrous/Right	5/4/43	

Note. M = group mean, SD = standard deviation, SES = socioeconomic status. For categorical data (i.e. sex, SES and handedness) the numbers in each group are reported instead of M and SD.

^a Reported scores are standardized scores (M = 98.15, SD = 16.66).

^b SES is based on the parental educational level of the mother.

itory training, and 13 children received a control game combined with the story-listening game without auditory training. All children were native Dutch speakers with bilateral normal hearing, had neither history of brain damage or neurological disorders, nor (preliminary) diagnosis of autism spectrum disorder (ASD) or attention deficit hyperactivity disorder (ADHD), did not receive any speech therapy due to language and/or articulatory problems and had already received a total pre-primary schooling period of at least 20 months by the start of the longitudinal study. All children scored above a norm score of 75.3 on the Raven's Colored Progressive Matrices (Raven et al., 1984). See Table 1 for participant characteristics.

In the course of the longitudinal study, EEG measurements were collected at three time points, corresponding to the time points implemented in the intervention study from which the participants were recruited. Data were collected at T0 (age: M = 5 years, 5 months; SD = 3 months; middle of third year of kindergarten), T1 (age: M = 5 years, 10 months, SD = 3 months; end of third year of kindergarten) and T2 (age: M = 7 years, 0 months; SD = 3 months; end of first grade of primary school). Even though the intervention is not of interest for the current study, we use the longitudinally collected EEG data from all three time points in order to investigate neural synchronization across development from pre-reading to beginning reading age.

At T0, we collected EEG data in all children. Measurements of 14 out of 208 conditions (four conditions per child) were excluded for the following reasons: (1) excessive noise levels, meaning that the mean peak-to-peak amplitude across epochs of the combined left or right channel (see 2.2.3 preprocessing) exceeded a threshold of six times the median of the mean peak-to-peak amplitudes across all channels, in line with earlier work in our research lab (2) measurement was ended prematurely, (3) data of the specific condition was not collected, (4) uncertainty about the child's hearing of the stimulus. Note that in case of excluded conditions, available conditions of a child are still included in analyses. At T1, five children discontinued participation. Additionally, 5 out of 188 conditions were excluded. Six children discontinued participation at T2. Here, 4 out of 184 conditions were excluded.

The study was approved by the Medical Ethical Committee of the University Hospital of Leuven, KU Leuven, and signed informed consents were obtained for all participants in line with the Declaration of Helsinki.

2.2. EEG measures

2.2.1. Recording parameters

EEG signals were recorded with the BioSemi ActiveTwo system using 64 active Ag/AgCl electrodes mounted in head caps according to the 10–20 electrode system. A sample rate of 16,384 Hz was used. The system uses a built-in low-pass filter with a cutoff frequency of 3276 Hz.

This sampling rate, even though relatively high considering the frequencies of interest in the current study, ensures comparability within our research lab and allows for accurate modeling of artifacts. Electrode offsets were kept between −25 mV and 25 mV. Recordings were carried out in a double-walled soundproof booth with Faraday cage. Children sat down in a comfortable chair during the measurement while watching a soundless movie of their choice. This passive listening paradigm has previously been used in pediatric ASSR studies (De Vos et al., 2017a; Vanvooren et al., 2014) and ensures a similar level of alertness and attention across subjects throughout the measurement. An experienced test leader accompanied the child in the EEG cabin for the entire duration of the measurement.

For each subject, we collected four EEG measurements (two modulation frequencies x two stimulus types). Each condition lasted approximately 9 min (532.48 s).

2.2.2. Auditory steady state responses

Stimuli used to evoke ASSRs consisted of continuous amplitude-modulated speech-weighted noise. The carrier noise was adopted from the “Leuven Intelligibility Sentence Test” (LIST; Van Wieringen & Wouters, 2008). This represents the long-term average speech spectrum of 730 sentences of a female speaker. The speech-weighted noise was 100% amplitude-modulated at approximately 4 and 20 Hz (exact frequencies 3.91 and 19.53 Hz) (Vanvooren et al., 2015), to measure neural synchronization of theta and beta oscillations respectively. For each modulation frequency, we created two conditions or stimulus types, see Fig. 1. In the sinusoidal amplitude-modulated condition (SAM) a sinusoidal envelope modulation was implemented. In the pulsatile condition (PULS), an envelope shape was applied with a linear rise time (the time it takes to go from minimal to maximal amplitude) fixed at 30 ms, no plateau, and a fall time fixed at 10 ms, without affecting amplitude modulation rates at 4 and 20 Hz. The PULS stimuli are similar to those used in the study of Van Hirtum et al. (2019a), except for the use of white noise instead of speech-weighted noise in their study. An exemplary representation of the stimuli is given in Fig. 1.

The calibration procedure matched the stimuli in peak-to-peak level. All stimuli were presented monaurally at 70 dBpSPL through a calibrated ER-3B insert earphone to the right ear.

2.2.3. Preprocessing

Preprocessing was performed in Matlab R2016b (The MathWorks Inc, 2016). First, the EEG signal was high-pass filtered with a second-order Butterworth filter with a cutoff frequency of 2 Hz to remove the DC component. After filtering, the signals were averaged across a pre-selected electrode configuration into one recording channel representing the left hemisphere and one channel representing the right hemisphere. Nine electrodes in the left (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. This configuration was based on previous research showing that these electrodes are most sensitive to pick up ASSRs in children (Vanvooren et al., 2014). The suitability of this electrode configuration was confirmed in the current dataset by calculating the average number of significant responses for all electrode pairs and all conditions included in the study. The average was 87% and 89% for 4 and 20 Hz respectively. Next, the signal was segmented into epochs of 1.024 s. We then applied an epoch-based artefact rejection to remove muscle potentials and other artifacts. The aim was to obtain 448 epochs per subject with the lowest amount of artifacts in all channels. The amplitude rejection level for this was set on an individual basis, until 448 epochs remained per electrode. The remaining 448 epochs were re-referenced to Cz. A Fast Fourier Transformation (FFT) algorithm was applied to calculate the complex frequency spectrum for each of the remaining epochs (Fig. 2). From the complex frequency spectrum, we obtained the response power, amplitude, and phase corresponding to the modulation frequencies used during the experiment (i.e. 4 and 20 Hz, the response spectrum). Mean response amplitudes

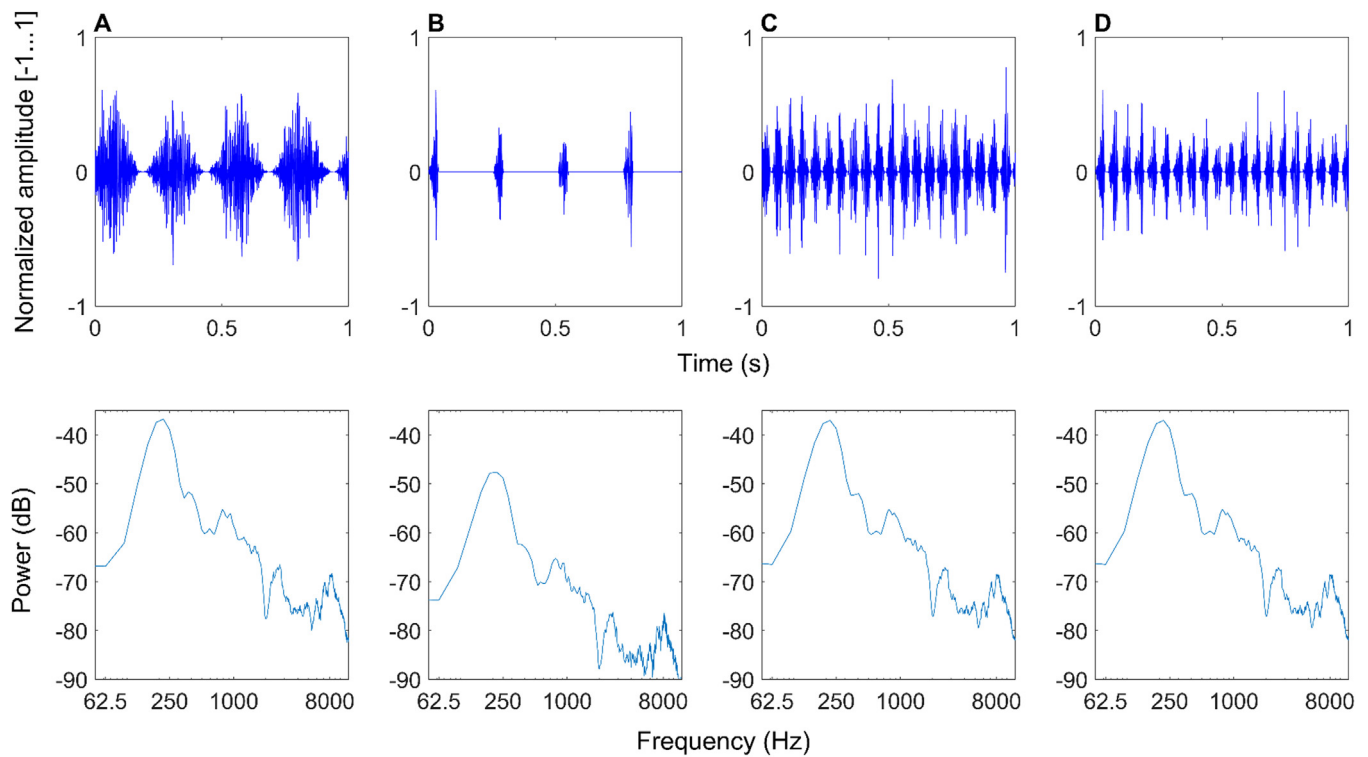


Fig. 1. SAM and PULS stimuli.

Note. A 1 s waveform (upper panels) and spectral representation (lower panels) of the (A) 4 Hz SAM, (B) 4 Hz PULS, (C) 20 Hz SAM and (D) 20 Hz PULS stimuli.

and phases were computed by vector averaging the complex response spectrum across epochs. The neural background noise was calculated based on the “standard deviation of the mean” (Gransier et al., 2017). This measure assumes that the measured ASSR, as present in the response spectrum, consists out of both the steady state response, constant in phase and amplitude over time, and the neural background activity, varying randomly in phase and amplitude over time. The “standard deviation of the mean”, calculated as the standard deviation over epochs divided by the square root of the number of epochs, therefore directly reflects the average amplitude across epochs of the neural background activity (Gransier et al., 2017). This measure, compared to the “neighboring bins estimate”, does not underestimate neural background noise when it is higher in the bin of interest compared to the neighboring bins. At both syllable and phoneme rates noise decreased over time. Median noise values at 4 Hz were 0.335 μ V, 0.330 μ V and 0.311 μ V for T0, T1 and T2 respectively. Median noise values at 20 Hz were 0.065 μ V, 0.066 μ V and 0.063 μ V for T0, T1 and T2 respectively. Finally, a one sample Hotelling T^2 test combining amplitude and phase was performed to determine whether the synchronized activity differed significantly from the neural background activity and hence whether a reliable ASSR (i.e. significant response) was present in the EEG signal (Picton et al., 2003). This test was performed at the modulation frequency bin.

2.3. Statistical analyses

Statistical analysis was performed in R (version 3.5.1) (R Core Team, 2018). Prior to analysis, the assumption of normality of the residuals was assessed using Kolmogorov-Smirnov tests. Levene tests were performed to test for homogeneity of variance. Both assumptions were violated, hence we adopted robust estimation methods for the analyses.

To assess the effects of the stimulus types on neural synchronization, as well as the impact of stimulus type on hemispheric specialization and maturation or development, robust linear mixed-effects models (robustlmm package) (Koller, 2016) were fitted for each modulation frequency (4 and 20 Hz) separately. Stimulus type (SAM and PULS), hemi-

sphere (left and right) and test phase (T0, T1 and T2) were included in the model as fixed effects. A random intercept was included per subject to account for repeated measures. P values with a significance level of $p < .05$ for the fixed effects and their interactions in the model were obtained by means of bootstrapping as suggested by Koller (2016). We used a parametric bootstrapping approach with 1000 simulations. Post-hoc comparisons on the interactions were performed using estimated marginal means with a Holm correction for multiple comparisons. Descriptives are reported as medians and interquartile ranges.

3. Results

3.1. Response amplitudes

Descriptive data for ASSR response amplitudes are provided in Table 2 and an illustration of the raw data can be found in Figs. 3 (4 Hz) and 4 (20 Hz). For 4 Hz response amplitudes, a significant main effect of test phase ($\chi^2(2) = 40.37, p < .001$) was found. Overall, 4 Hz response amplitudes were significantly smaller at T0 ($z = -6.757, p < .001$, 95% asymptotic CI $[-0.472, -0.225]$) and T1 ($z = -5.506, p < .001$, 95% asymptotic CI $[-0.416, -0.164]$) compared to T2, while response amplitudes did not differ between T0 and T1 ($z = -1.133, p = .257$, 95% asymptotic CI $[-0.183, 0.066]$). Apart from the main effect of test phase, the interaction between stimulus type and hemisphere was also significant ($\chi^2(1) = 24.50, p < .001$). Overall, there were larger responses to the PULS than to the SAM stimuli, in both the left ($z = 27.053, p < .001$, 95% asymptotic CI $[1.447, 1.742]$) and right ($z = 19.152, p < .001$, 95% asymptotic CI $[0.982, 1.276]$) hemisphere. Additionally, whereas in response to the SAM stimuli there was an overall larger response in the right hemisphere compared to the left hemisphere ($z = 3.344, p < .001$, 95% asymptotic CI $[0.050, 0.347]$), the opposite pattern, i.e. a larger response in the left hemisphere, was found in response to the PULS stimuli ($z = 4.578, p < .001$, 95% asymptotic CI $[0.121, 0.413]$). None of the interaction effects with test phase was significant (all $p > .05$).

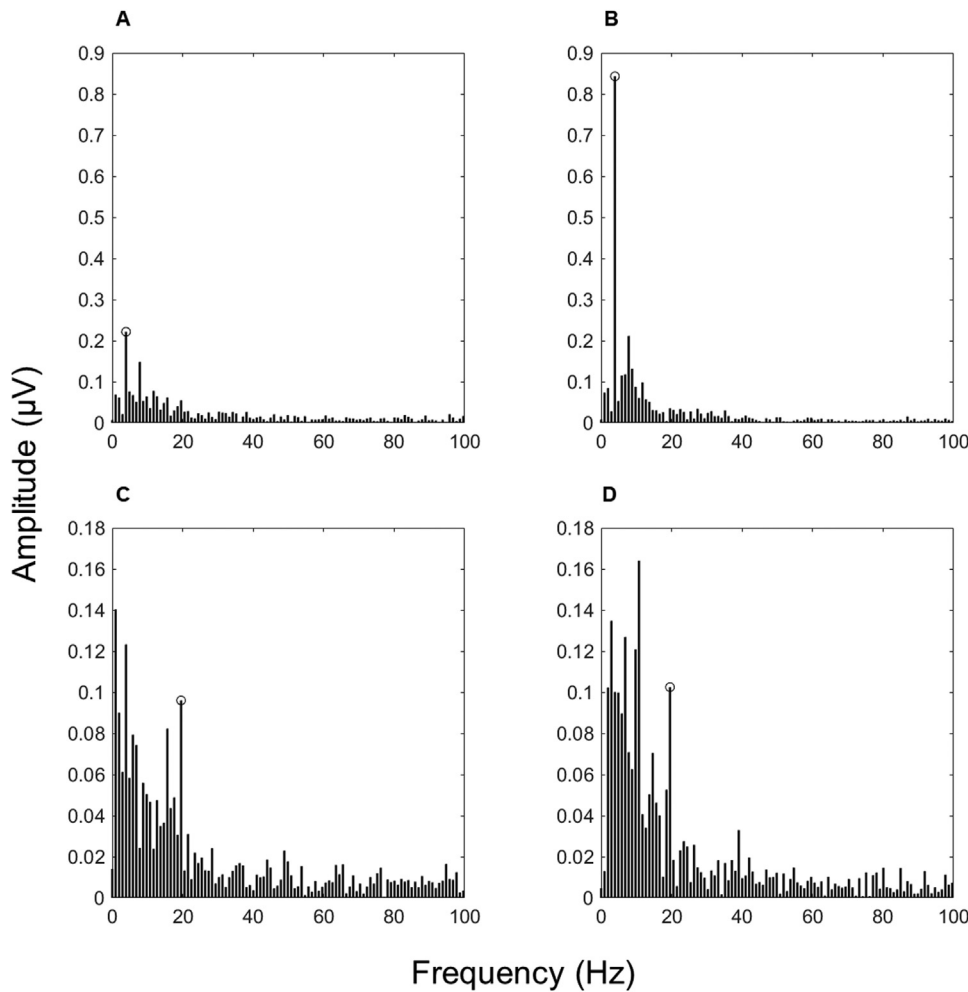


Fig. 2. Frequency spectra of the EEG signals. Note. The frequency spectrum of the recorded EEG of one randomly selected subject after pre-processing for the (A) 4 Hz SAM, (B) 4 Hz PULS, (C) 20 Hz SAM and (D) 20 Hz PULS conditions. The circle indicates the stimulation frequency in that specific condition.

Table 2

Descriptives of response amplitudes (in μV) for all frequencies, stimulus types, hemispheres and test phases separately.

Modulation frequency	Stimulus type	Hemisphere	T0		T1		T2	
			Mdn	IQR	Mdn	IQR	Mdn	IQR
4 Hz	SAM	Left	0.81	0.60	0.96	0.69	1.20	0.64
		Right	1.10	0.66	1.06	0.64	1.33	0.47
	PULS	Left	2.46	1.09	2.43	1.07	2.85	1.17
		Right	2.21	0.93	2.15	0.86	2.42	0.90
20 Hz	SAM	Left	0.30	0.30	0.28	0.26	0.32	0.24
		Right	0.29	0.27	0.30	0.26	0.36	0.23
	PULS	Left	0.28	0.25	0.31	0.28	0.34	0.23
		Right	0.27	0.21	0.27	0.26	0.33	0.25

Note. Mdn = median; IQR = interquartile range.

John et al. (2004) already emphasized that stimuli that elicit increased response amplitudes should shorten the time needed to measure significant ASSRs. The authors state that for stimuli with increased amplitudes you only need $1/X^2$ of the time to reach the same signal-to-noise ratio (SNR), with X representing the ratio of the response amplitudes of the two stimuli. This calculation rests on the principle in signal processing theory that signal averaging decreases the noise levels proportional to the square root of the number of measurements in the average (Schimmel, 1967; Vaughan, 1974), or, as in the present work, proportional to square root of the increase in response amplitude. This applies for random noise and identical signal responses. In the current study, the average response amplitude of the 4 Hz SAM stimuli is

1.12 μV , whereas that of the 4 Hz PULS stimuli is 2.52 μV . Hence, the time required to reach a certain SNR when using the PULS stimuli is $1/(2.52/1.12)^2$, which equals 0.1975 or 19.75% of the time required to reach this same SNR when using the SAM stimuli. The latter measure of time reduction was calculated across all subjects. When investigating this measure at the individual level, the median time required to reach a certain SNR with the PULS stimuli compared with the SAM stimuli is 19.81% (95% CI [17.20, 25.90]).

For 20 Hz response amplitudes, only the main effect of test phase reached significance ($\chi^2(2) = 21.10, p < .001$) (see Fig. 4). Similar to this main effect at 4 Hz, response amplitudes at 20 Hz did not differ between T0 and T1 ($z = -1.615, p = .106$, 95% asymptotic CI [-0.039, 0.008]),

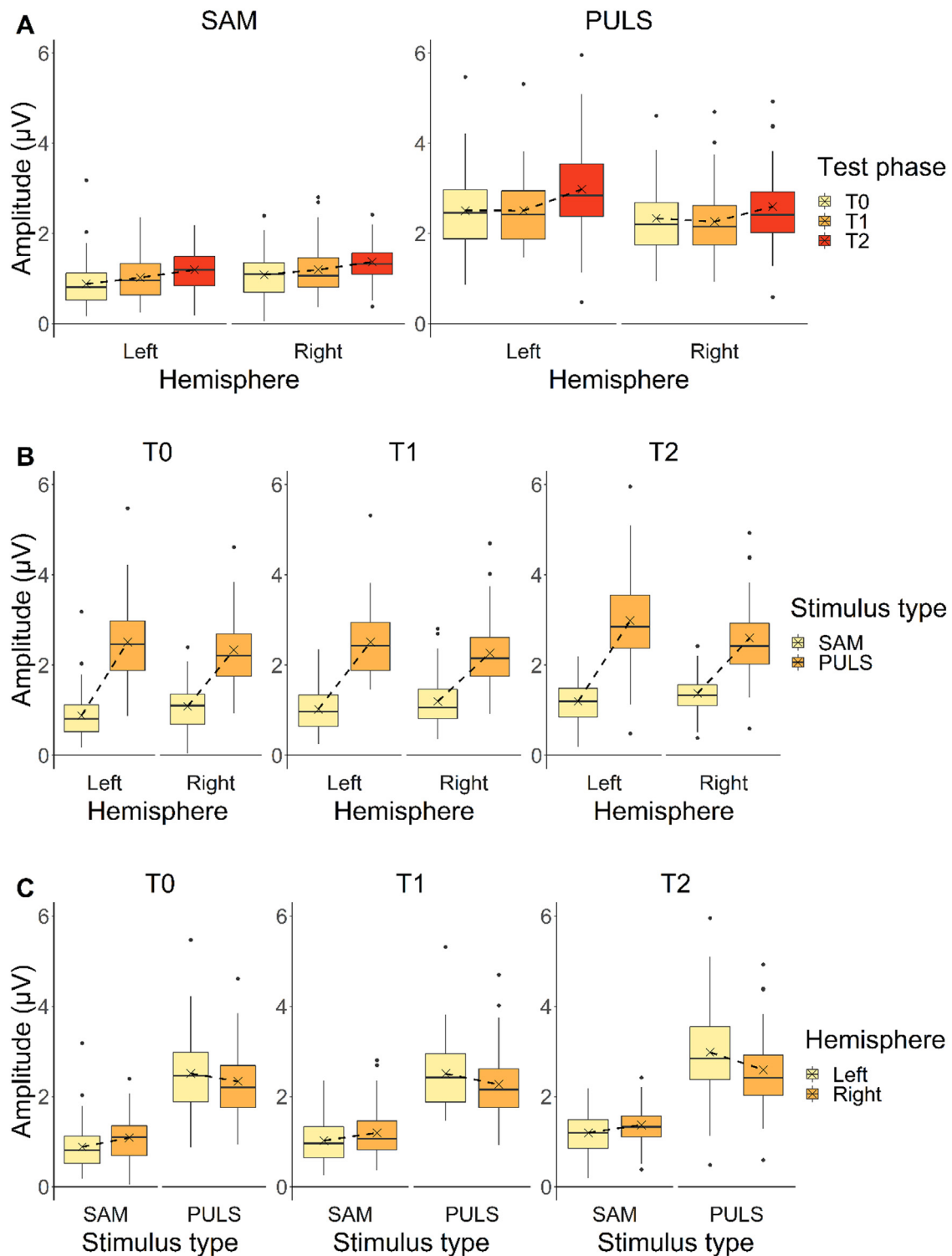


Fig. 3. Response amplitudes for the different stimulus types, hemispheres and test phases at 4 Hz

Note. Crosses indicate raw data mean response amplitudes. Individual points represent outliers, determined as all individual points above/below $Q1 \pm 1.5 \times \text{IQR}$. All three panels are different representations of the same data. The three panels depict the different significant effects found at 4 Hz. Dashed lines are used to clearly indicate the effect of interest. Panel A depicts the main effect of test phase. Panel B depicts the difference between the SAM and PULS stimulus types. Panel C depicts the interaction between stimulus type and hemisphere.

while they were significantly smaller at T0 ($z = -4.750$, $p < .001$, 95% asymptotic CI $[-0.070, -0.023]$) and T1 ($z = -3.106$, $p = .004$, 95% asymptotic CI $[-0.054, -0.007]$) compared to T2. None of the other effects reached significance (all $p > .05$).

3.2. Percentage significant responses

As a consequence of the significantly larger responses to the PULS compared to the SAM stimuli at 4 Hz, the question arose whether the percentage of significant responses would be higher for it. The percent-

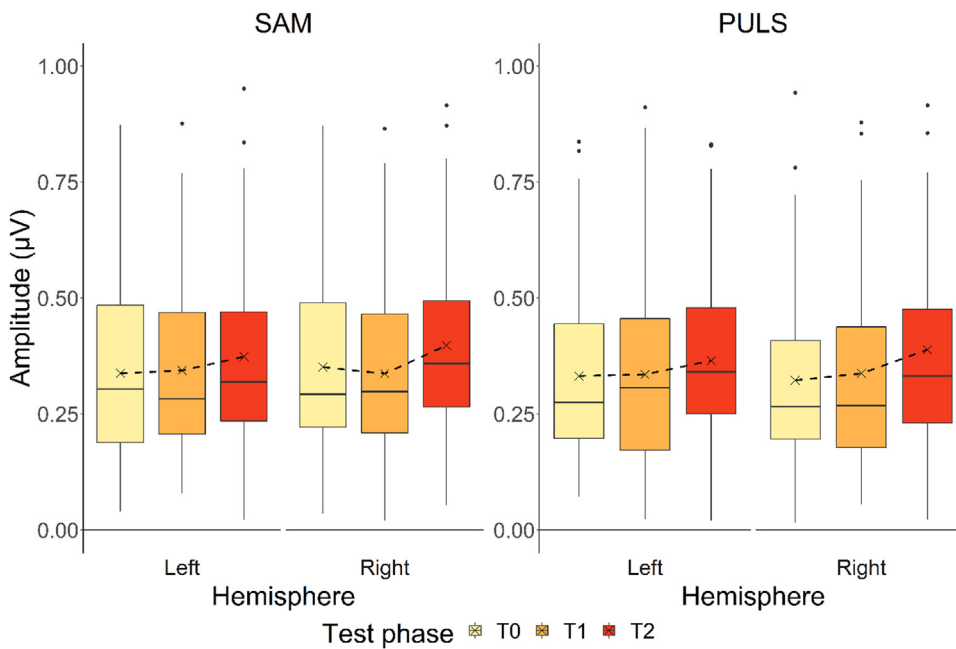


Fig. 4. Response amplitudes for the different stimulus types, hemispheres and test phases at 20 Hz, demonstrating the test phase differences. Note. Crosses indicate raw data mean response amplitudes. Individual points represent outliers, determined as all individual points above/below $Q1 \pm 1.5 \times IQR$. The dashed lines connect the means of the three test phases to clearly depict the main effect of test phase.

age significant responses, averaged over hemispheres and test phases was 82% for the 4 Hz SAM and 99% for the 4 Hz PULS stimuli.

4. Discussion

Measuring neural synchronization to SAM sounds by means of ASSR is a useful technique to investigate envelope processing (Alaerts et al., 2009; Picton, 2010; Picton et al., 2003; Rees et al., 1986; Wang et al., 2012). However, it has been argued that pulsatile stimuli with sharper rise times are more ecologically valid (Prendergast et al., 2010), and additionally, that they induce stronger responses than regular SAM sounds and are hence more efficient for response detection (John et al., 2002, 2004; Prendergast et al., 2010; Van Hirtum et al., 2019a). Interestingly, pulsatile stimuli have also been demonstrated to be effective for uncovering the neural mechanisms behind developmental disorders such as dyslexia (Van Hirtum et al., 2019a). If, however, we aim to apply pulsatile stimuli in developmental reading research aiming to uncover neural precursors of dyslexia, we first need to investigate their potential in the crucial age range of pre-reading to beginning reading age (Phan et al., 2021), which was the objective of the current longitudinal study. We compared responses to PULS and SAM stimuli from the middle of the last year of kindergarten (5 year olds) to the end of first grade (7 year olds) in Dutch-speaking typically-reading children. Neural synchronization was measured at syllable (4 Hz) and phoneme rate (20 Hz) using both SAM and PULS stimuli.

Our results revealed stronger synchronization to the PULS compared to the SAM stimuli, only at 4 Hz. At this same frequency, stimulus type impacted hemispheric specialization in the sense that responses at 4 Hz were lateralized to the right hemisphere with the SAM stimuli, but lateralized to the left hemisphere with the PULS stimuli. At both 4 and 20 Hz, there was an increase in synchronization from T0 and T1 to T2.

4.1. Synchronization to syllable rate information

4.1.1. PULS stimuli enhance synchronization

In the current study, responses at 4 Hz to the PULS stimuli were significantly enhanced compared to responses to the SAM stimuli. Whereas the median response amplitude was 1.10 μV for the SAM stimuli, the response for the PULS stimuli was significantly larger with a median response amplitude of 2.42 μV. These results thus support previous studies demonstrating increased responses to pulsatile stimuli (John et al.,

2002, 2004; Prendergast et al., 2010; Van Hirtum et al., 2019a), now extending this finding to pre-reading to beginning reading children. We hypothesized that stronger responses to the PULS stimuli could be related to discharge probabilities at the synapse to the auditory nerve fiber. This discharge probability peaks at stimulus onsets and is more prominent for steeper stimulus onset slopes (Delgutte, 1980, 1997; Geurts and Wouters, 1999), such as in the PULS stimuli. Nevertheless, we did not explicitly investigate the physiological basis of the findings in the current study, which would make an interesting research question for future research.

This finding entails multiple benefits. First, with respect to EEG data acquisition, the use of PULS stimuli should be more efficient than the use of SAM stimuli. As suggested by John et al. (2002) and John et al. (2004), using pulsatile stimuli should significantly shorten the time needed to measure significant ASSRs because of the increased response amplitudes to the stimuli. In the current study, we demonstrated that using the PULS stimuli reduced this time by 80%. A more efficient response detection is particularly convenient in a pediatric population such as our pre-reading to beginning reading children. EEG data acquisition requires considerable effort from both the child and the researcher. Sitting still and staying attentive during an EEG measurement for an extended period of time is a challenge for most children, and the resulting poor data quality is often frustrating for researchers. Stimuli that shorten the time needed to obtain significant ASSRs could ease the process for participating children and executing researchers. Furthermore, a shortened acquisition time can be decisive when applied in clinical environments where duration of tests is an important factor. Hence, the current results exert a major impact on both EEG research, especially in pediatric populations, and on clinical practice.

Second, the PULS stimuli at syllable rate might significantly contribute to for example developmental reading research. Van Hirtum et al. (2019a) revealed an atypical neural synchronization in dyslexic young adults only when using the PULS stimuli, and not when using the SAM stimuli. The authors thus demonstrated the added value of the PULS stimuli to reading research. An important period for developmental reading research is from pre-reading to beginning reading age, since research during this period allows to uncover causal neural mechanisms behind the disorder. We now demonstrated significantly stronger and more efficiently evoked responses to the PULS stimuli at syllable rate in this specific age range. Hence, the PULS stimuli are especially promising

for reading research conducted in younger children, with the potential of uncovering the neural precursors behind dyslexia.

Third, this increased synchronization to the PULS stimuli provides an explanation for the efficacy of speech envelope enhancement (EE) as a technique to improve speech perception (Van Hirtum et al., 2021; Van Hirtum et al., 2019b). EE was originally developed for use in cochlear implant users (Geurts and Wouters, 1999; Koning and Wouters, 2012, 2016) and specifically accentuates rise times in the speech envelope, which should facilitate their detection. More recently, Van Hirtum et al. (2019b) and Van Hirtum et al. (2021) demonstrated that applying EE in a speech in noise task instantaneously improved speech perception in young adults. The researchers hypothesized that EE, due to the accentuated rise times in the speech signal, enhanced synchronization to speech, hence resulting in improved speech perception. EE bears strong similarities to our PULS stimuli, since both techniques emphasize the temporal dynamics of the speech envelope, more specifically by sharpening the rise times. Importantly, amplified rise times in EE occur at approximately syllable rate (Van Hirtum et al., 2019b), whereas our results demonstrated that sharper, pulsatile stimuli enhance synchronization specifically at this rate. Therefore, it is highly plausible that EE indeed enhances synchronization to the speech signal, hence resulting in improved speech perception. An interesting question for future research is to investigate whether using EE on speech indeed enhances synchronization to the same extent as our PULS stimuli.

Whereas we could demonstrate clear differences in response between the SAM and PULS stimuli at 4 Hz, at 20 Hz, responses to both stimulus types were similar. This is not surprising if we look at the rise times of the stimuli. At 4 Hz, the pulsatile modulation decreased the rise time of the stimulus from 125 ms for the SAM stimulus to 30 ms for the PULS stimulus, creating a much more sudden onset for the PULS stimulus. On the contrary, for 20 Hz, the rise time of the PULS stimulus (30 ms) only differed slightly from that of the SAM stimulus (25 ms). Hence, at 20 Hz there is almost no difference between the rise times of the SAM and the PULS stimuli, which is why we propose we were not able to demonstrate differences in neural responses to both stimuli.

4.1.2. Hemispheric specialization is sensitive to stimulus type

Hemispheric specialization in the current study was sensitive to stimulus type. At 4 Hz, we demonstrated a rightward lateralization in response to the SAM stimuli, and a leftward lateralization in response to the PULS stimuli.

This result was rather unexpected given the consistency with which rightward lateralization is demonstrated at 4 Hz (De Vos et al., 2017a; Lizarazu et al., 2015; Luo and Poeppel, 2007; Poelmans et al., 2012; Vanvooren et al., 2014, 2015). The study by Van Hirtum et al. (2019a) who used very similar pulsatile stimuli to the ones in the current study could not confirm any effects of stimulus type on lateralization. Their study, however, included young adults, while the current study focused on pre-reading to beginning reading children. It is possible that the link between stimulus type and lateralization is only present in younger children in which the auditory system's sensitivity to syllable rate modulations is still developing (read more about this further on in the discussion), but does not persist into (young) adulthood. Indeed, lateralization has already been shown to undergo development over time (Ríos-López et al., 2020; Yamazaki et al., 2018).

An important question that remains to be answered is what the cause is of this specific pattern of hemispheric specialization. To the best of our knowledge, no studies have yet uncovered a leftward lateralization at 4 Hz with similar, pulsatile stimuli. However, even though rightward lateralization at theta rate is quite consistent, more recently, it has been shown that this rightward lateralization may diminish or even reverse under specific processing demands (Assaneo et al., 2019). Specifically, Assaneo et al. (2019) demonstrated that whereas right hemispheric synchronization at syllable rate reflects an intrinsic, bottom-up, oscillatory response, left hemispheric synchronization reflects a top-down mechanism from non-auditory cortical areas related to different factors

such as speech intelligibility or attention. These top-down influences to the left hemisphere may reverse the classical rightward lateralization to syllable rate modulations. This agrees with studies such as the one by Peelle et al. (2013) that showed a leftward lateralization at syllable rate in response to intelligible sentences. Hence, hemispheric specialization does not only occur due to asymmetric temporal sampling of purely acoustic features (Poeppel, 2003), but can be influenced by other cues such as linguistic content and attention (Assaneo et al., 2019; Peelle et al., 2013). It is unlikely that factors such as these contributed to the leftward lateralization to the PULS stimuli in the current study, but we do propose that cues unrelated to the rhythmic properties of the signal contribute to hemispheric specialization, at least in younger children.

An influential theory by Zatorre and Belin (2001) that preceded the AST theory (Poeppel, 2003) proposed that the left hemisphere is better suited for processing temporal information, whereas the right hemisphere is better suited for processing spectral information. Our results can be interpreted with respect to this proposal. Reducing the rise time of the envelope shape to create the PULS stimuli cut the PULS stimuli down to only temporal cues (Doelling et al., 2014; Van Hirtum et al., 2019a), whereas this was not the case for the SAM stimuli. The much stronger temporal information in the PULS stimuli compared to the SAM stimuli might have caused the leftward lateralization, consistent with the proposal by Zatorre and Belin (2001). Whereas the SAM stimuli possess smooth temporal modulation transitions of about 125 ms, the transitions in the PULS stimuli are much more sudden, namely about 30 ms. The slope of the PULS stimuli is therefore much steeper, creating a stronger temporal cue. This observation may be related to the increased discharge probability to the auditory nerve fiber at the onset of a stimulus, with a higher increase for steeper stimulus onset slopes (Delgutte, 1997; Geurts and Wouters, 1999). However, this remains a hypothesis, and future research should aim to uncover the specific mechanisms behind the effect of stimulus type on hemispheric specialization. Such a study should preferably longitudinally investigate different stimulus types to uncover at what point in development leftward lateralization to PULS stimuli evolves to rightward lateralization. At least one extra stimulus type should be included that falls somewhere in between the purely temporal PULS stimulus and the SAM stimulus to investigate whether a gradual transition from leftward to rightward lateralization can be exposed in younger children.

Additionally, one might suggest that the leftward lateralization to the PULS stimuli is merely the consequence of a contralateral processing preference based on an anatomical cross-over to the contralateral side (Bailey, 2010). However, hemispheric specialization may be the result of anatomical preference, as well as functional preference based on acoustic properties of the auditory system (Poeppel, 2003). In ASSR literature, rightward lateralization in response to theta rate stimulation has already been demonstrated with all stimulation modalities: monaural right ear stimulation, monaural left ear stimulation and bilateral stimulation (De Vos et al., 2017b; Poelmans et al., 2012). In line with this, several studies have shown rightward lateralization to right ear stimulation with similar ASSR stimuli as those implemented in the current study, in both adults (Poelmans et al., 2012; Vanvooren et al., 2014) and children (De Vos et al., 2017a; Granados Barbero et al., 2022; Vanvooren et al., 2015). This supports lateralization based on functional preference over anatomical preference. Furthermore, if the leftward lateralization in response to the PULS stimuli were due to purely anatomical contralateral lateralization, we would have expected to uncover this same pattern for the SAM stimuli. In contrast, responses to the SAM stimuli are lateralized to the right hemisphere. Therefore, we suggest that the current pattern of differential lateralization between SAM and PULS stimuli reflects substantial differences in central auditory processing rather than a confound resulting from right ear stimulation in the current study. Ideally, we would have included additional monaural left ear and bilateral stimulation modalities in the current study, but this was not possible due to time constraints and the young age of the children.

Even though our PULS stimuli contain no linguistic information, the pattern of hemispheric specialization in response to these stimuli aligns well with that in response to stimuli with higher language processing demands due to the presence of linguistic or semantic information (Assaneo et al., 2019; Peelle et al., 2013). Interestingly, it has been demonstrated that the strength of speech entrainment in the left auditory cortex is associated with speech intelligibility (Ahissar et al., 2001; Zoefel et al., 2018), while this is not the case for the right auditory cortex (Peelle et al., 2013). Taken together, we might suggest that a leftward lateralization, as seen in response to our PULS stimuli, more closely resembles natural speech envelope tracking. We propose that the PULS stimuli might be more ecologically valid than the SAM stimuli (Prendergast et al., 2010). However, this interpretation should be treated with caution. In order to empirically support this claim, we recommend future research to compare hemispheric specialization to the PULS stimuli and natural speech in the same population, at both scalp and source levels.

4.1.3. Synchronization to syllable rate information increases with age

Our results demonstrated a developmental increase in neural synchronization to syllable rate modulations. More specifically, at 4 Hz, responses were stronger at T2, compared to T0 and T1. There was no change in response between T0 and T1. These findings did not differ between SAM and PULS stimulus types.

This developmental increase in response is consistent with a study by Kolozsvári et al. (2021), who cross-sectionally demonstrated an increase from childhood to adulthood in coherence values between the brain signal measured with magneto-encephalography (MEG) and speech. The authors suggested this as evidence for an improved ability of the brain to track speech with age. Nonetheless, most previous studies on the topic showed either a decrease in syllable rate responses from childhood to adulthood (Tlumač et al., 2012; Vanvooren et al., 2015), or no difference at all (Lizarazu et al., 2015). However, all of these studies cross-sectionally compared children with adults, whereas in the current study we longitudinally investigated development from pre-reading (5 years old) to beginning reading age (7 years old). A possibility is that at this time, the sensitivity of the auditory system to syllable rate information is indeed still developing, and that a maturational decrease in response will only occur at a later point in development. Another study that looked at the same age range as the current study is the one by De Vos et al. (2017a). The authors could also not confirm a decrease in response from 5 to 7 years. However, in their study responses did also not increase as in the current study, but remained similar. A direct comparison between our results and those of De Vos et al. (2017a) is however complicated, considering that the authors used a different response measure and the studied populations slightly differed between our respective studies. Even though all children in the current study were classified as typical readers, they were recruited from an intervention study in children at cognitive risk for dyslexia. The increasing syllable rate synchronization could therefore also be specific to this population of children at risk for dyslexia that eventually develop typical reading skills. However, it has already been shown that (family) risk for dyslexia does not contribute to neural synchronization at both syllable and phoneme rate (De Vos et al., 2017a).

Despite inconsistencies in the literature, we suggest that our data demonstrate an ongoing development of the auditory system's sensitivity to syllable rate information in pre-readers to beginning readers.

4.2. Synchronization to phoneme rate information increases with age

Similar to our results at 4 Hz, responses at 20 Hz increased from T0 and T1 to T2, whereas responses did not change between T0 and T1. At 20 Hz, the findings did also not differ between SAM and PULS stimulus types.

This developmental increase is consistent with studies who also reported increasing phoneme rate responses during childhood (De Vos

et al., 2017a) and from childhood to adulthood (Lizarazu et al., 2015), although both Vanvooren et al. (2015) and Tlumač et al. (2012) reported no differences at this frequency between childhood and adulthood. Rather than maturation, this increasing sensitivity to phoneme rate modulations in the current study could be attributed to the development of phoneme awareness in beginning readers (De Vos et al., 2017a). The increase of 20 Hz response amplitudes occurs around the onset of formal reading instruction, and phoneme awareness is known to emerge as a consequence of reading acquisition (Goswami & Bryant, 2016). The link between increasing phoneme rate synchronization and the development of phoneme awareness is further supported by correlations between phoneme rate synchronization and behavioral phoneme awareness scores (Lizarazu et al., 2015). However, because some of the children in the current study received some kind of phonics-based training in between T0 and T1, we should remain careful in our interpretation of increasing phoneme rate synchronization as a consequence of pure formal reading instruction. Interestingly, an over-synchronization at phoneme rate is linked with dyslexia (De Vos et al., 2017a, 2017b; Lizarazu et al., 2015), hence suggesting that there is an optimal level of synchronization that becomes dysfunctional when exceeded.

4.3. Limitations

We need to acknowledge a few limitations in the current study. First, a limitation that goes up for all electrophysiological studies in young children is the dropout and data quality. In the current study, some conditions for which data were acquired could not be included because noise levels were too high to process the data or because the measurement was prematurely ended because the child was not willing to proceed anymore. However, using the PULS stimuli might alleviate some practical concerns such as these, by making data collection more time efficient.

Second, despite the advantages of using amplitude-modulated stimuli to investigate neural synchronization, we are only able to measure one specific modulation frequency at a time in this way. This approach is time-consuming, but moreover, insufficient to cover the auditory system's and brain's response to a frequency band (David et al., 2022; Gransier and Wouters, 2021). Gransier and Wouters (2021) developed the Temporal Envelope Speech Tracking or TEMPEST framework. The TEMPEST framework provides a solution to aforementioned issues and allows evaluation of the overall envelope processing ability of the auditory system using stimuli that contain a range of envelope modulations. Furthermore, different parameters of the stimuli, such as the envelope shape, can be adjusted, which allows for a more efficient evaluation of the effect of different rise times on neural synchronization. Hence, it would be a good idea for future studies to make use of the TEMPEST stimuli.

5. Conclusion

Our results show that pulsatile stimuli with sharper rise times enhance neural synchronization to 4 Hz amplitude modulations and greatly improve the efficiency of data acquisition (John et al., 2002, 2004). This provides an explanation for the improved speech perception in response to EE (Van Hirtum et al., 2021; Van Hirtum et al., 2019b). Additionally, at 4 Hz, using pulsatile stimuli resulted in a different hemispheric specialization, more closely resembling natural speech envelope tracking. Distilling the stimuli down to only temporal information, as is the case for the PULS stimuli, is hypothesized to have contributed to this. Further studies are required to investigate the specifics of the differential hemispheric specialization. Nevertheless, these results significantly contribute to the literature on envelope shapes with reduced rise times and demonstrate the applicability of PULS stimuli in pre-reading to beginning reading age. The greatest novelty of the current study lies in the empirical demonstration of an increased efficiency of data acquisition across a wide range of pre-reading and beginning reading stages,

which could have major implications on future pediatric EEG studies and clinical practice.

Funding sources

This work was funded by the Research Council of KU Leuven (C14/17/046).

Ethics approval statement

The study was approved by the Medical Ethical Committee of the University Hospital of Leuven, KU Leuven, and signed ethical consents were obtained for all participants in line with the Declaration of Helsinki.

Declaration of Competing Interest

The authors declare no competing interests.

Credit authorship contribution statement

Shauni Van Herck: Formal analysis, Investigation, Data curation, Writing – original draft, Visualization, Project administration. **Maria Economou:** Writing – review & editing, Project administration. **Femke Vanden Bempt:** Writing – review & editing, Project administration. **Pol Ghesquière:** Conceptualization, Methodology, Writing – review & editing, Supervision, Funding acquisition. **Maaïke Vandermosten:** Conceptualization, Methodology, Writing – review & editing, Supervision, Funding acquisition. **Jan Wouters:** Conceptualization, Methodology, Writing – review & editing, Supervision, Funding acquisition.

Data and code availability statement

The datasets generated and analyzed during the current study are available from the PI (Jan Wouters) on reasonable request. The data and code sharing adopted by the authors comply with the requirements of the KU Leuven and Medical Ethical Committee and the funding bodies.

Acknowledgments

We are most grateful to all children and parents for their cooperation in this study. Our special thanks goes to Toivo Glatz and Tilde Van Hirtum for assisting in data acquisition and Tilde Van Hirtum for help with the development of the stimuli. At last, we are grateful to colleagues at the Research Group ExpORL and the research unit of Parenting and Special Education and the Master students Speech Therapy and Audiology, Medicine and Educational Sciences that assisted in data acquisition and protocol preparation.

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