TITLE PAGE

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Subcortical auditory neural synchronization is deficient in pre-reading children who develop dyslexia

Running title

Subcortical auditory processing deficits in dyslexia

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Conflict of Interest Statement

The authors have no conflict of interest to declare.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author (astrid.devos@kuleuven.be) upon reasonable request.

MANUSCRIPT

Subcortical auditory neural synchronization is deficient in pre-reading children who develop dyslexia

RESEARCH HIGHLIGHTS

- Dyslexia is one of the most prevalent developmental disorders, affecting up to 7% of the population.
- Although remedial interventions are most effective during early stages of reading acquisition, dyslexia diagnoses are typically only given after several years of formal literacy instruction.
- Our study demonstrates that children with dyslexia differ from typically developing children with regard to subcortical neural synchronization (80 Hz ASSRs) prior to reading acquisition.
- Moreover, the strength of pre-reading subcortical ASSRs is predictive for later reading outcome.
- In the long term, subcortical synchronization deficits might thus serve as a pre-diagnostic marker for dyslexia. 80 Hz ASSRs are particularly suited for these purposes.

ABSTRACT

Auditory processing of temporal information in speech is sustained by synchronized firing of neurons along the entire auditory pathway. In school-aged children and adults with dyslexia, neural synchronization deficits have been found at cortical levels of the auditory system, however, these deficits do not appear to be present in pre-reading children. An alternative role for subcortical synchronization in reading development and dyslexia has been suggested, but remains debated. By means of a longitudinal study, we assessed cognitive reading-related skills and subcortical auditory steady-state responses (80 Hz ASSRs) in a group of children before formal reading instruction (pre-reading), after one year of formal reading instruction (beginning reading), and after three years of formal reading instruction (more advanced reading). Children were retrospectively classified into three groups based on family risk and literacy achievement: typically developing children without a family risk for dyslexia, typically developing children with a family risk for dyslexia, and children who developed dyslexia. Our results reveal that children who developed dyslexia demonstrate decreased 80 Hz ASSRs at the pre-reading stage. This effect is no longer present after the onset of reading instruction, due to an atypical developmental increase in 80 Hz ASSRs between the pre-reading and the beginning reading stage. A forward stepwise logistic regression analysis showed that literacy achievement was predictable with an accuracy of 90.4% based on a model including three significant predictors, i.e., family risk for dyslexia ($R = .31$), phonological awareness ($R = .23$), and 80 Hz ASSRs ($R = .26$). Given that (1) abnormalities in subcortical ASSRs preceded reading acquisition in children who developed dyslexia and (2) subcortical ASSRs contributed to the prediction of literacy achievement, subcortical auditory synchronization deficits may constitute a pre-reading risk factor in the emergence of dyslexia.

KEY WORDS

auditory steady-state responses (ASSRs); developmental dyslexia; neural synchronization; pre-reading; subcortical; temporal processing

1 INTRODUCTION

Developmental dyslexia is defined as a learning disability, characterized by severe and persistent difficulties with reading and/or spelling, despite adequate intelligence and instruction (Peterson & Pennington, 2012). To date, it is widely accepted that dyslexia is associated with a specific cognitive deficit in phonological processing, i.e., in the representation, storage, and retrieval of speech sounds (Vellutino, Fletcher, Snowling, & Scanlon, 2004). Other, somewhat more debated, theories have allocated these phonological processing problems to a dysfunction in basic sensory mechanisms (e.g., Goswami, 2015; Wright, Bowen, & Zecker, 2000). As such, a dominant theory in the auditory domain asserts that temporal processing deficits might obstruct the formation of speech sound representations, thereby compromising phonological and reading development (Goswami et al., 2002; Talcott et al., 2000; Tallal, 1980). Temporal properties of speech, including envelope (< 50 Hz), periodicity (50 - 500 Hz), and fine-structure (> 600 Hz) information, are indeed known to be important for different aspects of speech perception (Rosen, 1992). Given that the processing of temporal information is sustained by synchronized firing of neurons along the entire auditory pathway (Palmer & Summerfield, 2002), both cortical and subcortical synchronization deficiencies have been considered in dyslexia research.

At the level of the auditory cortex, neurons have an upper limit of synchronization of about 40 Hz (Joris, Schreiner, & Rees, 2004). Studies investigating cortical synchronization have therefore mainly focused on temporal processing of envelope information (see Goswami, 2011 for a comprehensive framework). The majority of these studies report atypical neural synchronization in school-aged children and adults with dyslexia, e.g., in delta (Cutini, Szűcs, Mead, Huss, & Goswami, 2016; Hämäläinen, Rupp, Soltész, Szűcs, & Goswami, 2012; Molinaro, Lizarazu, Lallier, Bourguignon, & Carreiras, 2016; Power, Colling, Mead, Barnes, & Goswami, 2016; Soltész, Szűcs, Leong, White, & Goswami, 2013), theta (Lizarazu et al., 2015), alpha and beta (De Vos, Vanvooren, Vanderauwera, Ghesquière, & Wouters, 2017b), and gamma range activity (Lehongre, Ramus, Villiermet, Schwartz, & Giraud, 2011; Lizarazu et al., 2015). However, we have recently demonstrated that at least some of these cortical synchronization deficits seem to reflect consequential effects rather than the underlying cause for reading problems in dyslexia (De Vos, Vanvooren, Vanderauwera, Ghesquière, & Wouters, 2017a).

Alternatively, speech and phonological processing problems might also result from synchronization deficiencies at subcortical levels of the auditory system. Given that the upper limit of synchronization for

neurons in the brainstem extends up to several hundred Hz, the main focus here has been on temporal processing of periodicity and fine-structure information. Studies in typical reading children and adults have demonstrated that the precision with which the auditory brainstem encodes these temporal properties is significantly related to behavioral measures of speech perception (Anderson, Skoe, Chandrasekaran, Zecker, & Kraus, 2010; Hornickel, Chandrasekaran, Zecker, & Kraus, 2011; Hornickel, Skoe, Nicol, Zecker, & Kraus, 2009), phonological processing (White-Schwoch & Kraus, 2013), and reading (Hornickel, Anderson, Skoe, Yi, & Kraus, 2012; Neef, Schaadt, & Friederici, 2017; Skoe, Brody, & Theodore, 2017). Accordingly, atypical auditory brainstem responses (ABRs) and frequency following responses (FFRs) have been found in individuals with a broad variety of learning problems (e.g., Cunningham et al., 2001; King et al., 2002; Purdy et al., 2002; Wible et al., 2004; Banai, 2005; Basu et al., 2010; Malayeri et al., 2014; for a review, see Banai et al., 2007). Studies in individuals with exclusive reading-based learning problems, i.e., without comorbid specific language impairments or attention deficit disorders, are however limited. The study of Poelmans et al. (2012) is, to the best of our knowledge, the only study that investigated subcortical auditory processing specifically in individuals with no other learning problems than dyslexia. In contrast to the studies mentioned above, Poelmans et al. (2012) found no evidence for subcortical synchronization deficiencies in their specific sample of adults with dyslexia. Nevertheless, interesting subcortical effects have recently been reported in pre-reading children with a family risk for dyslexia (Vanvooren, Poelmans, Hofmann, Ghesquière, & Wouters, 2014) or a cognitive risk for dyslexia (White-Schwoch et al., 2015; White-Schwoch & Kraus, 2013). Although these findings in pre-readers do suggest that abnormalities at subcortical levels might indeed be responsible for the disruption of certain auditory processing mechanisms that underlie a child's phonological and later reading development, a longitudinal follow-up is necessary in order to examine whether the observed effects are specific to children who go on to develop dyslexia.

The present study aims to elucidate the role of subcortical auditory temporal processing deficits in the emergence of dyslexia. Therefore, we longitudinally examined cognitive reading-related measures as well as subcortical auditory steady-state responses (80 Hz ASSRs) in a group of children at three different stages in reading development, i.e., prior to formal reading instruction (pre-reading), after one year of formal reading instruction (beginning reading), and after three years of formal reading instruction (more advanced reading). As will be described in more detail later, 80 Hz ASSRs provide an objective measure for the synchronization of neurons to temporal information, more specifically amplitude

modulations, at the level of the auditory brainstem (see 2.3). Our specific objectives were to determine (1) whether children who develop dyslexia demonstrate subcortical auditory temporal processing deficits, and if so, at which stage(s) of reading acquisition, (2) whether subcortical auditory temporal processing deficits also relate to family risk for dyslexia, and (3) whether pre-reading measures of subcortical auditory temporal processing provide added value to the prediction of literacy achievement, in addition to cognitive and genetic-environmental risk factors.

2 METHOD

2.1 Participants

The original sample consisted of 87 children attending the last year of kindergarten. All children were monolingual native Dutch speakers with normal non-verbal IQ (cutoff score > 85; Raven, Court, & Raven, 1984) and no history of long-term hearing loss, visual problems, brain injury, or neurological disorders (for a detailed description of the original sample, see Vanvooren et al., 2014). Note that approximately half of the children had an increased family risk for dyslexia, since they had at least one first-degree relative who was formally diagnosed with dyslexia. At the pre-reading stage, EEG measurements were collected in all children, however, four children were found to have an 80 Hz ASSR measurement that was too noisy to allow for further analyses. At the beginning and more advanced reading stage, respectively five and nine children decided not to participate and respectively three and six children were found to have a noisy 80 Hz ASSR measurement. To be in accordance with Vanvooren et al. (2014), we also excluded nine non-right handed children (Oldfield, 1971). Consequently, the present study reports on neurophysiological data of 74 children in the pre-reading stage, 70 children in the beginning reading stage and 63 children in the more advanced reading stage.

We retrospectively defined three participant subgroups: typically developing children without a family risk for dyslexia (FRD-DYS⁻), typically developing children with a family risk for dyslexia (FRD⁺DYS⁻), and children who developed dyslexia (DYS⁺). In order to be assigned to the DYS⁺ group, children were required to demonstrate (1) severe and persistent reading problems, implemented as consecutive test scores below the 10th percentile on the same standardized word (Brus & Voeten, 1973) or pseudoword (van den Bos et al., 1994) reading task, or (2) severe and persistent spelling problems, implemented as consecutive test scores below the 10th percentile on the same standardized spelling test (Dudal, 1997). Because dyslexia is mostly defined as a reading impairment, children fulfilling the second criterion were

additionally required to demonstrate reading scores below the 25th percentile at each measurement point. At the time of the final 80 Hz ASSR measurement, four children were formally diagnosed with dyslexia. Some parents reported signs of other learning, behavioral, or developmental problems than dyslexia, however, none of these had (yet) been formally diagnosed. Note that FRD-DYS⁺ and FRD⁺DYS⁺ children were combined into one DYS⁺ group, as the sample size of the FRD-DYS⁺ group was insufficient ($N = 2$) to allow for separate analyses. Participant characteristics for each subgroup are presented in TABLE 1. There were no significant group differences regarding age, gender, or non-verbal IQ (all $p > .10$).

This study was approved by the Medical Ethical Committee of the University Hospitals of Leuven. Written informed consents were obtained from the parents of all participating children in conformance with the Declaration of Helsinki.

2.2 Cognitive measurements

In kindergarten, we assessed pre-reading measures of phonological awareness, rapid automatized naming, and letter knowledge. *Phonological awareness* was evaluated through an end-rhyme and an end-phoneme identification task in order to assess both syllabic and phonemic levels of awareness (de Jong et al., 2000, adapted by van Otterloo & 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 had the same end rhyme or end phoneme as the given word by naming or by pointing to the corresponding picture. The raw 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. *Rapid automatized naming* was measured with a color and an object naming task (van den Bos et al., 2002; Boets et al., 2006). In both tasks, a card was presented containing five different symbols, each symbol displayed 10 times in a random order. Color symbols were represented by black, blue, red, yellow, and green rectangles. Object symbols were represented by drawings of a tree, a duck, a chair, a pair of scissors, and a bicycle. The child had to name the symbols on the card as fast and accurately as possible. Each of the five color or object symbols was named for the child prior to testing. The raw test score was calculated as the number of correctly named symbols per second. *Letter knowledge* was assessed by means of a productive task (Boets, Wouters,

van Wieringen, De Smedt, & Ghesquière, 2008). A card consisting of the 16 most frequently used letters in Dutch was presented. The child had to name each of these letters. The raw test score was calculated as the number of correctly identified letters, with a maximum score of 16.

After the start of formal reading instruction, we administered literacy measures of reading and spelling. *Reading* was assessed with a standardized word reading task (Brus & Voeten, 1973) and a standardized pseudoword reading task (van den Bos et al., 1994). In both tasks, a card was presented consisting of 116 items distributed over four columns. The child had to read the items on the card as fast and accurately as possible. The raw test score was determined as the number of correctly read words or pseudowords, within a time limit of respectively 1 and 2 minutes, with a maximum score of 116 for both tasks. *Spelling* was measured with a standardized grade-appropriate writing on dictation test (Dudal, 1997). Children were asked to spell single words in isolation or presented in a sentence context and short sentences. The raw test score represented the number of correctly spelled words, with a maximum score of 60.

2.3 Neurophysiological measurements

2.3.1 Stimulus parameters

ASSRs quantify the degree with which neurons at different stages of the auditory pathway fire synchronously to a temporal modulation (Picton, John, Dimitrijevic, & Purcell, 2003). In the present study, we used a speech-weighted noise carrier wave, which was 100% amplitude modulated at approximately 80 Hz. The carrier noise was adopted from the “Leuven Intelligibility Sentence Test” (LIST; van Wieringen & Wouters, 2008) and represents the long-term average speech spectrum of 730 sentences of a female speaker. As such, the spectrum of the stimulus closely resembles the spectral structure of realistic speech, without including linguistic content and with full control over the stimulus parameters (i.e., all parameters of the stimulus are known and adjustable). The modulation frequency of 80 Hz was chosen in order to evaluate neural synchronization at the level of the auditory brainstem. The assumption that 80 Hz ASSRs originate from subcortical structures is based on converging evidence from EEG (Herdman et al., 2002), fMRI (Harms & Melcher, 2002; Steinmann & Gutschalk, 2011; Tanaka et al., 2000), and PET studies (Pastor et al., 2002; Reyes et al., 2004), showing that high modulation frequencies (≥ 80 Hz) evoke responses at anatomical sites located at low levels of the auditory pathway. Specifically, the inferior colliculus has been identified as the dominant neural

generator underlying 80 Hz ASSRs (Giraud & Lorenzi, 2000). Alternatively, MEG studies have reported mainly cortical contributions to ASSRs, regardless of the modulation frequency (Ross, Borgmann, Draganova, Roberts, & Pantev, 2000; Schoonhoven, Boden, Verbunt, & de Munck, 2003; Tang, Brock, & Johnson, 2016). Given that MEG is relatively insensitive in recording sources with a radial orientation and sources that are deeply located in the brain, these findings were probably dominated by a (weak) cortical 80 Hz ASSR source. It has been claimed that recent advances allow MEG to accurately localize deeper structures and to measure brainstem activity as well. For example, Coffey et al. (2016) demonstrated a right-lateralized cortical contribution to the speech-evoked ABR using MEG, a finding that was replicated by means of EEG, fMRI and DWI (Coffey, Musacchia, & Zatorre, 2017). Nevertheless, EEG source analyses in adults have convincingly shown that subcortical generators dominate scalp-recorded 80 Hz ASSRs (Luke, De Vos, & Wouters, 2017). In addition, the consistent finding that 80 Hz ASSRs are not influenced by sleep or anesthesia (Aoyagi et al., 1993; Cohen, Rickards, & Clark, 1991) argues indirectly for minimal cortical contribution in the generation of this response. Note that the exact modulation frequency was 80.08 Hz, to ensure that each epoch contains an integer number of periods and to prevent electromagnetic artifacts occurring at integer frequencies (e.g., line noise at 50 Hz) on ASSR detection. To allow for comparison with our previous studies (Poelmans et al., 2012; Vanvooren, Hofmann, Poelmans, Ghesquière, & Wouters, 2015), the stimulus was presented monaurally to the right ear at 70 dB SPL through insert earphones.

2.3.2 Recording parameters

The EEG was recorded during 10 minutes (600 seconds) with the BioSemi ActiveTwo system using 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. During the measurements, children lay down on a bed in a double-walled soundproof booth with a Faraday cage and watched a soundless movie. A child-friendly 'space protocol' was designed, inspired by Theys et al. (2014). Alertness and movement were continuously monitored by an experienced test leader who was present in the EEG cabin.

2.3.3 EEG pre-processing

Pre-processing of the recorded EEG data was done in Matlab R2013a. Each EEG recording was divided into epochs of 1.024 seconds (s), resulting in 585 epochs per electrode (600 s / 1.024 s). 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 rejection was set on an individual basis, until 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. Artifact-free epochs were referenced to electrode Cz and clustered into sweeps of 64 consecutive epochs. This resulted in seven sweeps per electrode (448 epochs / 64 epochs), which were subsequently averaged into one sweep per electrode. Next, sweeps were averaged across two pre-selected electrode configurations, [TP7, P1, P3, P5, P7, P9, PO3, PO7, O1] and [TP8, P2, P4, P6, P8, P10, PO4, PO8, O2], resulting in the construction of two artificial “channels” representing the averaged time signal recorded over the left and right temporo-parietal, and occipital regions (FIGURE 1 [A]). These electrode configurations are based on previous research showing that these electrodes are most sensitive to pick up subcortical ASSRs in children (Vanvooren et al., 2014) as well as adults (Vanvooren et al., 2015). The averaged time signals of the two artificial channels were converted into a set of complex values that vary with frequency by means of a Fast Fourier Transformation (FFT) algorithm (FIGURE 1 [B] and [C]). Given an averaged sweep length of 65.5 s (64 epochs × 1.024 s), the FFT spectrum had a frequency resolution of 0.015 Hz. Finally, the inverse gain of the high-pass filter was added to the spectral power to compensate for the filter attenuation.

2.3.4 ASSR quantification

The ASSR appears in the FFT spectrum as a peak in the frequency bin corresponding to the modulation frequency f . To verify the presence of an ASSR an F test was applied, comparing the power of the Fourier component in frequency bin f (response power P_f) to the power of the Fourier components in 120 adjacent frequency bins (stimulus-induced noise power $P_f \pm 60$ bins). This results in an F ratio statistic with (2, 240) degrees of freedom. If the F ratio statistic corresponds to a p value below .05, the response is considered to be significantly different from the surrounding EEG noise (Dobie & Wilson, 1996; John & Picton, 2000). For each group, the percentage of participants with significant responses was $\geq 73\%$

for the left electrode region and $\geq 93\%$ for the right electrode region, with no significant differences between groups (all $p > .10$).

The ratio between the response power P_f and the stimulus-induced noise power $P_{f \pm 60 \text{ bins}}$, also referred to as the signal-to-noise ratio (SNR; FIGURE 1 [D] and [E]), was used as a measure to quantify the degree of synchronized neural activity, after conversion to dB by means of a logarithmic transformation:

$$\text{SNR (dB)} = 10 \times \log_{10} \left(\frac{P_f}{P_{f \pm 60 \text{ bins}}} \right)$$

It is important to note that group or developmental effects in terms of response SNR can be the consequence of (1) a difference in response power (or amplitude), (2) a difference in stimulus-induced noise power (or amplitude), or (3) a combination of both. In order to verify that none of our results were driven by differences in the stimulus-induced noise power, we systematically computed and compared the results for all three outcome measures (i.e., response amplitude, noise amplitude, and response SNR). No group or developmental effects were found in terms of stimulus-induced noise amplitude for 80 Hz ASSRs, thus, the observed effects in terms of response SNR are presumed to reflect differences in synchronized neural activity.

2.4 Statistical analyses

All statistical analyses were performed with IBM SPSS Statistics 24.0. The assumption of normality was assessed with Kolmogorov-Smirnov tests. If the distribution of a dependent variable was significantly different from a normal distribution, non-parametric analyses were used. Note that normality was not violated for dependent variables that were included in the mixed ANOVAs, nor for the standardized residuals of the logistic regression model. The assumption of homogeneity of variances was assessed with Levene tests. If variances were significantly different between groups, the Welch-Satterthwaite method was used to adjust the degrees of freedom. All analyses were two-tailed with significance levels set at .05 and measures for effect size (r) were calculated.

3 RESULTS

3.1 Cognitive results

Using independent t -tests for normally distributed data and Mann-Whitney U -tests for non-normally distributed data, we first compared FRD⁻DYS⁻ and DYS⁺ children to assess the effects of dyslexia.

Similarly, the effects of family risk for dyslexia were investigated by comparing FRD⁻DYS⁻ and FRD⁺DYS⁻ children. Results of the cognitive analyses are reported in TABLE 2.

3.1.1 Effects related to dyslexia

FRD⁻DYS⁻ and DYS⁺ children demonstrated significant differences already before the start of reading acquisition. DYS⁺ children performed significantly poorer than FRD⁻DYS⁻ children on pre-reading tasks measuring phonological awareness, rapid automatized naming, and letter knowledge (all $p < .05$, except for end-phoneme identification). DYS⁺ children also differed significantly from FRD⁻DYS⁻ children on all reading and spelling tests that were administered after the start of formal reading instruction (all $p < .01$), as was to be expected from the group classification.

3.1.2 Effects related to family risk for dyslexia

We found no significant differences between FRD⁻DYS⁻ and FRD⁺DYS⁻ children in pre-reading tasks measuring phonological awareness, rapid automatized naming, or letter knowledge (all $p > .05$), nor in reading and spelling tasks conducted after one year of formal reading instruction (all $p > .10$). However, a significant difference was found between FRD⁻DYS⁻ and FRD⁺DYS⁻ children in literacy tasks conducted after three years of formal reading instruction. More specifically, FRD⁺DYS⁻ children performed significantly poorer than FRD⁻DYS⁻ children on pseudoword reading ($t_{(45)} = 2.08$, $p = .043$, $r = .30$) and spelling ($t_{(45)} = 2.04$, $p = .047$, $r = .29$).

3.2 Neurophysiological results

Further analyses proceeded in two successive steps. Using a mixed ANOVA per developmental stage, we first compared neurophysiological results between FRD⁻DYS⁻ and DYS⁺ children to assess the effects of dyslexia per developmental stage. Similarly, the effects of family risk for dyslexia per developmental stage were investigated by comparing FRD⁻DYS⁻ and FRD⁺DYS⁻ children. Electrode region was included in both analyses as a within-subject factor with two levels, i.e., left and right. Secondly, using a mixed ANOVA per group, we compared neurophysiological results between pre-reading, beginning reading, and more advanced reading stages to assess developmental effects per group. Electrode region was again included as a within-subject factor. Results of the neurophysiological

analyses are reported in TABLE 3. Figures presenting single subject data are included in the Supporting information.

3.2.1 Effects related to dyslexia per developmental stage

No significant main effects of dyslexia were found at any developmental stage (all $p > .10$). However, there was a significant interaction effect between dyslexia and electrode region at the pre-reading stage ($F_{(1, 52)} = 4.25$, $p = .044$). More specifically, DYS⁺ children exhibited significantly lower 80 Hz response SNRs over the ipsilateral right electrode region in comparison to FRD·DYS⁻ children (MD = 2.75 dB, SE = 1.04 dB, $p = .011$, $r = .34$), whereas no such effect was present over the contralateral left electrode region (MD = .14 dB, SE = 1.37 dB, $p = .919$, $r = .01$). This lateralized group difference was no longer present after one year ($F_{(1, 47)} = 1.88$, $p = .177$) nor after three years ($F_{(1, 44)} = 0.35$, $p = .554$) of formal reading instruction. We also found significant main effects of electrode region at all developmental stages (all $p < .001$), indicating that 80 Hz response SNRs were consistently higher over the ipsilateral right electrode region than over the contralateral left electrode region (FIGURE 2).

3.2.2 Effects related to family risk for dyslexia per developmental stage

At the pre-reading stage, a significant main effect of family risk for dyslexia was found ($F_{(1, 56)} = 4.42$, $p = .040$). More specifically, we found that FRD⁺DYS⁻ children demonstrated significantly higher 80 Hz overall response SNRs in comparison to FRD·DYS⁻ children (MD = 1.79 dB, SE = 0.85 dB, $p = .040$, $r = .27$). Again, this group difference was no longer present after one year ($F_{(1, 53)} = 1.59$, $p = .213$) nor after three years ($F_{(1, 46)} = 1.86$, $p = .179$) of formal reading instruction. Significant main effects of electrode region were also found at all developmental stages (all $p < .001$), confirming an overall response dominance over the right electrode region in all groups. None of the interaction effects between family risk for dyslexia and electrode region were significant (all $p > .10$) (FIGURE 3).

3.2.3 Developmental effects per group

In DYS⁺ children, a significant main effect of developmental stage was found ($F_{(1, 14)} = 6.84$, $p = .020$), indicative of an increase in 80 Hz response SNRs between the pre-reading and the beginning reading stage (MD = 1.77 dB, SE = 0.67 dB, $p = .020$, $r = .57$). No further development was found between the beginning reading stage and the more advanced reading stage ($F_{(1, 13)} = 0.21$, $p = .651$). None of the

interaction effects between developmental stage and electrode region were significant (all $p > .10$) (FIGURE 4). We found no effects of developmental stage in FRD⁻DYS⁻ children, nor in FRD⁺DYS⁻ children (all $p > .10$).

3.3 A side note on the rationale for the group comparisons

One might argue that the effects of dyslexia should rather be assessed by comparing the DYS⁻ group (i.e., FRD⁻DYS⁻ and FRD⁺DYS⁻) to the DYS⁺ group. However, combining FRD⁻DYS⁻ and FRD⁺DYS⁻ groups into one DYS⁻ group holds some caveats. First, the resulting DYS⁻ group includes > 34% FRD⁺ children (as a consequence of the study design), leading to an overrepresentation of FRD⁺ children. The DYS⁻ group is thus less representative of a general population. Second, FRD⁺DYS⁻ children are sometimes found to differ either from FRD⁻DYS⁻ or DYS⁺ children and these differences may obscure effects between DYS⁻ and DYS⁺ groups. Because of these reasons, we (a priori) chose to report all results with regard to FRD⁻DYS⁻ as the control group. Alternatively, we refer to Vanvooren et al. (2014) for an analysis of the current data based on the comparison of FRD⁻ and FRD⁺ groups regardless of the dyslexia phenotype.

3.4 Pre-reading predictors for dyslexia

Finally, we assessed the role of family risk for dyslexia, pre-reading cognitive skills, and neurophysiological measures as predictors for the development of dyslexia. A forward stepwise logistic regression was conducted, with family risk for dyslexia (FRD⁻ or FRD⁺) as a categorical predictor, phonological awareness, rapid automatized naming, letter knowledge, and 80 Hz response SNRs as continuous predictors, and literacy achievement (DYS⁻ or DYS⁺) as outcome variable.

The results are presented in TABLE 4. The initial regression model is by default derived using only a constant in the regression equation (step 0). By predicting that all children developed normal reading and spelling skills, this model correctly classified 78.1% of the children. The residual chi-square statistic for this model was 30.80 ($p < .001$), indicating that the addition of one or more predictor variables would significantly affect the predictive power of the model. The final regression model was obtained after three steps ($\chi^2(3) = 33.39$, $p < .001$). Family risk for dyslexia (step 1), right 80 Hz response SNRs (step 2), and phonological awareness (step 3) were consecutively included as significant predictors for literacy achievement (all $p < .05$). The R statistic was .31 for family risk for dyslexia, .26 for right 80 Hz

response SNRs, and .23 for phonological awareness. The step statistic indicated a significant improvement of the predictive power of the model with each step (all $p < 0.01$). With this final model, an overall classification accuracy of 90.4% was reached. The residual chi-square statistic was 1.51 ($p = .679$), indicating that none of the remaining variables would significantly affect the predictive power of the model. Rapid automatized naming ($p = .909$), letter knowledge ($p = .579$), and left 80 Hz response SNRs ($p = .234$) were therefore not considered as significant predictors for literacy achievement.

4 DISCUSSION

Neural synchronization at the level of the auditory brainstem is known to be implicated in the encoding of temporal information in speech. Along similar lines, relations between subcortical synchronization and behavioral measures of speech perception, phonological processing, and reading have been reported. Since children with developmental dyslexia typically experience problems in these domains, impairments in the synchronization of subcortical activity might be causally related to the onset of dyslexia. To investigate if and how abnormalities in subcortical synchronization affect reading development, we measured 80 Hz brainstem-evoked ASSRs in a group of children followed longitudinally throughout different stages of reading acquisition.

4.1 Subcortical synchronization in children who developed dyslexia

4.1.1 A pre-reading deficit

Children who developed dyslexia demonstrated significantly lower 80 Hz responses at the pre-reading stage, in the electrode region covering the right temporo-parietal and occipital area. Importantly, none of the children in our sample had received formal reading instruction at the time of the first 80 Hz ASSR measurement, in accordance with the guidelines of the Flemish government (<http://onderwijs.vlaanderen.be/>). The inability to synchronize subcortical activity thus seems to predispose certain children to the development of dyslexia, already before the onset of reading acquisition. As such, subcortical synchronization deficits might constitute a risk factor in the emergence of dyslexia. Note that the observed pre-reading deficit is quite specifically localized over the right electrode region. The right electrode region is also the electrode region where higher 80 Hz response SNRs were found, consistent with an overall response dominance over the right electrode region as reported in other studies (Goossens et al., 2016; Poelmans et al., 2012; Vanvooren et al., 2015, 2014).

We presume that, because of these higher response SNRs, the electrode region covering the right hemisphere is probably optimally suited for the identification of group differences in 80 Hz ASSRs.

Besides complementing a large number of studies that have reported subcortical neural synchronization deficits in school-aged children with learning problems (including specific language impairments and attention deficit disorders; for a review, see Banai et al., 2007), the present results especially extend the findings of two preceding studies in pre-readers with a cognitive or family risk for dyslexia (Vanvooren et al., 2014; White-Schwoch & Kraus, 2013). Although both studies identified pre-reading subcortical abnormalities in children at risk for dyslexia, these findings cannot be directly interpreted as effects contributing to the development of dyslexia. For example, only 40 - 60% of children with a family risk for dyslexia will eventually develop dyslexia themselves (Grigorenko, 2001). Consequently, effects that are observed in at risk groups might be obscured or driven by the influence of children that were at risk, but eventually did not develop dyslexia. By means of a retrospective analysis, our study is the first to establish that pre-reading subcortical deficits are specific to those children who develop dyslexia later on. In addition, our findings suggest that the deficit in dyslexic children is not restricted to neural processing of speech-specific information, but that it concerns fundamental subcortical problems with the processing of non-speech stimuli. The latter contradicts the presumption that subcortical processing deficits in individuals with learning problems are speech-specific (e.g., Song et al., 2006; Banai et al., 2009; Hornickel and Kraus, 2013). However, a behavioral study using stimuli that were adequately controlled for acoustical complexity found that auditory temporal processing deficits in dyslexia are in fact not speech-specific (Vandermosten et al., 2010), and a recent ABR study showed that non-speech brainstem processing is related to literacy skills in adults (Skoe et al., 2017). For future studies, it seems advisable to combine different subcortical neurophysiological measures (click- and speech-evoked ABR, and ASSR) in a longitudinal design. Note that, if it can be assumed that 80 Hz ASSRs are generated by the same neurons as speech-evoked ABRs (Bidelman, 2015; Chandrasekaran & Kraus, 2010), it might also be the anatomical location rather than the stimulus characteristics that determine the origin of the synchronization deficit.

4.1.2 An atypical developmental trajectory

Children who developed typical reading skills showed no developmental effects between pre-reading and early reading stages. This is in line with the general assumption that subcortical auditory processing

matures relatively early in life, changing little beyond approximately two years of age (Eggermont, 1992; Pethe, Mühler, Siewert, & von Specht, 2004; Salamy, 1984; Tlumak, Durrant, Delgado, & Boston, 2012). Yet, Vanvooren et al. (2015) reported maturational differences between typically developing 5-year-old children and adults with regard to 80 Hz ASSRs. Prolonged subcortical development in typical readers is thus not to be excluded, but seems to take place over a long time period, which was recently also suggested by an extensive click- and speech-ABR developmental study (Skoe, Krizman, Anderson, & Kraus, 2015).

Children who developed dyslexia, however, exhibited an increase in subcortical synchronization over the course of only two years, i.e., between the pre-reading and the beginning reading stage. Due to this developmental increase, the observed pre-reading deficit is no longer present after one year of reading instruction. We suggest two possible explanations for this effect. The first possibility is that the increase in subcortical synchronization is reflective of delayed subcortical maturation. Children who develop dyslexia do appear to attain adequate levels of subcortical synchronization, however, this occurs only after the onset of reading acquisition. Cognitive deficits, which are presumed to emerge due to pre-reading subcortical immaturity, may persist despite the disappearance of the subcortical deficit, because the required level of subcortical synchronization was not reached by a critical developmental time point. The latter not only delays, but also puts long-lasting limits on further development (for a similar reasoning, see Wright & Zecker, 2004). Pre-reading abnormalities in the maturational trajectory of subcortical auditory processing may thus set certain children at a disadvantage, even though these children develop normal 80 Hz ASSRs at later stages in reading development.

A second possibility is that the increase in subcortical synchronization is related to effects of literacy intervention. This hypothesis is particularly interesting, given that its validation might indicate that the observed pre-reading deficit is susceptible to early interventional measures. We evaluated whether children received literacy intervention by means of a parent questionnaire, which included open questions regarding, inter alia, the timing (start and end date) and the form (additional support at school or therapy by a speech language pathologist) of the provided interventional measures. The number of children that received literacy intervention (in either form) between the pre-reading and the beginning reading stage was limited ($N = 4$). Most children received literacy intervention from the beginning reading stage onwards, or even later. If changes in subcortical synchronization are related to literacy intervention, major neural changes are to be expected between the beginning and the more advanced

reading stage, which does not seem to be the case. However, the current assessment of interventional measures is rather indirect and limited. Therefore, we believe that a systematic investigation of the effects of (early) intervention on subcortical measures of neural synchronization is a valuable suggestion that may guide future studies.

An alternative account is that the pre-reading deficit remains present at post-reading stages, but is no longer detectable due to statistical power problems. To assess this option, we calculated the statistical power at the beginning and more advanced reading stage using the effect size of the pre-reading group difference ($r = .34$, see TABLE 3). As such, we determined the power of our statistical test to detect a similar effect at post-reading stages, while taking into account the smaller sample sizes. The hypothetical power to detect an effect size of $r = .34$ at the beginning and the more advanced reading stage was equal to $\beta = .70$ ($N = 49$) and $\beta = .67$ ($N = 46$), respectively. In comparison to the pre-reading stage ($\beta = .74$, $N = 54$), the statistical power at post-reading stages decreases by only .04 - .07. If similar group differences were to be present at the beginning or the more advanced reading stage, our chance of detecting them as statistically significant effects would still be situated around a quite acceptable level of ~ 70%. Hence, the disappearance of the pre-reading deficit does not seem to be the consequence of statistical power problems. The latter is confirmed by comparing the true effect sizes between pre- and post-reading developmental stages. Effect sizes quantify the size of the difference between two groups, without confounding it with sample size. As shown in TABLE 3, we found a medium effect size at the pre-reading stage ($r = .34$), while the effect sizes at the beginning ($r = .09$) and more advanced ($r = .01$) reading stage were small. It appears that the post-reading group differences are too small to be considered as statistically relevant, regardless of the statistical power.

The disappearance of the pre-reading deficit at later stages of reading development might seem at odds with prior studies who have found post-reading subcortical effects in relation to typical and atypical reading abilities (for a review, see Banai et al., 2007). However, there are some crucial methodological differences between the present study and prior post-reading studies. We used non-speech stimuli (vs. speech stimuli) to investigate the neural encoding of the modulation envelope (vs. fine structure) by means of steady-state responses (vs. transient responses) throughout the first stages of reading development (vs. in experienced readers) in a strictly selected set of children who developed dyslexia (vs. individuals with reading problems and / or general learning difficulties). The observed differences between our and prior studies might thus rather be complementary than contradictory. To the best of

our knowledge, the study of Poelmans et al. (2012) is the only post-reading study that is methodologically comparable to our work. In line with our post-reading results, they found no differences in subcortical steady-state responses between normal reading and dyslexic adults.

4.2 Subcortical synchronization in children with a family risk for dyslexia who developed typical reading skills

Children with a family risk for dyslexia who developed typical reading skills were found to exhibit significantly higher 80 Hz responses at the pre-reading stage, regardless of the electrode region. As such, the ability to increase subcortical synchronization seems to protect certain children with a family risk from the development of dyslexia. In contrast to the pre-reading deficit observed in children who developed dyslexia, the increase in 80 Hz response SNRs in FRD⁺DYS⁻ children was not specifically localized over one of the electrode regions. This might suggest that additional sources of activity are recruited. However, the implications of this specific result should be nuanced, given that this effect, was no longer significant after correction for multiple comparisons.

Nevertheless, the FRD⁺DYS⁻ group appears to behave remarkably different in comparison to the DYS⁺ group (compare dark and light grey bars in FIGURE 2 and 3). This post hoc observation is particularly intriguing given that the DYS⁺ group also consists of ~ 90% (i.e., 14 out of 16) of family risk children. In an attempt to explain why the FRD⁺DYS⁻ group behaves so differently, a correlation analysis was performed. When all children with a family risk for dyslexia (i.e., FRD⁺DYS⁻ and FRD⁺DYS⁺) were combined into one FRD⁺ group, a positive relation was found between right hemispheric 80 Hz response SNRs at the pre-reading stage and later word reading ($r = .55$, $p = .002$), pseudoword reading ($r = .53$, $p = .003$), and spelling ($r = .59$, $p = .001$) skills. Higher levels of pre-reading subcortical synchronization appear to relate to better literacy scores in FRD⁺ children, irrespective of reading outcome. We consider this as a novel hypothesis that requires further investigation beyond the scope of the present paper, but it seems that some FRD⁺ children are able to engage increased subcortical processing and go on to develop normal reading skills, whereas other FRD⁺ children are unable to engage increased subcortical processing and will develop dyslexia. Interestingly, a recent paper investigating the impact of two prominent dyslexia risk genes (KIAA0319 and DCDC2) on auditory processing at brainstem level, revealed a similar distinction. Children with DCDC2 risk variants had more stable brainstem responses, whereas children with a risk loading of the KIAA0319 gene demonstrated noisier brainstem responses

(Neef, Müller, et al., 2017). Heterogeneity at the genetic level could thus explain the neural, and in turn also cognitive, differences observed between FRD^+DYS^- and DYS^+ children. If validated, this hypothesis might have interesting implications with regard to both diagnostic and interventional aspects of developmental dyslexia. Not only does the pre-reading level of subcortical synchronization hold a clear distinction between those FRD^+ children who develop dyslexia and those who do not, it also seems that the ability to increase subcortical synchronization constitutes a protective factor, at least in children with a family risk for dyslexia.

4.3 Identifying multi-level risk factors for dyslexia

A better understanding of the risk factors that contribute to the emergence of dyslexia allows novel methods for early identification, improved remediation, and preventive care to be developed. Hence, the ultimate purpose of the present study was to investigate whether pre-reading measures of subcortical synchronization provide added value to the prediction of later reading outcome. We considered multiple factors, i.e., at the cognitive, neural, and genetic-environmental level (Pennington, 2006; van Bergen, van der Leij, & de Jong, 2014). The final model retained pre-reading phonological awareness, 80 Hz ASSRs measured over the right temporo-parieto-occipital region, and family risk for dyslexia as significant predictors for literacy achievement. Altogether, literacy achievement was predictable with an accuracy of ~ 90%.

In line with the multiple deficit model, these findings demonstrate that the complexity characterizing developmental disorders such as dyslexia cannot be explained by one single factor, but rather is the result of a dynamic interplay between cognitive, neural, and genetic-environmental factors (Pennington, 2006; van Bergen, van der Leij, & de Jong, 2014). Our results show that, above all, the combined contributions of pre-reading measures of phonological awareness, subcortical neural synchronization, and family risk are highly important for reading outcome. The influential role of subcortical neural synchronization is emphasized by the fact that pre-reading 80 Hz ASSRs are identified as an independent predictor of literacy achievement, above and beyond the standard measures that are widely used to indicate a risk for dyslexia. In this context, it is noteworthy that the predictive value of 80 Hz ASSRs is also promising on a more practical basis. In effect, 80 Hz ASSRs are reliably measurable in young children (Levi, Folsom, & Dobie, 1993; Luts, Desloovere, & Wouters, 2006), robust against influences of alertness and attention (Tlumak, Durrant, Delgado, & Robert Boston, 2012; Varghese,

Bharadwaj, & Shinn-Cunningham, 2015), and identifiable using an objective response detection criterion (Dobie & Wilson, 1996; John & Picton, 2000).

4.4 Relations between subcortical and cortical synchronization deficits?

Since temporal processing takes place at different levels of the auditory system, subcortical and cortical deficits are not mutually exclusive, but rather seem to be inextricably linked, and in turn related to cognitive deficits associated with reading disability. There is indeed evidence for functional relations between subcortical and cortical auditory processing. In particular, subcortical and cortical activity are suggested to modulate each other through ascending and descending auditory pathways (e.g., Abrams et al., 2006; for a review, see Chandrasekaran et al., 2014). A number of studies have thus proposed that abnormal relations between brainstem and cortical auditory processing might be responsible for the observed subcortical deficits in children with learning disabilities (Banai, 2005; King et al., 2002; Wible, Nicol, & Kraus, 2005). Specifically the corticofugal pathway, a system responsible for top-down regulation of sensory processing in the inferior colliculus, is thought to host deficiencies leading to abnormal brainstem processing (Song, Banai, & Kraus, 2008). Nonetheless, the results of the present longitudinal study rather support a bottom-up account, as subcortical deficits were observed in the absence of cortical deficits (De Vos et al., 2017a).

4.5 Limitations and future directions

Longitudinal designs are essential in the context of research on developmental disorders such as dyslexia. However, our study design also has some limitations that should be considered. The first limitation concerns the issue of attrition. Although the attrition rate in the present study is reasonable ($N = 5$ at the beginning reading stage and $N = 9$ at the more advanced reading stage), it is not randomly distributed across groups, given that the majority of children that decided to leave the study belonged to the FRD·DYS group ($N = 4$ at the beginning reading stage and $N = 6$ at the more advanced reading stage). We assessed the influence of missing data by repeating all the analyses concerning the pre-reading stage while excluding these children. The results of these additional analyses led to the same conclusions, indicating that there was no significant influence of longitudinally missing data. A second limitation regards to the sample size of the DYS⁺ group. Since our study included pre-reading children, the number of children with dyslexia was a priori unknown. We kept this uncertainty under control by

recruiting children from families in which dyslexia tends to run strongly. In children with a family risk for dyslexia, the chance of developing dyslexia indeed increases up to 40 - 60% (Grigorenko, 2001), compared to 7% in the general population (Peterson & Pennington, 2012). Given that 14 children from the group of children with a family risk (41%) and two children from the group of children without family risk (5%) eventually met our predetermined criteria for dyslexia diagnosis, the final sample size of children with dyslexia is in line with our expectations based on the reported prevalence numbers, but remains relatively small. The statistical power of our main finding, i.e., the effect of dyslexia at the pre-reading stage, is therefore somewhat lower than the recommended power level of .80 ($\beta = .74$, $N = 54$). An additional downside of our recruitment approach is that the group of dyslexic children without family risk is severely underrepresented.

In order to validate our results and examine the generalizability of the observed effects, future studies using similar designs should at least target a larger sample of children with dyslexia, thereby considering the inclusion of children with a cognitive risk for dyslexia to allow for separate investigation of the FRD-DYS⁺ group. In addition, studies using interventional designs are necessary to allow for an investigation of the potentially causal relation between our findings and the development of dyslexia.

5 CONCLUSION

Based on a longitudinal investigation of 80 Hz ASSRs, we found that (1) children who develop dyslexia exhibit a pre-reading deficit and an atypical developmental trajectory with regard to neural synchronization of subcortical activity and (2) reading outcome was predictable with an accuracy up to ~ 90% based on a model including family risk for dyslexia, phonological awareness, and 80 Hz ASSRs. Despite of a number of limitations related to the study design, we believe that these results provide added value to the understanding of the risk factors that contribute to the emergence of dyslexia, and in the long term, might lead to the development of novel methods for early identification, improved remediation, and preventive care. 80 Hz ASSRs seem to be particularly suited for these purposes, given that these responses are easily measurable, but also hold an important robustness in response generation and objectivity in response detection.

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FIGURE LEGENDS

FIGURE 1 Characteristics of an 80 Hz ASSR in time and frequency domain. Panel [A] represents four cycles of the grand mean averaged response waveforms for all 64 electrodes. The pre-selected electrode configuration is indicated with asterisks. Panel [B] and [C] represent the FFT spectra of the EEG signals recorded over the left and right temporo-parietal and occipital hemispheric regions for a randomly selected subject after pre-processing. The circles indicate the response amplitude and the shaded grey areas indicate the noise amplitude. The peak at 50 Hz in panel [C] is caused by line noise. Panel [D] and [E] represent the corresponding calculation method of the response SNR.

FIGURE 2 Effects related to dyslexia. Overall, left, and right hemispheric response SNRs (dB) are presented for FRD⁻DYS⁻ children (black) and DYS⁺ children (dark grey) as pre-readers, beginning readers, and more advanced readers. The dotted line represents the SNR level corresponding to a significant *F* ratio statistic (4.8 dB, $p < .05$). Error bars indicate ± 1 SE. Two-tailed significances are indicated using * for $p < .05$. We kindly refer the reader to FIGURE A in the Supporting information for an analogous figure showing the individual data points.

FIGURE 3 Effects related to family risk for dyslexia. Overall, left, and right hemispheric response SNRs (dB) are presented for FRD⁻DYS⁻ children (black) and FRD⁺DYS⁻ children (light grey) as pre-readers, beginning readers, and more advanced readers. The dotted line represents the SNR level corresponding to a significant *F* ratio statistic (4.8 dB, $p < .05$). Error bars indicate ± 1 SE. Two-tailed significances are indicated using * for $p < .05$. We kindly refer the reader to FIGURE B in the Supporting information for an analogous figure showing the individual data points.

FIGURE 4 Developmental effects. Overall response SNRs (dB) are presented for FRD⁻DYS⁻ children (black), DYS⁺ children (dark grey), and FRD⁺DYS⁻ children (light grey) per developmental stage. The dotted line represents the SNR level corresponding to a significant *F* ratio statistic (4.8 dB, $p < .05$). Error bars indicate ± 1 SE. Two-tailed significances are indicated using * for $p < .05$. We kindly refer the reader to FIGURE C and D in the Supporting information for analogous figures showing the individual data points.

TABLES

TABLE 1 Participant characteristics.

	FRD·DYS⁻	DYS⁺	FRD⁺DYS⁻	FRD·DYS⁻ vs. DYS⁺	FRD·DYS⁻ vs. FRD⁺DYS⁻
Pre-reading	<i>N</i> = 38	<i>N</i> = 16	<i>N</i> = 20		
Age (in months)	62 (4)	61 (3)	61 (3)	<i>p</i> = .275	<i>p</i> = .207
Gender (M / F)	24 / 14	8 / 8	12 / 8	<i>p</i> = .545	<i>p</i> = 1.000
Non-verbal IQ	111 (10)	106 (13)	114 (12)	<i>p</i> = .137, <i>r</i> = .21	<i>p</i> = .321, <i>r</i> = .13
Beginning reading	<i>N</i> = 34	<i>N</i> = 15	<i>N</i> = 21		
Age (months)	85 (3)	85 (3)	85 (3)	<i>p</i> = .737	<i>p</i> = .628
Gender (M / F)	21 / 13	8 / 7	13 / 8	<i>p</i> = .754	<i>p</i> = 1.000
Advanced reading	<i>N</i> = 31	<i>N</i> = 15	<i>N</i> = 17		
Age (months)	109 (4)	109 (3)	109 (3)	<i>p</i> = .861	<i>p</i> = .499
Gender (M / F)	20 / 11	7 / 8	11 / 6	<i>p</i> = .341	<i>p</i> = 1.000

Group means, standard deviations (SD), and *p* values of independent *t*-tests are presented for age and non-verbal IQ. Non-verbal IQ scores were standardized (mean = 100, SD = 15) and ranged between 87 and 131. For gender, the number of males (M) / females (F) and *p* values of Fisher's exact tests are shown.

TABLE 2 Cognitive results.

	FRD-DYS ⁻	DYS ⁺	FRD ⁺ DYS ⁻	FRD-DYS ⁻ vs. DYS ⁺	FRD-DYS ⁻ vs. FRD ⁺ DYS ⁻
Pre-reading	N = 38	N = 16	N = 20		
Phonological awareness					
End rhyme ³	9 (3)	8 (6)	10 (3)	p = .033, r = .45	p = .810, r = -.03
End phoneme	4 (3)	3 (2)	5 (2)	p = .138, r = .21	p = .107, r = .22
Composite	0.07 (0.70)	-0.54 (0.82)	0.31 (0.87)	p = .008, r = .36	p = .256, r = .15
Rapid automatized naming					
Colors	0.70 (0.17)	0.56 (0.13)	0.62 (0.17)	p = .004, r = .39	p = .076, r = .24
Objects	0.67 (0.16)	0.56 (0.17)	0.61 (0.16)	p = .032, r = .30	p = .202, r = .17
Composite ²	0.12 (1.24)	-0.50 (0.64)	-0.38 (0.88)	p = .003, r = -.40	p = .111, r = .21
Letter knowledge ^{1, 2, 3}	2 (4)	0 (3)	2 (10)	p = .015, r = -.33	p = .821, r = -.03
Beginning reading	N = 34	N = 15	N = 21		
Word reading ³	26 (23)	8 (5)	19 (13)	p < .001, r = .79	p = .129, r = -.21
Pseudoword reading	22 (9)	7 (3)	19 (8)	p < .001, r = .80	p = .177, r = .18
Spelling	54 (4)	37 (16)	53 (6)	p = .002, r = .71	p = .442, r = .11
Advanced reading	N = 31	N = 15	N = 17		
Word reading	56 (13)	29 (11)	52 (10)	p < .001, r = .72	p = .368, r = .13
Pseudoword reading	46 (14)	16 (6)	37 (13)	p < .001, r = .83	p = .043, r = .30
Spelling	45 (10)	25 (13)	39 (9)	p < .001, r = .67	p = .047, r = .29

Group means, SD, as well as *p* and *r* values of independent *t*-tests are presented in case of normally distributed data in all participant groups. Medians, interquartile ranges, as well as *p* and *r* values of Mann-Whitney *U*-tests are presented in case of non-normally distributed data in one or more participant groups. For more information on the units and maximum scores of each cognitive measure, we refer to section 2.2. Significant group differences (*p* < .05) are indicated in bold. Correcting these results for multiple comparisons per developmental stage (Benjamini-Hochberg procedure) did not change the results for FRD-DYS⁻ vs. DYS⁺ comparisons. However, the results for FRD-DYS⁻ vs. FRD⁺DYS⁻ no longer reached significance.

¹ Non-normally distributed in FRD-DYS⁻ group, ² Non-normally distributed in DYS⁺ group, ³ Non-normally distributed in FRD⁺DYS⁻ group.

TABLE 3 Neurophysiological results.

	FRD·DYS ⁻	DYS ⁺	FRD ⁺ DYS ⁻	FRD·DYS ⁻ vs. DYS ⁺	FRD·DYS ⁻ vs. FRD ⁺ DYS ⁻
Pre-reading	<i>N</i> = 38	<i>N</i> = 16	<i>N</i> = 20		
Overall	12.1 (0.5)	10.7 (0.9)	13.9 (0.7)	<i>p</i> = .171, <i>r</i> = .19	<i>p</i> = .040, <i>r</i> = .27
Left	8.7 (0.7)	8.6 (1.1)	10.8 (1.0)	<i>p</i> = .919, <i>r</i> = .01	<i>p</i> = .087, <i>r</i> = .23
Right	15.6 (0.5)	12.8 (0.9)	17.0 (0.6)	<i>p</i> = .011, <i>r</i> = .34	<i>p</i> = .077, <i>r</i> = .23
Beginning reading	<i>N</i> = 34	<i>N</i> = 15	<i>N</i> = 21		
Overall	12.0 (0.6)	12.3 (0.9)	13.2 (0.8)	<i>p</i> = .768, <i>r</i> = .04	<i>p</i> = .213, <i>r</i> = .17
Left	9.0 (0.9)	10.3 (1.3)	10.2 (1.1)	<i>p</i> = .398, <i>r</i> = .12	<i>p</i> = .396, <i>r</i> = .12
Right	15.0 (0.6)	14.4 (0.9)	16.3 (0.8)	<i>p</i> = .554, <i>r</i> = .09	<i>p</i> = .204, <i>r</i> = .17
Advanced reading	<i>N</i> = 31	<i>N</i> = 15	<i>N</i> = 17		
Overall	11.5 (0.7)	11.9 (1.1)	13.2 (1.0)	<i>p</i> = .794, <i>r</i> = .04	<i>p</i> = .179, <i>r</i> = .20
Left	9.0 (1.0)	9.7 (1.4)	10.6 (1.3)	<i>p</i> = .650, <i>r</i> = .07	<i>p</i> = .323, <i>r</i> = .15
Right	14.0 (0.7)	14.0 (1.1)	15.8 (1.0)	<i>p</i> = .969, <i>r</i> = .01	<i>p</i> = .153, <i>r</i> = .21

Group means, standard errors of response SNRs (dB), as well as *p* and *r* values of mixed ANOVA post hoc comparisons are presented. Significant group differences (*p* < .05) are indicated in bold. Correcting these results for multiple comparisons per developmental stage (Benjamini-Hochberg procedure) did not change the results for FRD·DYS⁻ vs. DYS⁺ comparisons. However, the results for FRD·DYS⁻ vs. FRD⁺DYS⁻ no longer reached significance.

TABLE 4 Forward stepwise logistic regression model for literacy achievement (DYS⁻ or DYS⁺).

Step		B (SE)	Wald (df)	Sig.	R	-2LL	Step statistic	Sig.
0	Constant	2.36 (1.95)				76.78		
1	Family risk for dyslexia	2.77 (0.91)	9.15 (1)	<i>p</i> = .002	.31	61.85	14.93	<i>p</i> < .001
2	80 Hz response SNR (right)	-0.38 (0.14)	7.38 (1)	<i>p</i> = .007	.26	51.35	10.50	<i>p</i> = .001
3	Phonological awareness	-1.25 (0.50)	6.13 (1)	<i>p</i> = .013	.23	43.39	7.96	<i>p</i> = .005

The log-likelihood is multiplied by -2 to approximate a chi-square distribution and is therefore referred to as -2LL. $R^2 = .43$ (Hosmer & Lemeshow), .37 (Cox & Snell), .56 (Nagelkerke). Other methods of logistic regression (i.e., forced entry and backward stepwise methods) led to similar results.

FIGURE 1 Characteristics of an 80 Hz ASSR in time and frequency domain. Panel [A] represents four cycles of the grand mean averaged response waveforms for all 64 electrodes. The pre-selected electrode configuration is indicated with asterisks. Panel [B] and [C] represent the FFT spectra of the EEG signals recorded over the left and right temporo-parietal and occipital hemispheric regions for a randomly selected subject after pre-processing. The circles indicate the response amplitude and the shaded grey areas indicate the noise amplitude. Panel [D] and [E] represent the corresponding calculation method of the response SNR.

FIGURE 2 Effects of dyslexia. Overall, left, and right hemispheric response SNRs (dB) are presented for FRD-DYS- children (black) and DYS+ children (dark grey) as pre-readers, beginning readers, and more advanced readers. The dotted line represents the SNR level corresponding to a significant F ratio statistic (4.8 dB, $p < .05$). Error bars indicate ± 1 SE. Two-tailed significances are indicated using * for $p < .05$. We kindly refer the reader to FIGURE A in the Supporting information for an analogous figure showing the individual data points.

177x47mm (600 x 600 DPI)

FIGURE 3 Effects of family risk for dyslexia. Overall, left, and right hemispheric response SNRs (dB) are presented for FRD-DYS- children (black) and FRD+DYS- children (light grey) as pre-readers, beginning readers, and more advanced readers. The dotted line represents the SNR level corresponding to a significant F ratio statistic (4.8 dB, $p < .05$). Error bars indicate ± 1 SE. Two-tailed significances are indicated using * for $p < .05$. We kindly refer the reader to FIGURE B in the Supporting information for an analogous figure showing the individual data points.

177x47mm (600 x 600 DPI)

FIGURE 4 Developmental effects. Overall response SNRs (dB) are presented for FRD-DYS- children (black), DYS+ children (dark grey), and FRD+DYS- children (light grey) per developmental stage. The dotted line represents the SNR level corresponding to a significant F ratio statistic (4.8 dB, $p < .05$). Error bars indicate ± 1 SE. Two-tailed significances are indicated using * for $p < .05$. We kindly refer the reader to FIGURE C and D in the Supporting information for analogous figures showing the individual data points.

164x50mm (600 x 600 DPI)