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Auditory brainstem responses to stop consonants predict literacy

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Abstract

Objective: Precise temporal coding of speech plays a pivotal role for sound processing throughout the central auditory system which in turn influences literacy acquisition. The current study tests whether an electrophysiological measure of this precision predicts literacy skills.

Methods: Complex auditory brainstem responses were analyzed from 62 native-German speaking children aged 11-13 years. We employed the cross-phaseogram approach to compute the quality of the electrophysiological stimulus contrast [da] and [ba]. Phase shifts were expected to vary with literacy.

Results: Receiver operating curves demonstrated a feasible sensitivity and specificity of the electrophysiological measure. A multiple regression analysis resulted in a significant prediction of literacy by delta cross-phase as well as phonological awareness. A further commonality analysis separated a unique variance explained by the physiological measure from a unique variance explained by the behavioral measure, and common effects of both.

Conclusions: Despite multicollinearities between literacy, phonological awareness, and subcortical differentiation of stop consonants, a combined assessment of behavior and physiology strongly increases the ability to predict literacy skills.

Significance: The strong link between the neurophysiological signature of sound encoding and literacy outcome suggests that the delta cross-phase could indicate the risk of dyslexia and thereby complement subjective psychometric measures for early diagnoses.

Keywords:

reading disorder, auditory brainstem responses, phonological awareness, early diagnosis, speech

Highlights

- Speech-evoked brainstem potentials convey the temporal precision of early speech sound encoding.
- Poor subcortical distinction related to poor literacy skills in 11 to 13 year olds.
- Delta cross-phase could become a potential preclinical marker for the risk of developing dyslexia.

1. Introduction

1.1. Dyslexia

Dyslexia is a developmental reading and spelling disorder with a complex genetic architecture (Fisher and DeFries, 2002). The cumulative incidence rate is high with 5-12% (Shaywitz SE *et al.*, 1990). Dyslexia persists in 4-6% of adults (Schulte-Körne and Remschmidt, 2003) disadvantaging employment, and compromising participation in daily life. Prevention requires early sensitive screenings that need to assess several cognitive domains as well as multiple senses because literacy acquisition evolves from the interplay between linguistic competencies, attention, memory, audition, vision, and gaze-control (Mcanally and Stein, 1996; Stein and Walsh, 1997; Carlisle, 2000; Snowling, 2001; Ahissar *et al.*, 2006; Goswami, 2011, 2015; Carreiras *et al.*, 2014; Lobier and Valdois, 2015). As a consequence, broad, time consuming test batteries are necessary to account for heterogeneous cognitive fingerprints that characterize various subtypes of dyslexia (Heim *et al.*, 2008; Heim and Grande, 2012). An additional physiological parametrization of involved processes offers several advantages. First, a differentiation of underlying physiological mechanisms combined with reliable behavioral measures could provide a better understanding of underlying mechanisms and thus helps advancing theories, specifying treatments, and evaluating treatment outcome. Second, physiological features might be evident before clinical features emerge, and, thus, help detecting children at risk even before literacy acquisition. Third, early physiological diagnostic procedures that would not require an active cooperation of tested individuals would help to overcome uncertainties inherent to behavioral tests.

1.2. Dyslexia and the auditory system

The majority of individuals with dyslexia have phonological impairments (Bradley and Bryant, 1983; Wagner and Torgesen, 1987; Heim and Grande, 2012; Saksida *et al.*, 2016), and, thus, struggle with the sound structure (Shovman and Ahissar, 2006). In addition, phonological awareness is deficient in individuals with dyslexia (Bruck, 1992). Phonological awareness is the awareness of and the access to the phonology of one's language (Mattingley 1984; Wagner and Torgesen 1987) as reflected in the ability to substitute the initial sound of a word (e.g. bee – tee, sound – round). Accumulating evidence links these phonological difficulties and poor reading to auditory processing disorders (Goswami, 2011; Tallal, 2012). Poor psychoacoustic performance of individuals with dyslexia has been shown for various perceptive tasks, such as auditory discrimination (duration, frequency, or rise time) and detection of auditory modulation (amplitude or frequency)(for a comprehensive review see (Hämäläinen *et al.*, 2013). This inaccurate auditory is conjointly mirrored in irregular physiological correlates to speech and non-speech stimuli throughout the central auditory system (Kraus *et al.*, 1996; Chandrasekaran *et al.*, 2009; Schulte-Körne and Bruder, 2010; Díaz *et al.*, 2012).

The current study links poor literacy to scalp-recorded brainstem responses and hereby to very early neural processes in the auditory pathway (Mcanally and Stein, 1996; Banai *et al.*, 2005; Chandrasekaran *et al.*, 2009; Strait *et al.*, 2011). Complex auditory brainstem responses (cABRs) to speech or music stimuli reflect phase-locked activity of lower structures of the central auditory pathway, primarily the inferior colliculus, lateral lemniscus, and cochlear nucleus (Smith *et al.*, 1975; Glaser *et al.*, 1976; Sohmer *et al.*, 1977; Skoe and Kraus, 2010; Bidelman, 2015). These cABRs reflect the synchronous firing of neurons to stimulus-related periodicities (Marsh *et al.*, 1975). Peak latencies of these responses possibly encode fast transients of speech sounds (Johnson *et al.*, 2008; Bidelman and Krishnan, 2010). Accordingly, cABRs capture the temporal precision of firing neurons in the auditory midbrain signaling high-fidelity and stability of early auditory encoding (Skoe and Kraus, 2010).

Characteristic fast transients of speech sounds are the distinct formant transitions of stop consonants and formant-related harmonics. Formants reflect resonance frequencies of the vocal tract that change with its shape and stiffness. Fast articulatory gestures such as opening the mouth for [ba] or lowering the tongue for [da], cause fast transitions of lower formants as shown in the spectrograms of the acoustic stimuli (Fig. 1). In the spectrogram of the syllable [ba], the first and the second formant rise during the first 50 ms. In contrast, for the syllable [da], the first formant rises, but the second formant falls. These formant transitions, in turn, constitute important spectrotemporal features that enable us to recognize and distinguish speech sounds. Certain features of cABRs to these formant transitions co-vary with reading and phonological skills. Poor readers show unstable speech-evoked cABRs to the stop-consonant syllables [ga], [da], and [ba] (Hornickel and Kraus, 2013). Furthermore, poor readers and children with poor phonological awareness exhibit less distinct sound specific latency-shifts of certain peaks in cABRs to stop-consonant syllables (Hornickel *et al.*, 2009). These latency-shifts are distinctive for sound-specific spectro-temporal features of the stimuli with earlier latencies for fast transitions in higher frequency bands (e.g. [ga] or [da]) and later latencies for fast transients in lower frequency bands [ba] (Johnson *et al.*, 2008). However, the quantification of critical peak latencies requires a visual inspection of individual responses, and, is therefore, less objective and time consuming. A less time consuming and more objective metric that captures the brainstems ability to discriminate between spectro-temporal dynamic of speech sounds, such as stop consonants, is the *cross-phaseogram*. Time-varying frequency differences in speech stimuli display as phase shifts (Skoe *et al.*, 2011) and emerge in the frequency spectrum covered by the phase-locking capability of the auditory brainstem. First evidence for a sensitivity of this measure to relate to phonological skills has been reported for preliterate children. Phase shifts were less distinct in 4 year old pre-readers with poor phonological awareness (White-Schwoch and Kraus, 2013) compared to age matched peers with good phonological awareness. This observation led the authors to suggest that a potentially slower maturation of early auditory neural processes could hinder phonological development, and, thus, challenge later reading acquisition. Whether and how this physiological metric co-varies with literacy skills has not been investigated yet.

1.3. The present study

It remains open, whether the *cross-phaseogram* approach is sensitive to distinguish children with good literacy skills from children with poor literacy skills and how this metric co-varies with phonological skills in literate children. The present study tested whether the electrophysiological distinction of stop-consonants varies with performance in reading, spelling, and phonological awareness in children after at least 6 years of reading and spelling instruction. We recorded cABRs to synthesized syllables kindly provided by the Auditory Neuroscience laboratory of Nina Kraus (Johnson, 1959; Skoe *et al.*, 2011) in children that were former participants of the German Language Developmental Study (GLAD, Friedrich and Friederici, 2004). We quantified phase-shifts to the [da] and [ba] syllable and tested expected relations to behavior: a reduced phase shift is associated with poor literacy skills as well as with poor phonological awareness. To keep the experimental burden on recruited teenagers arguable, we combined behavioral measures from the current and previous studies (Schaadt et al., 2016; Schaadt et al., 2015). Literacy was determined by averaging percentiles across a standardized German reading test and a standardized German spelling test. The results of the current study support theories on a pivotal role of the auditory system in literacy acquisition. The precision of speech coding in lower central auditory nuclei relates to the formation of phonological skills thereby constituting an important prerequisite of literacy acquisition.

2. Methods

2.1. Participants

Sixty four native-German speaking children aged 11.4 to 13.8 (37 males) were recruited through the GLAD database (Friedrich and Friederici, 2004). Most participants took part in previous EEG studies on dyslexia (Schaadt et al., 2016; Schaadt et al., 2015). All children gave documented verbal assent; and all parents gave written informed consent prior to the experiment. Families received monetary compensation for their participation. Experimental procedures were approved by the University of Leipzig Ethical Review Board.

All children had normal hearing, passing a hearing screening at a 25 dB hearing level (air conduction) for octaves from 250 to 4000 Hz, and normal click-evoked brainstem responses with peak V latencies > 6.0 ms, and no neurological diseases. Seventeen participants had one or more first degree relatives with a diagnosed reading disorder, whereas 45 children had no family history. The handedness of all participants but 4 was right according to a questionnaire that was filled out by the child's parents. Handedness was confirmed by the spelling test, while children held a pencil when writing. One participant aborted the experimental session. Another participant was discarded from the analysis due to excessive artefacts in the electrophysiological data (characterized as outliers according Grubbs' test for outliers, http://graphpad.com/quickcalcs/Grubbs1.cfm). To the best of our knowledge, none of the participants were formally diagnosed with a reading disorder.

Nonverbal intelligence was determined by the Kaufman Assessment Battery for Children (K-ABC) (Kaufman *et al.*, 2009) and information was missing for one participant. Nonverbal IQ was in the normal range (i.e., ≥85, Table 1). Reading comprehension and reading speed (*Lesegeschwindigkeits- und -verständnistest für die Klassen 6-12* (LGVT) (Schneider *et al.*, 2007) as well as performance in spelling (*Deutscher Rechtschreibtest* (DERET) (Stock and Schneider, 2008) were tested with standardized tests. Percentile ranks were averaged across reading comprehension, reading speed and spelling to quantify literacy. In addition, a non-standardized word and nonword reading test (Schulte-Körne, 2001) was employed to measure phonological skills. The time and accuracy in reading 30 German words and 30 nonwords were measured. Furthermore, phonological awareness was assessed with the BAKO 1-4 testing basal competencies for reading and spelling (*Basiskompetenzen für Lese-Rechtschreibleistungen*, (Stock *et al.*, 2003) The BAKO measures phonological processing skills at the phoneme level (phoneme categorization, phoneme deletion, phoneme permutation, vowel length assignment, and vowel replacement) and at the word level (word inversion and pseudoword segmentation). DERET, BAKO and K-ABC were conducted along with a previous EEG study three years earlier (March – November 2011, Schaadt et al., 2016; Schaadt et al., 2015), while a hearing screening, LGVT and word and pseudoword reading was assessed together with the here reported brainstem measures (April - December 2014).

2.2. Stimuli

The Klatt-synthesized [da] and [ba] syllables were provided by Nina Kraus (Hornickel *et al.*, 2009; Hornickel and Kraus, 2013). Both syllables were 170 ms long with a pitch onset (100 Hz) at 10 ms. The formant transition durations were 50 ms composed of a linear rising F1 (400 – 720 Hz), a linear falling F3 (2580 – 2500 Hz), and flat F4 (3300 Hz), F5 (3750 Hz) , and F6 (4900 Hz). The syllables differed only in the starting point of F2 (/ba/ 900 Hz, /da/ 1700 Hz) shifting to 1240 Hz. The steady-state vowel lasted 110 ms. The spectrograms and the oscillograms of both syllables are shown in the upper panel of Figure 1. The spectrograms illustrate opposing transitions of the second formant.

2.3. Procedure

Children were seated comfortably in a relaxing chair in an electrically shielded, soundproof booth and were allowed to watch a movie of their choice (SPL < 45 dB) as usually done during this procedure (Chandrasekaran *et al.*, 2009; Hornickel and Kraus, 2013; White-Schwoch and Kraus, 2013). Before and after stimulation with the syllables a train of 2000 clicks was presented to test the integrity of the auditory pathway and to ensure stable recording conditions throughout the experiment. The two syllables were presented in separate blocks to the right ear through Etymotic ER-3 insert earphones (Etymotic Research, Elk Grove Village, IL) at an intensity level of 80 dB SPL, at a rate of 4.35 Hz, and with both polarities (condensation and rarefaction). Each of the two blocks lasted approximately 25 minutes, until 6200 responses had been recorded (see Supplementary Figure S1). Stimulus presentation was counterbalanced across participants. Behavioral tests were conducted either before or after brainstem recordings. The whole procedure lasted approximately 1.5 hours.

2.4 Data recording and analysis

Brainstem responses were collected using BrainVision V-Amp in combination with an EP-PreAmp, an extremely low-level noise bipolar amplifier (BrainVision) at 20 kHz sampling rate. Three single multitrode Ag/AgCl electrodes were attached to the scalp from Cz-to-ipsilateral earlobe, with forehead as ground (see Supplementary Figure S1). Impedances were down-regulated (< 5 kΩ) and the inter-electrode impedance difference was not higher than 1.5 kΩ. The continuous signal was off-line filtered with the firfilt EEGLAB plugin (Windowed Sinc FIR-filter, bandpass 70 – 2000 Hz, Kaiser window, beta = 7.8572, filter order = 100300, fs = 20 kHz), epoched from -40 to 190 ms, and baseline corrected to a 40 ms interval preceding sound onset. Epochs with any activity exceeding ±35 µV were rejected and a total of 6000 epochs were considered for further analyses. In the lower left and the lower middle panel, Figure 1 illustrates the spectrograms and the oscillograms of the resulting frequency following responses (FFRs) for a representative participant. Especially spectrograms illustrate that scalp-recorded far-field potentials from the auditory brainstem cover phase-locking in a lower frequency range up to 1500 Hz.

2.5. Delta cross-phases

The frequency dimension of a sound wave represents the cycles of compression and rarefaction which can be visualized in form of a sine wave that can be transformed into a circular motion. One complete cycle of 360 ° represents one full period of the sine wave. The angles of this cycle refer to a certain phase of the sine wave. A time shift between two sounds of the same frequency causes a shift between the corresponding sinusoidal waves. Such a shift can be expressed by the difference of corresponding phase angles. The delta cross-phase quantifies a frequency dependent difference of such phase angles, and, thus, captures frequency-specific time delays. Delta cross-phase of the [da] versus [ba] contrast were calculated in MATLAB 8.2 (Mathworks, Natick, MA) by applying the cross-power spectral density (CPSD) function in a sliding-window fashion (Skoe *et al.*, 2011). Baseline-corrected, detrended data were separated into 211 windows with the first window beginning at 40ms pre stimulus onset and the last window beginning at 170 ms, and a 1 ms step size. Each data window of 20 ms was divided into 8 sub-windows overlapping by 50 percent and tapered by a hamming window, resulting in a frequency resolution of 225 Hz. A Fourier transformation was employed with a virtual frequency resolution of 4 Hz. The angle function was applied to extract the cross-phase from the complex cross-spectral densities. To extract phase shifts that are expected in the formant transition of the stimulus contrast [da] versus [ba], we considered mean radians at 20-40 ms between 400-720 Hz (Skoe *et al.*, 2011; White-Schwoch and Kraus, 2013) and calculated the circular mean (circ_mean function of the Circular Statistics Toolbox; Berens, 2009) thereby considering the real distance between angels on a circle.

In addition to the FFRs of a representative participant, the right column of Figure 1 depicts cross-phaseograms of the acoustic stimuli. It is important to note, that opposing F2 transitions occur between 900 Hz and 2480 Hz in the acoustic stimuli and corresponding phase shifts appear in the same range in the corresponding cross-phaseogram (Fig. 1 right upper panel). Notwithstanding, phase-shifts in the cross-phaseogram of the electrophysiological signals occurred in a deeper frequency range (Skoe *et al.*, 2011; White-Schwoch and Kraus, 2013) where actual physical stimuli are similar (Fig. 1 right lower panel).

2.5. Statistical analysis

To test the predictive value of the *delta-cross phase* on literacy skills, a multiple regression analysis was calculated. Multiple covariates were entered in the model because of their known influence on literacy acquisition. These covariates were age, sex (e.g. (Quinn and Wagner, 2015), familial risk (Pennington and Lefly, 2001), parental education e.g. (Friend *et al*., 2008), intelligence e.g. (Hatcher and Hulme, 1999), and phonological awareness e.g. (Wagner and Torgesen, 1987). We report all zero-order Pearson correlations as well as the partial correlation between mean literacy and delta cross-phase. Finally, a regression commonality analysis was calculated in order to separate the contribution of the main predictors of literacy (Nimon, 2010). In order to determine the receiver operating characteristic (ROC) curve, children were assigned to one of two groups with regard to literacy proficiency. Poor literacy (Lit_-) was assigned given an averaged percentile rank <25 across all standardized literacy tests, considering reading comprehension, reading speed and spelling. Good literacy (Lit_+) was assigned given an averaged percentile rank >25. Using a percentile rank of 25 as cutoff criterion is in accordance with the norms of the used tests (i.e., DERET, LGVT), defining average/above-average performance by a percentile rank above 25 and below-average performance by a percentile rank below 25 (Schneider et al., 2007; Stock and Schneider, 2008). In one case information on performance in spelling was missing and averaged percentile rank resulted from reading comprehension and reading speed only.

The combination of both, reading skills and spelling skills gave a robust estimate of literacy over time, and, thus, ensured that the sample of cases included participants who continuously struggled with literacy. Altogether, 13 children were assigned to the Lit_- group (aged 12.1 to 13.8 years, 11 males) and 49 children were assigned to the Lit_+ group (aged 11.4 to 13.6 years, 27 males). Table 1 includes descriptive group statistics as well as group comparisons for all critical measures. Because group-sizes were unequal nonparametric tests were employed to test for group differences with regard to age, intelligence, phonological awareness, literacy skills and the electrophysiological measures.

Two approaches have been applied to test the predictive power of the delta cross-phase on literacy outcome. This exhaustive procedure has been applied to address the problem of imbalanced group sizes ($N_{Lit+=}49$ vs. $N_{Lit-} = 13$). First, receiver operating characteristic (ROC) curve and the area under the ROC curve were calculated to determine sensitivity and specificity of delta cross-phase in order to classify children with poor literacy skills. Second, hierarchical binary logistic regression analyses were calculated to investigate whether the delta cross-phase could predict literacy beyond phonological awareness. Four different literacy prediction models were specified and hierarchically introduced to the analysis. The first model included age, sex, familial risk, parental education in the first step, and intelligence in the second step as predictors to control for a potential confounding effect of intelligence. The second model additionally included phonological awareness in the second step, as tested three years prior the recording of the brainstem potentials, to test the effect of this literacy precursor. The third model considered delta cross-phase as a further additional predictor in the second step to test the predictive power of the electrophysiological measure, which constituted the independent variable of interest in the current study. The fourth model considered in addition nonword reading speed as a measure of phonological skills at the time, when cABRs were actually taken. Statistics were calculated with SPSS (SPSSInc., Chicago, IL, USA).

3. Results

3.1. Delta cross-phase and phonological awareness predict literacy

A multiple linear regression was calculated to predict literacy based on delta cross-phase, phonological awareness, intelligence, familial risk, parental education, sex, and age. A significant regression equation was found ($F(7, 54) = 5.822$, $p < 0.001$), with an R^2 of 0.430. Participants predicted literacy is equal to 12.830 + 13.717 (delta cross-phase) + 0.196 (phonological awareness), where delta cross-phase is measured in radians, and phonological awareness is coded as percentile rank. Participant’s literacy increased 1.37% for each 0.1 radian of delta cross-phase and participant’s literacy increased 0.196% for each percent of phonological awareness. While delta cross-phase and phonological awareness were significant predictors of literacy all other variables did not predict literacy in the current sample ($p_{IQ} = 0.179$; $p_{familial\_risk} = 0.198$, $p_{parental\_education} = 0.063$, $p_{age} = 0.470$, $p_{sex} = 0.778$).

Multicollinearities between chosen variables required more fine-grained analyses to finally enable a faithful interpretation of the current results. Figure 2A-H illustrates all significant zero-order correlations. When not controlling for covariance participant's *literacy* was positively correlated with *delta cross-phase* (Fig. 2A, $r = 0.436$, $p < 0.001$), *phonological awareness* (Fig. 2B, $r = 0.525$, $p < 0.001$), *nonverbal intelligence* (Fig. 2C, $r = 0.327$, $p = 0.01$), and *parental education* (Fig. 2D, $r = 0.366$, $p = 0.003$). *Delta cross-phase* was in addition positively correlated with *phonological awareness* (Fig. 2E, $r = 0.325$, $p = 0.01$) and girls showed a higher delta cross-phase compared to boys (Fig. 2F, $r = 0.266$, $p = 0.036$). *Phonological awareness* was positively correlated with *parental education* (Fig. 2G, $r = 0.312$, $p = 0.014$), and *nonverbal intelligence* (Fig. 2H, $r = 0.388$, $p = 0.002$). A correlation matrix illustrates all linear correlations (Fig 2I).

Because predictors, in particular phonological awareness and delta cross-phase, were correlated with literacy as well as with each other we decomposed the variance of R^2 into unique and common/shared effects (Table 2). The total variance explained by phonological awareness was 27.5 % while the total variance explained by delta cross-phase was 19 %. Of most interest was the minimum explanatory power of phonological awareness and delta cross-phase on literacy, because this shows the variance explained uniquely by the physiological or behavioral variable. 6.6% variance was uniquely accounted for by phonological awareness while 5.2% variance was uniquely accounted for by the delta cross-phase as indicated by part correlations. The additional common variance explained by phonological awareness and delta cross-phase was 3.8 %. A further partial correlation between *literacy* and *delta cross-phase* was $r = 0.289$, $p(54) = 0.031$, when controlling for phonological awareness, intelligence, parental education, sex, familial risk, and age. A partial correlation between *phonological awareness* and *delta* *cross-phase* was $r = 0.245$, $p(55) = 0.066$ when controlling for intelligence, parental education, sex, familial risk and age.

3.2. Assignment to poor literacy group and group statistics

Receiver operating characteristic (ROC) analysis is a common tool in clinical research to express the diagnostic accuracy of e.g. a physiological measure (Eng, 2005). The analysis is based on a binary classification of real cases, which, in the current study, is obtained by assigning all children with a mean literacy smaller then 25th percentile in standardized tests to the Lit_- group, whereas all children with a mean literacy larger then 25th percentile were assigned to the Lit_+ group. All group statistics are based on this categorization and are summarized in Table 1.

Accordingly, performance in spelling, reading speed and reading comprehension was impoverished in children in the Lit_- group compared to children of the Lit_+ group. Further psychometric tests yielded that Lit_- children were slower than Lit_+ children in reading the word list ($\text{mean}_{\text{Lit-}}$: 59 s; $\text{mean}_{\text{Lit+}}$: 31 s, $U = 146.0$, $p < 0.003$), and the nonword list ($\text{mean}_{\text{Lit-}}$: 88 s; $\text{mean}_{\text{Lit+}}$: 52 s, $U = 141.0$, $p = 0.002$), and less accurate in word reading ($\text{mean}_{\text{Lit-}}$: 85 %; $\text{mean}_{\text{Lit+}}$: 97 %; $U = 430.0$, $p = 0.04$). However, accuracy in reading the nonword list was not significantly worse in the Lit- group compared to the Lit+ group ($\text{mean}_{\text{Lit-}}$: 72 %; $\text{mean}_{\text{Lit+}}$: 81 %; $U = 395.0$, $p = 0.182$). Furthermore, Lit_- children showed poor phonological awareness skills (mean percentile rank: 32) compared to Lit_+ children (mean percentile rank: 54; $U = 447.5$, $p = 0.026$). Nonverbal intelligence was higher in Lit_+ children compared to Lit_- children ($\text{mean}_{\text{Lit+}}$: 112; $\text{mean}_{\text{Lit-}}$: 107; $U = 449.0$, $p = 0.024$), but individual intelligence scores were > 85, and, thus, in accordance with the inclusion criteria.

3.3. Diagnostic performance of the electrophysiological measure - delta cross-phase

The area under the ROC curve (*AUC*) gives an overall indication of the diagnostic accuracy of delta cross-phase for literacy outcome. ROC analysis revealed an *AUC* of 0.829 ($p < 0.001$, $CI_{.95} = 0.711, 0.947$) indicating a feasible distinction between Lit_{+} and Lit_{-}. Interestingly, an additional ROC analysis testing the diagnostic accuracy of phonological awareness revealed an *AUC* of 0.703 ($p < 0.026$, $CI_{.95} = 0.512, 0.893$) suggesting a better performance of the objective electrophysiological measure to diagnose literacy outcome. Figure 3 depicts ROC curves. Finally, binary hierarchical logistic regression analyses were computed to exhaustively test the predictive power of delta cross-phase. The first model investigated the effect of intelligence on the predictability of literacy skills. Intelligence revealed a significant improvement compared to the null model ($\chi^2 = 4.28$, $p = .039$). Nagelkerke's R^2 was 0.205 with an overall prediction success of 77.4 % (93.9 for Lit+ and 15.4 for Lit-). The second model investigated the effect of phonological awareness as measured with the BAKO, which revealed marginal improvement of the model ($\chi^2 = 5.94$, $p = .051$). Nagelkerke's R^2 was 0.240 with an overall prediction success of 79.0 % (93.9 for Lit+ and 23.1 for Lit-). The third model investigated the effect of delta cross-phase, which revealed remarkable improvement of the model ($\chi^2 = 17.56$, $p < .001$). Nagelkerke's R^2 was 0.466 with an overall prediction success of 82.3 % (93.9 for Lit+ and 38.5 for Lit-). Eventually, the fourth model investigated the effect of delta cross-phase, which revealed remarkable improvement of the model ($\chi^2 = 22.33$, $p < .001$). Nagelkerke's R^2 was 0.546 with an overall prediction success of 90.3 % (98.0 for Lit+ and 61.5 for Lit-).

4. Discussion

The desire of translational research is to develop and improve diagnostic tools to assist clinical decisions or to evaluate treatment outcome. Early detection, assessment, and treatment of reading disorders is the ultimate way to optimally support affected individuals. Beside behavioral assessment batteries, the measurement of auditory brainstem responses seems to be a potential promising tool to support early diagnosis (Hornickel and Kraus, 2013; White-Schwoch and Kraus, 2013). Here, we provide first evidence that delta cross-phase, a measurement of the temporal precision of early sound processing, which is highly associated with phonological awareness as an important precursor for successful literacy acquisition, is sensitive to separate children with good literacy skills from children with poor literacy skills in a German cohort.

4.1. Phonological awareness and literacy

Phonological awareness is one of the most recognized precursor competence of literacy acquisition (Whitehurst and Lonigan, 1998; Oakhill and Cain, 2012), which is often impaired in individuals with a reading disorder (Bird *et al.*, 1995; Schulte-Körne and Bruder, 2010; Heim and Grande, 2012; Melby-Lervåg *et al.*, 2012). Results of the current study are in line with this interrelation; children with poor literacy skills performed poor in phonological awareness tasks, whereas children with good literacy skills performed well in phonological awareness tasks. The close link between phonological awareness and literacy is mainly based on the alphabetic principle of alphabetic systems. Inherent to this principle is the correspondence between phonemes and graphemes (Liberman *et al.*, 1990). To acquire reading and spelling, phonemes need to be identified and translated to graphemes and vice versa. Thereby, phonological awareness and literacy acquisition mutually influence each other (Bentin and Leshem, 1993). The emergence of phonological awareness requires a previously developed sensitivity to phonology and thus is closely linked to phonological skills. It has been suggested that individuals with reading disorders struggle with phonological processes, which might be caused by underspecified phonological representations (Wagner and Torgesen, 1987), a deficient access to phonetic representations (Ramus and Ahissar, 2012; Boets *et al.*, 2013), or by a failure to establish phoneme categories (Noordenbos *et al.*, 2013). Further views suggest that the phonological deficit is based on impaired oscillatory phase locking for low frequency temporal coding in auditory cortex (Goswami, 2011), or that a decreased sensitivity to rapidly changing phonological features could drive the impoverished distinction between speech sounds (Tallal, 1980). Despite a considerable amount of research, mechanisms that contribute to robust phonological processing, and its impairment in reading disorders, remain a subject of debate. Studies of the neural coding of phonemes throughout the auditory pathway, like the present work, are necessary to determine underlying mechanisms.

4.2. *Delta cross-phase*

Phonological awareness was also related to the physiological discrimination of stop consonants. Children with poor phonological awareness skills showed small phase shifts, and, thus, a diminished neural discrimination of sounds, whereas children with good phonological awareness had a superior neural discrimination. The same relationship has been previously reported for pre-school children (White-Schwoch and Kraus, 2013). The authors discussed that these children were preliterate and that it remains to be shown whether children with weak phonological awareness and weak subcortical differentiation of consonants will struggle with literacy acquisition or whether a normalization of the physiological differentiation of sounds due to maturation will facilitate reading outcome. Here, we show that children with a reading disorder have both, poor phonological awareness and poor physiological discrimination of sounds as measured with delta cross-phase of [da] versus [ba]. The correlation between the goodness of literacy skills and the stability of speech-evoked brainstem responses is consistent with previous reports (Hornickel and Kraus, 2013). Employed metrics are capable of showing the noisiness of subcortical sound encoding. However, the sensitivity to physiologically distinguish between sounds such as stop consonants is not considered. A first step towards such a distinction has been provided by a further work (Hornickel *et al.*, 2009). The authors took advantage of the fact that the brainstem encodes temporal and spectral cues of voiced stop consonants. The first few milliseconds of the noise burst of the stop consonants together with the formant transition are reflected in the phase-locking, and, thus, the neural response timing of involved neurons. Response timing seems to be the neurophysiological feature that encodes spectral cues (Gorga *et al.*, 1988). Because, the syllable [da] contains higher frequencies in the phase of the formant transition than the syllable [ba], [da] evokes earlier responses (Johnson *et al.*, 2008). This was a first metric for a subcortical differentiation of speech sounds. The advantage of the later introduced cross-phaseogram approach is, that it automatically and objectively quantifies these fine differences in peak latencies because they emerge as phase shifts in the delta cross-phase (Skoe *et al.*, 2011). A time consuming and rater dependent labeling of peaks of the FFR is not necessary anymore.

4.3. Combined measures have more power

Multicollinearities characterize the relationship between literacy skills, phonological awareness, and delta cross-phase. Given the strong interrelation between literacy and phonological awareness (Bentin and Leshem, 1993), and between phonological awareness and delta cross phase (White-Schwoch and Kraus, 2013), the high correlation between all these variables was not unexpected. The overarching objective of our work is the improvement of clinical early diagnosis of reading disorders. The cross-phaseogram approach has several advantages as summarized earlier (Skoe *et al.*, 2011). It is an objective and automated technique that is based on non-invasive measurements but no active commitment of tested individuals. However, it will only be considered by clinicians if it adds power to the already powerful assessment of behavioral features such as phonological awareness. For this reason we calculated a receiver operating curve analysis, a commonality analysis, and hierarchical binary logistic regression analyses. All analyses strongly support the idea that speech-evoked brainstem potentials might support future diagnostic procedures. The ROC analysis demonstrated that phonological awareness as well as delta cross-phase are eligible for clinical classification of subjects with literacy problems. The combination of phonological awareness and delta cross-phase by means of a principal component analysis revealed individual factor scores that likewise support a diagnostic categorization as shown in Figure 4. The commonality analysis revealed the unique explained variance of literacy by phonological awareness (6.6 %), of literacy by delta cross-phase (5.2 %), and the common explained variance of phonological awareness and delta cross-phase on literacy (3.8 %). Thus, delta cross-phase explained 9 % when considering the unique and the shared variance explained. Moreover, considering further influencing factors, such as phonological awareness, parental education, non-verbal intelligence, familial risk, sex, and age, delta cross phase explains 13.8 % of the variance of literacy, which is more than twice the amount of variance explained by phonological awareness alone, which is quite considerable. For a clinical application it would be most desirable to be able to reliably decide on whether a child will develop a reading disorder or not. For such a decision it is necessary to develop a binary measure. While the ROC approach is based on such a binary dependent variable, the multivariate regression only allows for a continuous dependent variable. The problem of the current study is that the group sizes are imbalanced (N_{Lit+} = 49 versus N_{Lit}- = 13), a fact that actually confounds the robustness of the ROC approach. A binary logistic regression is an alternative method that treats literacy as a binary variable and estimates the predictive value of the potential physiological and psychological variables. The outcome of this approach suggests an advantage of the physiological measure over the psychological measure. Still, our findings are the first of its kind and thus preliminary. Future studies are necessary to confirm the here reported findings.

4.4. Limitations and prospective

Several modifications can be anticipated to improve the precision of our approach to establish a neurophysiological measure of early sound processing and to elucidate its interrelation with reading disorders. Due to the fact that we tested all children from the GLAD cohort (Friedrich and Friederici, 2004; Schaadt et al., 2016; Schaadt et al., 2015) that volunteered to participate in the study, the sample size is small and the distribution of cases and controls is imbalanced. The regression approaches somehow overcomes this problem, thereby considering the ratio of reading disorders in the whole population. Given the fact, that the control group is characterized by 32 % familial risk whereas the group of cases accumulated 62.5 % of familial risk, a proportion of 21 % occurrence of reading disorders is reasonable. The male to female ratio was relatively high with 1:3 in the current cohort of children with poor literacy skills. Previous reports range from 1:1.2 to 1: 7 (Quinn and Wagner, 2015). Because girls showed a higher delta cross-phase compared to boys, we additionally calculated a partial correlation with sex, intelligence, parental education, familial risk and intelligence as variates of no interest, thereby controlling for the influence of sex. Because the correlation was also significant after controlling for the above mentioned variates of no intrest, we infer that the delta cross-phase and literacy are related to each other despite an influencing effect of sex (p = 0.031). Nonetheless, future studies would benefit from larger sample sizes and a balanced proportion of cases and controls. A further critical aspect is the accumulation of behavioral data over time. Phonological awareness and spelling skills were measured three years before the actual brainstem measures were undertaken (Schaadt et al., 2016; Schaadt et al., 2015). Reading speed and reading comprehension were measured at the same time period when the brainstem measures were acquired. The combination of both, reading skills and spelling skills, gives a robust estimate of literacy over time and thereby ensures that the sample of cases includes participants who continuously struggled with literacy. In addition, this proceeding seemed better suited because it lowered the overall experimental burden the 11 to 13 year old participants were exposed to. Future studies that consider larger sample sizes and especially a large amount of cases would also allow acknowledging heterogeneous cognitive fingerprints (Heim *et al.*, 2008; Heim and Grande, 2012). Finally, the best way of delivering what concerns most, are longitudinal studies. Detailed information on the developmental trajectories of physiological and behavioral correlates of reading disorders will help identifying core deficits. The assessment of phonological awareness and speech-evoked brainstem responses in pre-school children and its reevaluation during reading acquisition will inform us about a possible late maturation of the affected subcortical system or the persistency of imprecise temporal coding throughout development in affected children.

Together, these modifications are likely to improve our ability to characterize the physiological grounding of phonological deficits in children with reading disorders. Moreover, the strong correlation between literacy and the physiological discrimination of stop consonants in the auditory brainstem makes this approach to a likely potential complement of early behavioral assessments. A potential next step could be to evaluate the method in a clinical study that includes cases with a formal diagnosis of dyslexia. Further work that incorporates this paradigm may also produce a viable neurophysiologic marker for subtyping these children in conjunction with genetic and behavioral analyses.

Conflict of interest

None of the authors have potential conflicts of interest to be disclosed.

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Tables

Table 1. Participants' characteristics. Professional education was operationalized with an ordinal scale with 1 = without professional education; 2 = Professional School, Vocational School; 3 = Master Craftsman, Technical College, Bachelor, University of Cooperative Education; 4 = Upscale Official Career; 5 = University of Applied Sciences; 6 = University Degree; State Examination, PhD; ^{U}Independent Samples Mann-Whitney U Test, ^{W}Related Samples Wilcoxon Signed Rank Test, ^{M}Independent Samples Median Test, BR=brainstem responses, pCPSD=phase of cross power spectral density, DERET=German spelling test, LGVT=German reading test, values represent group averages (*SD*) unless otherwise indicated

N	**missing data**	**Lit$_+$** **49**	**Lit$_-$** **13**	***P*-Value**
Demographics				
Age (years)		12.7 (0.7)	12.8 (0.5)	0.7^U
Age range (min – max)		11.4–13.6	12.1–13.8	
Sex (male/female)		27/22	10/3	
Familial risk (no risk/risk)		37/12	8/5	
Parental education				
Profession mother (median)		2	2	0.08^M
Profession father (median)		2	2	0.9^M
Brainstem measures				
Peak-V-latency				
Pre-speech-evoked BR (ms)	1	5.47 (0.19)	5.57 (0.18)	0.16^W
Post-speech-evoked BR (ms)	1	5.48 (0.18)	5.60 (0.17)	
Cross-Phase				
pCPSD (rad)		0.57 (0.35)	0.26 (0.44)	**0.002**^{U}
Psychometrics				
Literacy				
DERET – spelling skills (mean PR)	1	52 (27)	14 (14)	**<0.001**^{U}
LGVT – reading speed (mean PR)		43 (23)	20 (12)	**<0.001**^{U}
LGVT – reading comprehension (mean PR)		49 (22)	15 (11)	**<0.001**^{U}
Literacy across DERET and LGVT (meanPR)		48 (18)	17 (6)	**<0.001**^{U}
Word reading (mean %correct)		97 (5)	85 (22)	**0.040**^{U}
Word reading speed (s)		31 (12)	59 (52)	**0.003**^{U}
Nonword reading (mean %correct)		81 (14)	72 (21)	0.182^U
Nonword reading speed (s)		52 (21)	88 (65)	**0.002**^{U}
Phonological awareness				
BAKO (mean PR)		54 (30)	32 (34)	**0.026**^{U}
Intelligence				
Intelligence (mean IQ)		112 (10)	107 (7)	**0.024**^{U}
Intelligence range (min – max)		86–126	92–116	
Handedness (right/left)		45/4	13/-	

Table 2. Results from regression and commonality analyses predicting literacy. Multiple R = correlation coefficient of the multiple regression analysis; *β* = standardized beta coefficient; *p* = p-value; SE = standard error; CIL = 95% confidence interval lower bound; CIU = 95% confidence interval upper bound; %R² = % of R² of zero-order Pearson correlation; %U = % of R² of part correlation (unique effect) meaning the residual of the independent variable when correlated with all other independent variables correlated with literacy; %C = % of R² of (common effect) identify how much variance is common to the independent variable and all other independent variables; %P = % of R² of partial correlation meaning the residual of the independent variable when correlated with all other independent variables, correlated with the residual of literacy when correlated with all other independent variables.

Predictor	**Multiple *R***	***R²***	***R²_{adj}***	***β***	***P***	**SEM**	**CIL**	**CIU**	**%R² total**	**%C common**	**%U unique**	**%P part**
	0.656	0.430	0.356		0.000							
Phonological awareness				0.303	0.015	0.121	0.061	0.546	27.5	20.9	6.6	10.4
Delta cross-phase				0.253	0.031	0.114	0.024	0.481	19.0	13.8	5.2	8.4
Parental Education				0.209	0.063	0.110	-0.012	0.430	13.4	9.6	3.8	6.2
Nonverbal intelligence				0.159	0.179	0.117	-0.075	0.394	10.7	8.7	2.0	3.3
Familial Risk				0.139	0.198	0.107	-0.075	0.353	3.0	1.2	1.8	3.1
Sex				0.032	0.778	0.112	-0.192	0.256	2.3	2.3	0.1	0.1
Age				-0.079	0.470	0.109	-0.297	0.139	0.2	-0.4	0.6	1.0

Figure Legends

Figure 1. Stimuli and resulting frequency following responses.

Plots of the left and middle column depict spectrograms, corresponding time-amplitude wave forms at the bottom ([da] - orange, [da] – blue), and spectra of Fourier transformations for the time range of the formant transitions (FFT) at the right.

Right plots depict the cross-phaseograms to [da] and [ba] resulting from a calculation of phase differences. On the bottom of these cross-phaseograms the amplitude wave forms of [ba] and [da] are overlaid focussing the time range of the formant transitions.

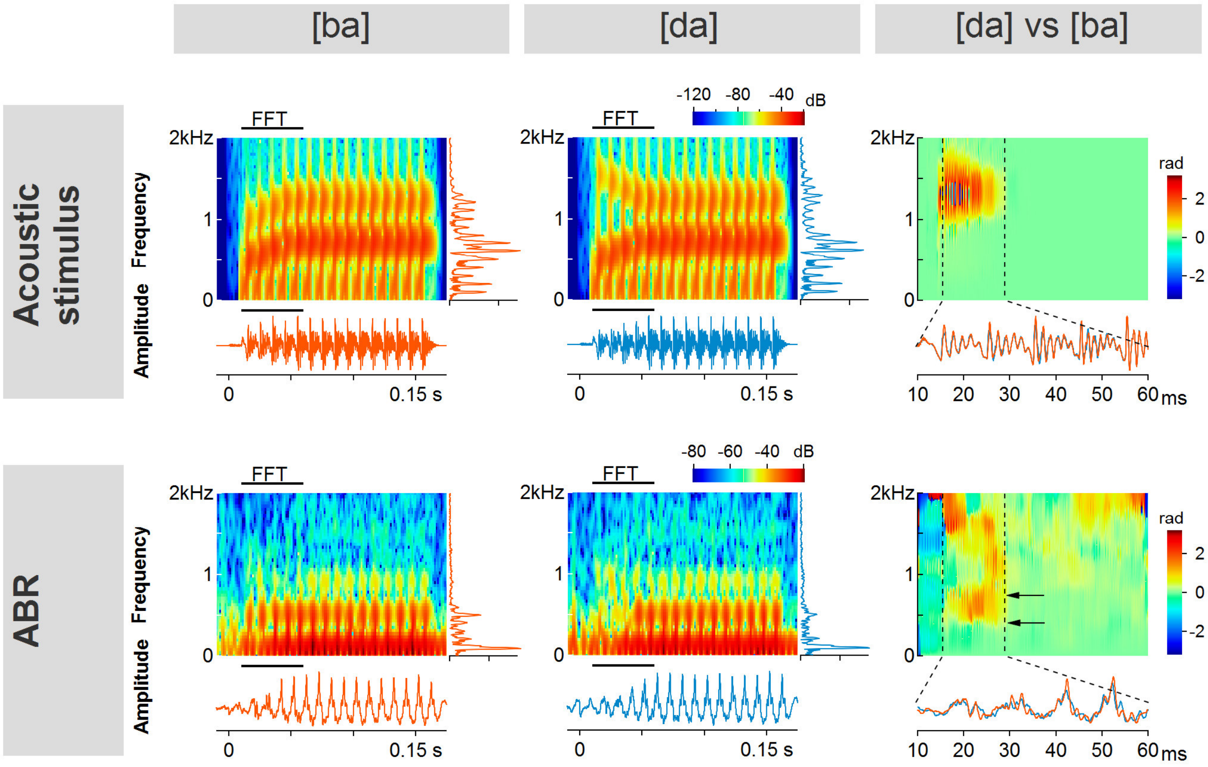
The acoustic stimuli-spectrograms illustrate the opposing transitions of the second formant in [ba] and [da]. The corresponding cross-phaseogram shows a prominent phase-shift in the frequency range of these formant transitions indicating the physical differences between stimuli between 900 and 1700 Hz. The second cross-phaseogram shows phase shifts evident in auditory brainstem responses (ABRs) of a healthy 13-year old German-speaking boy with typical hearing, phonological awareness, and literacy. Remarkable is the apparent phase-shift in the previously reported (Skoe *et al.*, 2011) frequency range (720 – 400 Hz).

Figure 2. Covariance of literacy and influencing factors. Scatter plots show positive correlations between participant’s mean literacy skills and (A) delta cross-phase, (B) phonological awareness, (C) nonverbal intelligence, and (D) parental education. Further scatter plots show positive correlations between participant’s delta cross-phase and (E) phonological awareness, and (F) sex as well as positive correlations between participant’s phonological awareness and (G) parental education, and (H) nonverbal intelligence. The high covariance between the dependent variable ‘literacy’ and all other independent variables is visualized in a correlation matrix (I). The partial correlation plot (J) depicts the standardized residuals of the correlation between literacy and phonological awareness, nonverbal intelligence, parental

education, familial risk, age and sex on the y-axis; and the standardized residuals for the correlation between delta cross-phase and phonological awareness, nonverbal intelligence, parental education, familial risk, age, and sex on the x-axis. Significance is coded as *p < 0.05, **p< 0.01, ***p<0.001, and † corrected p<0.05 across all panels. Red circles indicate cases of poor literacy and blue circles indicate cases of good literacy. Dotted black lines in scatter plots depict regression line.

Figure 3. Good diagnostic performance of delta cross-phase. Category plots depict group means (±SEM) for children with poor literacy skills (Lit_{-}, PR<25) and children with good literacy skills (Lit_{+}, PR>25). The physiological measure delta cross-phase (A) as well as the psychological measure phonological awareness (C) was reduced in children with poor literacy skills. Receiver operating characteristic curves of delta cross-phase (B) and phonological awareness (D) showed a feasible detection of cases of poor literacy. The area under the curves suggests that the electrophysiological measure outperforms the psychological measure.

Figure 4. Multidimensional scaling across delta cross-phase and phonological awareness was achieved by calculating a Principal Component Analysis. Group means (±SEM) of the individual factor scores are shown in the bar plot. The yellow ROC curve is based on these individual factor scores. The dotted lines depict the ROC curves of delta cross-phase (black) and phonological awareness (blue), respectively.


[ba]
[da]
[da] vs [ba]
Acoustic stimulus
ABR
Frequency
Amplitude
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60
ms

Fig. 1

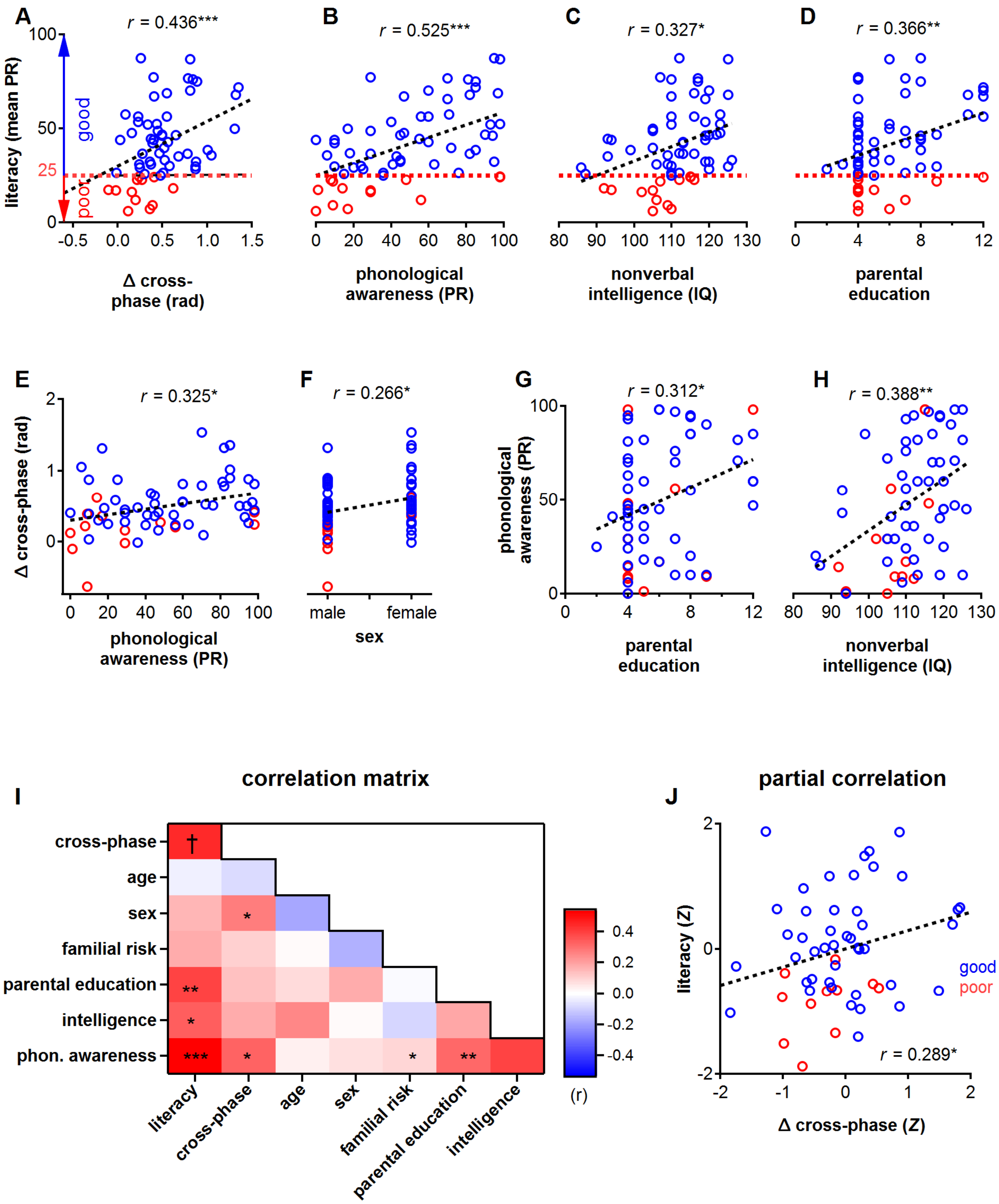
A
r = 0.436***
literacy (mean PR)
100
50
25
0
good
poor
-0.5
0.0
0.5
1.0
1.5
Δ cross-phase (rad)
B
r = 0.525***
0
20
40
60
80
100
phonological awareness (PR)
C
r = 0.327*
80
90
100
110
120
130
nonverbal intelligence (IQ)
D
r = 0.366**
0
4
8
12
parental education
E
r = 0.325*
Δ cross-phase (rad)
2
1
0
phonological awareness (PR)
F
r = 0.266*
male
female
sex
G
r = 0.312*
phonological awareness (PR)
100
50
0
parental education
H
r = 0.388**
nonverbal intelligence (IQ)
I
correlation matrix
cross-phase
age
sex
familial risk
parental education
intelligence
phon. awareness
†
*
**
*
***
*
*
**
0.4
0.2
0.0
-0.2
-0.4
(r)
literacy
cross-phase
age
sex
familial risk
parental education
intelligence
J
partial correlation
literacy (Z)
2
0
-2
-1
1
good
poor
r = 0.289*
Δ cross-phase (Z)

Fig. 2

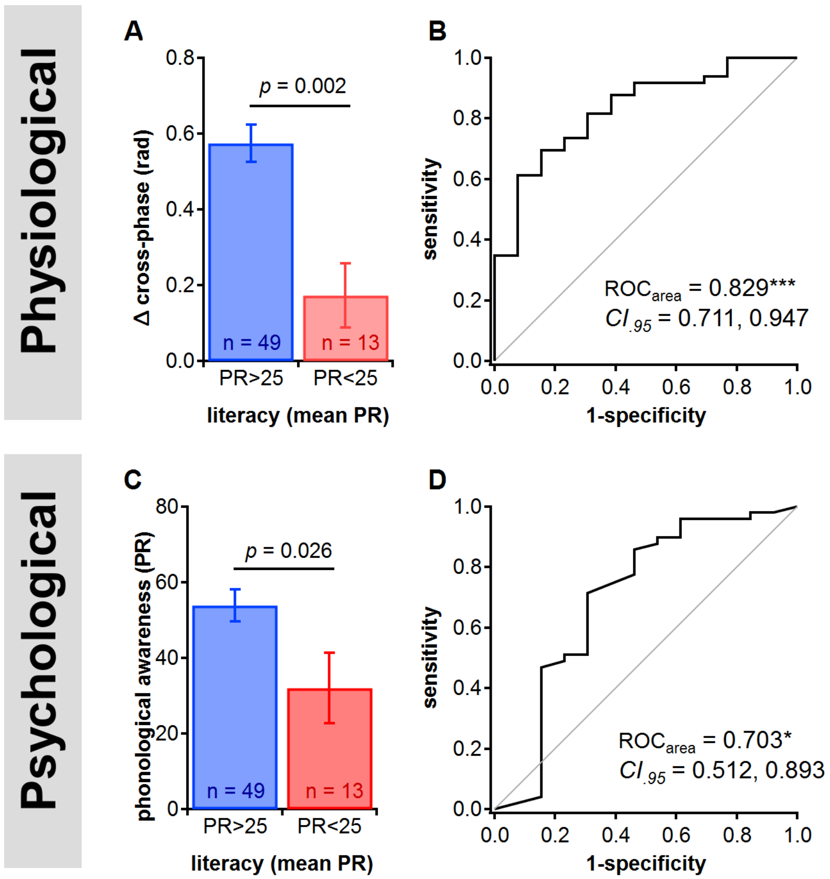
Physiological
A
Δ cross-phase (rad)
0.0
0.2
0.4
0.6
0.8
p = 0.002
n = 49
n = 13
PR>25
PR<25
literacy (mean PR)
B
sensitivity
1.0
0.8
0.6
0.4
0.2
0.0
ROCarea = 0.829***
CI.95 = 0.711, 0.947
0.0
0.2
0.4
0.6
0.8
1.0
1-specificity
Psychological
C
phonological awareness (PR)
0
20
40
60
80
p = 0.026
n = 49
n = 13
PR>25
PR<25
literacy (mean PR)
D
sensitivity
ROCarea = 0.703*
CI.95 = 0.512, 0.893
1-specificity

Fig. 3

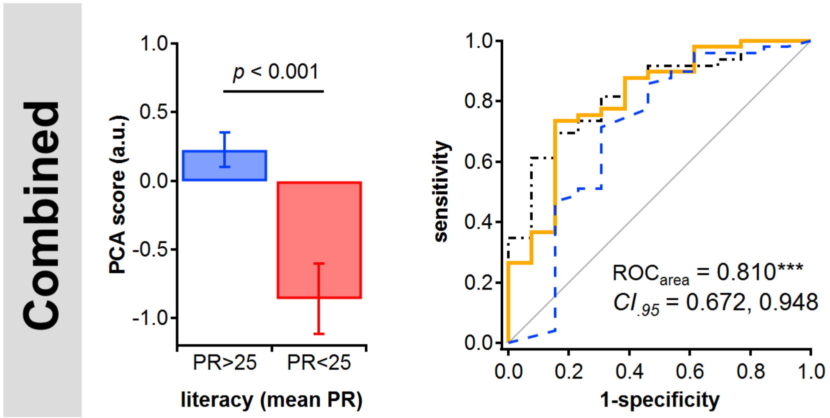
Combined
PCA score (a.u.)
1.0
0.5
0.0
-0.5
-1.0
p < 0.001
PR>25
PR<25
literacy (mean PR)
sensitivity
1.0
0.8
0.6
0.4
0.2
0.0
ROC_area = 0.810***
CI_.95 = 0.672, 0.948
0.0
0.2
0.4
0.6
0.8
1.0
1-specificity

Fig. 4