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Children at risk for dyslexia show deficient left-hemispheric memory representations for new spoken word forms

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ABSTRACT

Developmental dyslexia is a specific learning disorder with impairments in reading and spelling acquisition. Apart from literacy problems, dyslexics show inefficient speech encoding and deficient novel word learning, with underlying problems in phonological processing and learning. These problems have been suggested to be related to deficient specialization of the left hemisphere for language processing. To examine this possibility, we tracked with magnetoencephalography (MEG) the activation of the bilateral temporal cortices during formation of neural memory traces for new spoken word forms in 7–8-year-old children with high familial dyslexia risk and in controls. The at-risk children improved equally to their peers in overt repetition of recurring new word forms, but were poorer in explicit recognition of the recurring word forms. Both groups showed reduced activation for the recurring word forms 400–1200 ms after word onset in the right auditory cortex, replicating the results of our previous study on typically developing children (Nora et al., 2017, Children show right-lateralized effects of spoken word-form learning. PLoS ONE 12(2): e0171034). However, only the control group consistently showed a similar reduction of activation for recurring word forms in the left temporal areas. The results highlight the importance of left-hemispheric phonological processing for efficient phonological representations and its disruption in dyslexia.

1. Introduction

Developmental dyslexia is a specific learning disorder characterized by problems in reading and writing despite normal intelligence and education. In the Finnish language, which has transparent orthography with high grapheme-phoneme correspondence, the most prominent symptom for dyslexia is slow and effortful reading (Everatt and Elbeheri, 2008). The most severely affected individuals, however, have great difficulties in learning the letter-sound correspondences and consequently persistent problems in learning to read. In these cases, a strong familial background may be expected. Dyslexia is a familial trait with moderate to high heritability (Peterson and Pennington, 2015). To date, at least nine genetic risk loci and over ten different candidate genes have been associated with this disorder (Kere, 2014). The consensus is that the underlying neurobiological cause lies in phonological processing, i.e. extracting phoneme units from spoken language, establishing and maintaining sound-based representations in memory, and recoding orthographic units into sound-based representations (e.g. Shaywitz and Shaywitz, 2005). Phonological processing and memory are fundamental in language acquisition, and, besides reading impairments, dyslexic individuals typically also display problems in language learning, especially in vocabulary acquisition and foreign language learning, as shown in the Jyväskylä Longitudinal Study of Dyslexia and other studies (Dal, 2008; Lyytinen et al., 2015, 2005).

Here, we investigate the neural correlates of phonological learning in 7-to-8-year-old children with a familial background for problems in reading acquisition, and compare them with a control group of beginning readers. The phonological problems in dyslexia are highlighted when there is less support from existing linguistic knowledge, e.g. when trying to decipher and utter new written or spoken words. Behavioral studies indicate that dyslexics are less accurate or slower than controls in learning new phonological word forms, but with fairly typical acquisition of semantic associations (Alt et al., 2017; Elbro and Jensen, 2005; Litt and Nation, 2014; Mayringer and Wimmer, 2000; Messbauer and de Jong, 2003; Vellutino et al., 1995). The phonological decoding of written words and vocabulary acquisition both depend on phonological storage, and phonological storage deficits are reflected in pseudoword repetition (Gathercole, 2006). Indeed, pseudoword repetition, especially the repetition of lengthier sequences that tax the phonologi-

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cal storage component, is impaired in children with poor reading abilities (e.g. Snowling, 1981). Pseudoword repetition with an incidental learning component could thus be especially sensitive in revealing the phonological learning deficits associated with dyslexia.

In line with this view, brain imaging studies show abnormal phonological processing in dyslexics compared to controls. Difficulties in phonological analysis of spoken words have manifested as delayed or smaller brain responses (Helenius, 2000, 2002a,b) and abnormal fMRI BOLD activation patterns (Richards et al., 2007). These might be associated with underlying deficits in auditory processing, i.e. rapid temporal sampling of the auditory signal, auditory memory, or discrimination of subtle contrasts (for reviews see Goswami, 2015; Heim and Keil, 2004; Hämäläinen et al., 2013; Schulte-Körne and Bruder, 2010; Shaul, 2008). Children with a familial risk for dyslexia show abnormal cortical processing of auditory information already at birth, linked with later reading and language skills (Guttorm et al., 2010; Hämäläinen et al., 2013; Leppänen et al., 2010; Lyytinen et al., 2005). Thus, these auditory and phonological processing deficits appear to impose a risk for later reading problems. Recent findings have established that cortical phonemic/phonological sublexical representations are deficient in children with a familial risk for dyslexia, but these deficient representations do not directly predict later dyslexia diagnosis (Vandermosten et al., 2020). However, due to phonological working memory deficits, a bigger bottle neck in dyslexia might lie in representing longer, word-level phonological sequences in the brain and mapping them onto grapheme form. To our knowledge, no neuroimaging studies have investigated the neural basis of word-level phonological learning deficits in children with dyslexia risk. In adulthood, deficits in phonemic/phonological representations may be diminished or compensated, even if the representations still remain somewhat less easily accessible (Boets et al., 2013). Thus, to identify the cortical underpinnings of phonological deficits associated with dyslexia, neuroimaging studies need to investigate the at-risk children early on.

The problems in phonological processing have been suggested to stem from deficient specialization of the left hemisphere for language processing during development, reflected in weaker structural and functional (i.e. during language tasks) left-hemispheric dominance (Bishop, 2013; Heim and Keil, 2004). However, the clinical significance of atypical left-hemispheric processing in dyslexics has remained unclear, and there is an on-going debate on whether it might, instead, be a consequence of poor phonological skills or deficient reading (Bishop, 2013). A special role in dyslexia has further been attributed to the left frontal regions: Dyslexia has been hypothesized to be related to faulty connections between left-hemispheric temporal and frontal brain areas that are responsible for maintaining and accessing perceptual-motor representations, which are crucial for phonological processing (Boets et al., 2013; Heim and Keil, 2004; López-Barroso et al., 2013; Peterson and Pennington, 2015). However, it has remained unknown whether the motor learning of novel phonological sequences is impaired in children with dyslexia risk. Here, we utilize a task that involves both input and output phonological processes and has been shown to engage bilateral temporal auditory and frontal motor areas (Nora et al., 2012; Nora et al., 2015). In our earlier studies this task has also revealed differences between typically developing children and adults (Nora et al., 2017).

While there have been no combined neuroimaging and behavioral studies on learning of new word forms in dyslexia risk children, some M/EEG and fMRI studies have examined neural habituation to recurring linguistic stimuli in dyslexia. Dyslexic adults and language impaired adults and children show weaker than normal cortical effects of repeated presentations of words or pseudowords, indicating an abnormally rapid decay of the short-term auditory representations (Helenius et al., 2009; Helenius et al., 2014). In 9–11-year-old children with developmental language disorder (DLD), who display more severe phonological problems than dyslexics, these repetition effects were missing in the left hemisphere but intact in the right hemisphere (Helenius et al., 2014). In 6–9-year-old children with dyslexia, adaptation to familiar spoken words was seen in bilateral temporal regions, was abnormally weak for the dyslexia risk group, and was related to the children's preliterate skills (Perrachione et al., 2016). In a recent study, effects of online adaptation to a single phonological sequence were more salient in 9–12-year-old controls than in dyslexics (Kimppa et al., 2018). This evidence implies that dyslexia represents an impairment in perceptual learning of recurring phonological stimuli; most notably, this impairment is then reflected in the learning of the robust categorical speech sound representations necessary for sound-to-symbol connections during reading acquisition (Bradley and Bryant, 1983).

The current study investigates phonological learning in children who were identified, behaviorally and through their familial background, to have a risk for dyslexia at the early stages of starting to learn to read. We focus on children who have difficulties in learning letter-sound correspondences and acquiring basic reading skills in the first grade. We use an incidental phonological learning task that is expected to be especially taxing for the phonological processing system and reveal the underlying differences in cortical processing between affected and non-affected individuals, also with respect to the roles of the two hemispheres.

2. Materials and methods

2.1. Participants

23 children with high dyslexia risk and 12 normally reading 7-to-8-year-old children from the greater Helsinki area participated in the study at the end of their 1st school year (age ranged from 7y 4 m to 8y 4 m at the time of MEG measurements in both groups). In addition, 16 more individuals (7 dyslexia risk children and 9 control group child) participated in the study, but they were discarded after pretesting / MEG measurements due to too low / high performance on nonverbal intelligence measures or movement artefacts / technical problems in the measurement. The dyslexia risk children were identified among first-graders attending normal school curriculum, who were training to learn letter-sound-correspondences in a version of the GraphoLearn digital game (Lyytinen et al., 2009) and whose teachers reported that they had problems in learning to read despite the game-based and other support forms offered at schools (for a more detailed description of the identification process, see; Ronimus et al., 2020). The parents of these children were contacted to invite the children to participate in further testing and intervention. All but 2 of the children in the dyslexia risk group had a parent-reported familial risk for dyslexia, i.e. a family member (parent, sibling, grandparent or cousin) had been diagnosed with dyslexia. The children in the control group were typically reading children selected from the same classrooms as the dyslexia risk children.

Only monolingual, right-handed children were accepted as participants. Handedness was confirmed with an adapted version of the Edinburgh Handedness Inventory (Oldfield, 1971). Exclusion criteria were general learning disorders, developmental language disorder, severe oral motor problems as well as neurological disorders and hearing problems. Two of the control group children and 7 of the dyslexia risk children had delays in production of some individual phonemes (e.g. /r/). Participants were screened for compatibility for neuroimaging (no metal in the body, no fear of enclosed spaces).

2.2. Cognitive and reading tests

Participants in both groups were screened with pre-tests that measured literacy, intelligence, and phonological skills. Intelligence was assessed with Wechsler Intelligence Scale for Children IV (WISC-IV; Wechsler, 2003) subtests block design, vocabulary and digit span. To be included in the study, all children had to reach the criterion of not having scores below one standard deviation (SD) in the WISC block design subtest, a measure of nonverbal intelligence (i.e., minimum standard score was 7). In addition, high performers in block design (standard

score < 14) were excluded. Measures of verbal intelligence (vocabulary) and working memory (digit span) were not used as inclusion criteria, as the children with reading difficulties were presumed to perform on the lower end of average or worse than average on these measures.

Literacy was assessed with standardized Finnish tests. Letter naming was assessed with a test from ARMI test battery (Lerkkanen et al., 2006). LukiLasse (Häyrinen et al., 2013) was used to test the accuracy and speed of reading single words aloud within the time limit of 2 min. Accuracy and speed of reading was further assessed with a story text that has been used previously in the Jyväskylä Longitudinal Study of Dyslexia (Puolakanaho et al., 2008), and pseudoword list reading (Lerkkanen et al., 2018). Phonological skills were assessed with naming and deletion of the first phoneme of a word and first syllable removal (Poskiparta et al., 1994). Phonological short-term memory was assessed with pseudoword repetition (Repetition of Nonsense Words -task of the Finnish version of the NEPSY; Korkman, 1998) and naming speed of objects and letters with rapid naming tests (Ahonen et al., 2003). In addition, the participants performed two experimental computer-based tests developed in the ReadAll research project (Hautala et al., 2020). These included an incidental associative learning test, where participants learnt to connect two-letter syllables (ma, ta, ha, ra, sa) to meaningless symbols. There were five syllable-symbol pairs to learn in 25 trials. In the beginning of the task, the child was told once which syllable corresponded to which symbol. In each trial, the child first heard a syllable, then selected the symbol corresponding to the syllable from the five alternatives shown on the screen. Feedback followed immediately after each trial. The other test measured the auditory threshold for perceiving small duration differences in double consonant (sounds perceived as /ata/ or /atta/). Participants indicated by button press which of the two sounds was longer.

The control group participants performed in the average range (> −1 SD) or better in all the reading tests, and had not been suspected by their teachers or parents to display problems of language or literacy development. The children included in the dyslexia risk group fulfilled the inclusion criteria of having clearly below average performance (< −2 SD, 26 words or less read in two minutes) in the LukiLasse 2 standardized word list reading test in the early spring of the first school year (Häyrinen et al., 2013).

As expected, the children who had difficulties in reading despite support offered at schools clearly differed from their schoolmates in terms of performance in most cognitive tests, although their nonverbal cognitive performance was in the average range (Table 1). The children were initially selected based on an average performance in block design test, but the groups still differed somewhat in this measure, as the dyslexia risk group performed in the low end of the normal range. Deficits in visuospatial skills in dyslexia have been reported in previous studies (Helenius et al., 2014). In the vocabulary subtest, 6/23 children in the dyslexia risk group performed clearly below average (5 or less in the standard score), whereas no children in the control group performed below normal range. The dyslexia risk children had impaired verbal working memory, indicated by digit span and pseudoword repetition performance. They also showed slower naming speed, and none of the dyslexics could yet name all the letters of the alphabet. A higher threshold for discrimination of small duration differences in speech sounds was also observed in the dyslexia risk group. However, the groups performed similarly in an associative learning task, thus the dyslexia risk group showed no clear deficit in associative learning.

At the end of the 2nd grade, one year after the MEG measurement, the reading problems of the dyslexia risk children were evaluated again based on a compound measure of reading tests (text reading, word reading and pseudoword reading). This was done using a rating scale, where severe is < −2 SD, moderate is < −1 SD, mild is < 25th percentile, i.e. <−0.675 SD, and no dyslexia is >25th percentile (Galuschka et al., 2014). Based on this evaluation, remaining reading problems ranged from non-noticeable to severe (Z-score ranging from −2.6 to 0.46, i.e. reading performance ranged from 0.5th to 68th percentile); 6 of the 23 children in the dyslexia risk group did not classify as dyslexics at this stage.

2.3. Stimuli and procedure

The stimuli in the MEG experiment were 320 native (Finnish) pseudowords from our previous studies of phonological learning (Nora et al., 2012, 2017, 2015). They were four-syllable words, or four-syllable compounds composed of pairs of two-syllable words, no longer in use, that were phototactically legal in the Finnish language, e.g. /täkkähöke/, /napponurtus/, /sosteriska/ (Lönnrot, 1874–1880). The words were mostly nouns, and all words were in basic form. The duration of the words varied from 1000 to 1300 ms (mean 1200 ms). All stimuli began with a consonant. The words were recorded by a female native Finnish speech pathology student in 24-bit wav format using a sampling rate of 48 kHz. To minimize background noise, the word stimuli were low-passed, on average, at 6 kHz (gradual from 4 kHz to 14 kHz). A 10-ms ramp was added to the beginning and end of each word.

The participant's task was to listen to each word, presented through a panel speaker with 75 dB gain, and to repeat it as accurately as possible. Participants were not instructed to memorize or learn the words. After each stimulus presentation and 300 ms of silence, a 50-ms beep prompted the participant to overtly reproduce the word. Participants had a 2-s interval for each repetition (Fig. 1a). The responses were recorded using a digital recorder and later evaluated for accuracy. On Day 1, half of the stimuli (80) were presented four times ("Recurring") and half (80) only once ("New"). The stimuli were presented in four blocks, each containing one presentation of the Recurring items (80), intermixed with 1/4 (20) of the New items of Day 1 (Fig. 1b). On the consecutive Day 2, the same Recurring stimuli (80) were presented once more (the fifth time), randomly mixed with 160 completely New word forms and one presentation of the stimuli that had been presented as New stimuli during Day 1 (80; this second repetition of Day 1 New stimuli on Day 2 was not included in the analysis). During each session, participants were given 4 short breaks inside the scanner and one longer break outside the shielded room. To control for the variation in difficulty between individual words, the words for each stimulus category (New, Recurring) were counterbalanced between participants. The distribution of initial consonants was similar in the different stimulus categories.

On Day 2, the pseudoword repetition task was followed by a behavioral recognition task. Participants heard a randomly selected subset of the words from Day 1 (20 of which were Recurring and 20 words that had been presented only once during Day 1) mixed with 40 words they had not heard before. The stimulus words were presented through headphones, and the participants' task was to indicate by a button press for each word if it had been presented before.

2.4. MEG recording

Magnetic fields associated with neural current flow were recorded in a magnetically shielded room with a 306-channel whole-head neuromagnetometer (Elekta Oy, Helsinki) in the Aalto NeuroImaging MEG Core. The sensor array is composed of 102 triple sensor elements, each with one magnetometer and two planar gradiometers. Planar gradiometers yield maximum signal for a cortical current directly beneath them, whereas magnetometers are sensitive to far away sources as well. The MEG signals were band-pass filtered between 0.03 and 200 Hz and sampled at 600 Hz. Eye movements and blink artefacts were monitored by electro-oculogram (EOG) and motor artefacts related to mouth movements by electro-myogram (EMG), each measured with two electrodes that were placed diagonally around the eyes and the mouth, respectively. The position of the participant's head within the MEG helmet was defined using five head position indicator coils, attached to the participant's scalp. The locations of these coils were determined with

Table 1
Age and results of cognitive and reading tests in the dyslexia risk group and control group.

	Dyslexia risk children (n = 23)mean (SD)	**Control children** (n = 12)mean (SD)	**significance**(t-test)
Age (years) at time of MEG measurement	7.8 (0.3)	7.8 (0.3)	n.s.
Reading tests at 1st grade spring			
Letter knowledge[a]	21.9 (4.4)	28.9 (0.3)	p<0.01
Word list reading[b]	6.6 (6.1)	58.8 (20.2)	p<0.01
Text reading[c]	1.5 (3.1)	44.8 (25.0)	p<0.01
Cognitive tests			
WISC-IV: Block design[d]	9.5 (2.7)	11.4 (2.1)	p=0.013
WISC-IV: Vocabulary[d]	8.0 (3.4)	12.4 (2.7)	p<0.01
WISC-IV: Digit span[d]	7.0 (2.2)	11.0 (2.5)	p<0.01
Pseudoword repetition[e]	8.9 (2.6)	11.2 (2.2)	p=0.014
Initial phoneme naming[f]	7.7 (2.4)	10.0 (0)	p<0.01
Phoneme deletion[f]	0.6 (0.8)	9.5 (1.2)	p<0.01
Syllable deletion[f]	2.1 (2.0)	8.9 (1.0)	p<0.01
Rapid automatized naming, objects (RAN)[g]	70.8 (16.9)	56.8 (10.6)	p=0.01
Rapid automatized naming, letters (RAN)[g]	61.4 (18.0)	35.3 (7.2)	p<0.01
Auditory discrimination threshold[h]	85.1 (22.3)	37.4 (27.8)	p<0.01
Associative learning[i]	15.1 (4.4)	14.3 (4.8)	n.s.

[a] Number of correctly named letters out of 29.
[b] Number of correctly read words in a list in 2 min.
[c] Number of correctly read words in a narrative in 1 min.
[d] Normal scaled score in WISC-IV.
[e] Number correct out of 16.
[f] Naming / removing phonemes / syllables within words, max score.
[g] Time (s) for naming objects/letters in a matrix.
[h] Detection threshold for consonant duplication in pseudowords.
[i] Score (max 25, chance level 5/25) for learning symbol-sound-correspondences.

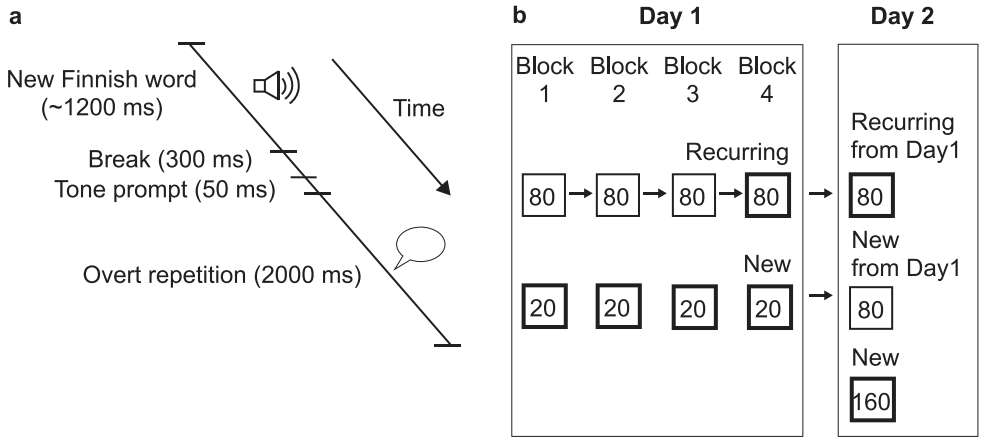

Fig. 1. Experimental design. **a) Stimulus presentation, one trial.** Subjects listened to and reproduced new, four-syllable native words. No explicit instructions to memorize the words were given. In each trial, after the stimulus presentation and 300 ms of silence, a 50-ms beep prompted the participant to overtly repeat the item. **b) Stimulus types.** On Day 1, subjects heard 80 Recurring items (4 times) and 80 New items (20 in each of the four blocks). On the consecutive Day 2, the same Recurring stimuli (80) were presented once, randomly mixed with 160 completely New word forms (a subset of 80 was used in the analysis) and one presentation of the stimuli (80) that had been presented as new stimuli during Day 1 (80; their single presentation on Day 2 was not used in the analysis).

respect to three anatomical landmarks (nasion and two preauricular reference points) with a 3D digitizer, and with respect to the sensor array by briefly feeding current to the coils. Head movements were monitored continuously (Uutela et al., 2001).

2.5. Anatomical magnetic resonance imaging

Anatomical magnetic resonance images (MRIs) were obtained at Aalto NeuroImaging with a 3T MRI scanner (Magnetom Skyra, Siemens) for all except two children who declined; for these children, an anatomical head model was used that was an average model of multiple participants (fsaverage surface template, distributed in the Freesurfer software). The scan included a 3-plane localizer and a T1-weighted anatomical image. To enable attribution of MEG activation patterns to anatomical loci, the MEG data were co-registered in the same coordinate system with the individual MR images.

2.6. Behavioral analysis

The overt repetitions produced by the participants were rated in a scrambled order by a native Finnish speaker, unaware of the different participant groups and experimental conditions. The responses included repetitions from the 1st (80) and 4th block (80) of Day 1, and a randomly selected subset (~80) of stimuli from the middle of the session on Day 2. Rating was done on word and syllable level, but the results were similar, thus only word level results are reported. One point per word/syllable was given if all the phonemes in the word/syllable could be perceived, i.e. if none were omitted, replaced or transposed; otherwise zero points. Repetition data of three participants in the dyslexia risk group was not available from all blocks because of technical failure, and therefore those participants were removed from the analysis.

Recognition performance was evaluated as hits to previously heard (Recurring) words, false alarms to New words (presented for the first time in the recognition task), and a discriminability measure *d'* between these two, calculated individually for each participant.

2.7. MEG data analysis

The MEG signal analysis focused on the perception phase before overt production. Spatio-temporal signal space separation (tSSS; Taulu and Simola, 2006), and movement compensation algorithms

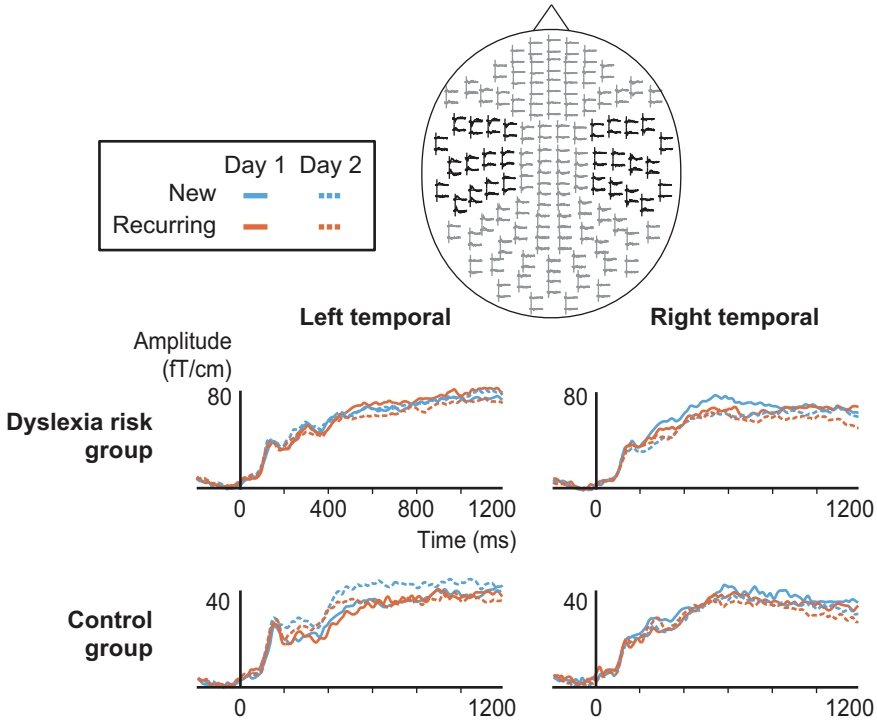

Fig. 2. Sensor level responses (areal mean signals) over the temporal cortices. Sensor-level responses, averaged across participants and stimulus conditions, and across 14 sensors over the left / right temporal cortices (shown on top). Dyslexia risk group is plotted above, control group below.

(Uutela et al., 2001) were applied offline to the raw data using MaxFilter™ software (Elekta Neuromag) to remove the effects of external interference and to compensate for head movements during the measurement. To obtain an estimate of the artefact signals caused by blinks, the MEG signals were averaged with respect to salient patterns in the EOG signal. Principal component analysis (PCA) was performed on this average, and the magnetic field component produced by the eye movements was removed from the raw data (Uusitalo and Ilmoniemi, 1997). Similar artefact removal was done for cardiac artefacts, for which averaging was done based on thresholding the MEG signal in channels containing the most salient cardiac response.

Only gradiometer signals were used for further analysis. The signals were averaged from 200 ms before to 1200 ms after the stimulus onset. Trials contaminated by large artefacts (signal strength exceeding 3000 fT/cm) were rejected. On average 77 ± 6 (mean ± SD) artefact-free epochs for the dyslexia risk children and 79 ± 5 for the control children were gathered for each of the categories (maximum = 80). The averaged MEG responses were baseline corrected to the 200-ms interval immediately preceding the stimulus onset and low-pass filtered at 40 Hz.

An overview of the responses in the sensors above the auditory cortices was obtained by calculating areal mean signals over 10–20 sensor pairs in 10 areas of the cortex (incl. average of 14 sensor pairs above the left/right auditory cortex). These signals were visually inspected to discover the main components and their timings in the event-related responses (Fig. 2). The cortical sources were then estimated by means of Equivalent Current Dipole modeling (ECD; Hämäläinen et al., 1993), similarly to previous studies using this same paradigm (Nora et al., 2012, 2017, 2015). ECD analysis can distinguish between multiple spatially close neural sources with different orientations of current flow. Only ECDs explaining more than 80% of the local field variance were accepted in the model. This criterion led to inclusion of 2–3 ECD components per participant. For any one participant, the ECDs represented well the data of all recording sessions. The time courses of the identified spatiotemporal components (source waveforms) were estimated by fixing their location and orientation parameters while allowing their strengths to vary to best account for the signals detected by all MEG sensors over the entire analysis interval. To locate the ECD components anatomically, the center of activation of each component was displayed on the individual MR images of each participant. For group-level visualization, the locations were transformed to the surface template of one participant.

2.8. Statistical analysis

Repetition accuracy was evaluated with a 2 × 2 × 3 ANOVA, with the between-subjects factor of participant group (at-risk vs. control) and within-participants factors of recurrence (New vs. Recurring) and time (1st block of Day 1, 4th block of Day 1, Day 2). Recognition performance (discriminability measure *d'*) for the Recurring words on Day 2 was compared between the at-risk group and the control group with a *t*-test.

The MEG source waveforms were investigated in three distinctive time windows (100–200 ms, 200–400 ms and 400–1200 ms), identified in the Areal Mean Signals to capture distinguishable components in the responses. The signal strength of the highest peak at 100–200 ms in the left and right temporal source waveforms was identified individually for each participant and condition. At 200–400 ms and 400–1200 ms time windows, the average signal strength was calculated. These values were subjected to a 2 × 2 × 2 ANOVA with the between-subject factor of participant group (at-risk vs. control) and within-subject factors of recurrence (New vs. Recurring words) and time (Day1 vs. Day 2).

For evaluating the relationship between behavioral and cortical effects, Spearman's pairwise correlation was computed between the cortical learning effects and the improvement in repetition accuracy between New and Recurring items as well as recognition accuracy. For this analysis, the dyslexia risk and control groups were combined into one group. The groups were combined as each group alone was too small on its own to reliably observe correlations, and the behavioral (especially recognition accuracy) as well as neural measures showed more variability across groups than within each group alone. The neural measure was signal change (percentage) between cortical response to the New (Nonrecurring) items and the Recurring items during Day 1, normalized to each participant's average activation level. The improvement in behavioral repetition accuracy was estimated as the difference in repetition accuracy between the New (Nonrecurring) items and the Recurring items

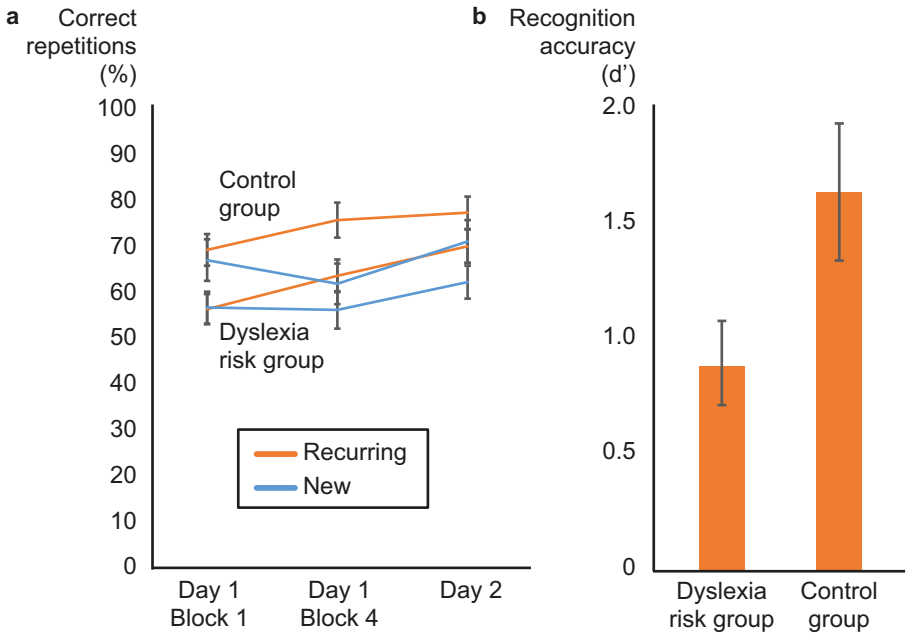

Fig. 3. Behavioral learning effects. **a)** Percentage of correctly repeated Recurring and New words (mean ± SEM) for the at-risk and control groups during the 1st and 4th block of Day 1 (both blocks containing 80 Recurring and 20 New words) and Day 2 (in a randomly selected subset of items containing approximately 20Recurring and 40 New word forms). **b)** Recognition accuracy (d') for Recurring words (mean ± SEM) for the at-risk and control groups.

during Day 1, normalized to each participant's average repetition performance level. We also investigated the correlation of the cortical and behavioral learning effects to reading measures at 1st and 2nd grade spring.

3. Results

3.1. Repetition and recognition accuracy

Repetition accuracy improved over the course of the two sessions (effect of time: $F(2,30) = 16.3$, $p < 0.001$), and more so for the recurring words (effect of Recurrence: $F(1,60) = 18.9$, $p < 0.001$; interaction Time x Recurrence: $F(2,60) = 6.5$, $p = 0.003$; Fig. 3a). There were no significant group differences in overall repetition accuracy or improvement in repetition accuracy for the recurring word forms (effect of group: $F(1,30) = 2.7$, $p = 0.11$; interaction Recurrence x Time x Participant group: $F(2,60) = 1.08$, $p = 0.35$). However, the dyslexia risk group showed significantly poorer recognition of the recurring words on Day 2 compared to the control group ($t(30) = 2.05$, $p = 0.049$; Fig. 3b).

3.2. Cortical learning effects

The responses at 100–200 ms did not show any significant effects. The subsequent responses in the bilateral temporal cortices showed an effect of experimental day manifested as reduced response amplitudes at 200–400 ms (left $F(1, 31) = 12.2$, $p = 0.001$, right $F(1, 31) = 4.4$, $p = 0.043$; see Figs. 2 and 4), similarly to our previous work (Nora et al., 2012, 2017, 2015).

As in those previous studies that used the same paradigm, effects related to learning the recurring word forms were primarily restricted to the sustained responses (400–1200 ms) in temporal and frontal regions (Fig. 4). Cortical sources of these sustained responses were found bilaterally in the superior temporal areas in all the children. For most children (32/35 on the left and 34/35 on the right), these temporal sources had a dorsal-to-ventral oriented current flow; only these responses were included in the further analysis to ensure maximally similar functionality of the neural response over subjects (Nora et al., 2012, 2017, 2015).

The left temporal sources showed a significant reduction of activation for the Recurring stimuli at 400–1200 ms ($F(1, 31) = 17.8$, $p < 0.001$), but mainly for the control group (interaction Recurrence x Participant group: $F(1,31) = 6.5$, $p = 0.016$; paired comparisons New vs. Recurring words: controls $t(9) = 3.9$, $p = 0.004$; dyslexia risk participants $t(22) = 1.5$, $p = 0.14$; Bonferroni corrected alpha 0.0042, calculated for 3 time windows x 2 ROIs x 2 paired comparisons; Fig. 4).

In the right temporal sources, there was a reduction of activation for the recurring words at 400–1200 ms over the two participant groups ($F(1, 33) = 7.6$, $p = 0.009$), but no interaction (Recurrence x Participant group: $F(1,33) = 0.24$, $p = 0.63$; paired comparisons New vs. Recurring words: controls $t(12) = 2.3$, $p = 0.045$; dyslexia risk participants $t(22) = 1.8$, $p = 0.079$; Bonferroni corrected alpha 0.0042, calculated for 3 time windows x 2 ROIs x 2 paired comparisons).

An additional left frontal source was found in 9/35 children (6 dyslexia risk participants and 3 controls). The left frontal sources seemed to show increased responses for recurring word forms, similarly to our previous studies (Nora et al., 2012, 2017, 2015). However, with only a few participants showing this frontal activation in the present study, the main effect of recurrence at 400–1200 ms approached significance ($F(1,8) = 5.31$, $p = 0.050$), with no significant differences between groups.

3.3. Correlations between behavioral and cortical learning effects and reading skills

The left temporal learning effect correlated with improvement in repetition accuracy over the course of the Day 1 session: the more the repetition improved for recurring compared to new items, the more the left temporal activation was reduced (Spearman's rho = 0.39, $p = 0.038$; Fig. 5). A similar correlation was not observed on Day 2. The right temporal learning effects did not show significant correlations to behavioral learning effects.

There were no significant correlations of the cortical learning effects to reading or phonological skills at 1st or 2nd grade. However, the recognition performance for the newly-learned pseudowords correlated with reading skills at 1st grade spring (word list reading: rho = 0.51, $p = 0.002$; pseudoword list reading: rho = 0.51, $p = 0.005$; text reading: rho = 0.43, $p = 0.010$).

4. Discussion

Dyslexia is a specific learning disorder, impairing phonological processing and learning, and, consequently, reading acquisition. To our

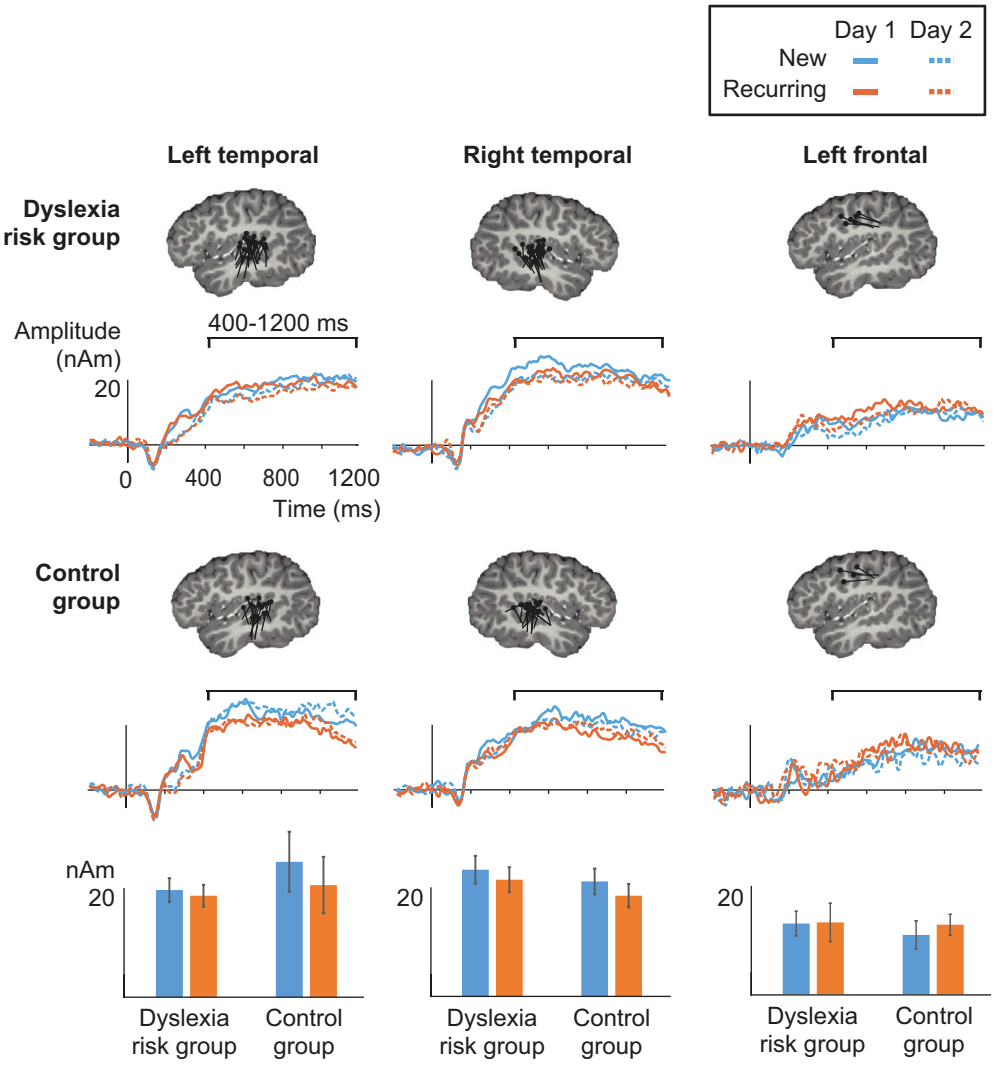

Fig. 4. Cortical learning effects. Time courses of activation in sources modeling left temporal, right temporal and left frontal responses. Equivalent Current Dipole (ECD) clusters are displayed on a sagittal plane of a standard brain. Each dot represents the center of an active cortical patch in one subject, and the attached line denotes the mean direction of current flow in that area. Grand average source waveforms (activation strength in nanoamperemeters, nAm) are displayed for each ECD cluster, separately for the dyslexia risk group (above) and the control group (below). Summaries of significant effects in the marked time window of interest (400–1200 ms) are shown as bar graphs (activation strength for New vs. Recurring words, averaged over Day 1 and Day 2). Error bars indicate standard error of mean (SEM).

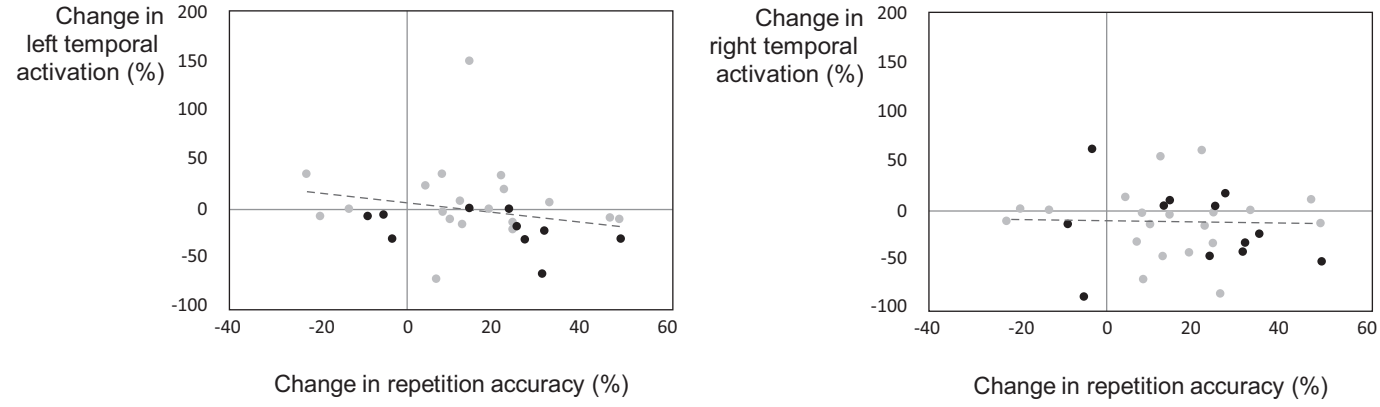

Fig. 5. Correlation of cortical and behavioral learning effects. Scatterplots of change in left and right temporal cortical activation as a function of change in repetition accuracy over the course of the Day 1 learning session. The y-axis shows the relative (percent) change in the temporal activation at 400–1200 ms, and the x-axis shows the relative (percent) difference in repetition accuracy (4th repetition of Recurring items minus single repetition of Nonrecurring items, normalized to the average for the participant). Gray dots represent at-risk participants and black dots represent control group participants. A significant correlation of repetition improvement was only observed to the change in left temporal activation.

knowledge, no neuroimaging studies have previously investigated the neural basis of deficits in novel word form acquisition in dyslexia. Here, we investigated the neural correlates of phonological learning in 7-to-8-year-old children with high dyslexia risk, and compared them with a control group of beginning readers. MEG responses were measured in the spring of the first school year, thus before extensive literacy training, while the children perceived and overtly repeated novel recurring word forms (pseudowords) of the native language. Dyslexia risk children showed an improvement in repetition accuracy for the recurring word forms, comparable to that in the control group, but poorer recognition of the recurring word forms. Effects of phonological word form familiarity were seen in sustained responses (at 400–1200 ms) originating in temporal areas, as reduced neural activation for recurring word forms compared to new items, in both participant groups. In the left temporal cortex, the control group children showed a stronger effect, and in children with high dyslexia risk consistent effects of word form recurrence were mainly observed in the right temporal cortex.

Previous behavioral studies indicate that dyslexics might be slower than controls in learning new phonological word forms (Alt et al., 2017; Elbro and Jensen, 2005; Litt and Nation, 2014; Mayringer and Wimmer, 2000; Messbauer and de Jong, 2003; Vellutino et al., 1995). As vocabulary acquisition depends on phonological storage (Gathercole, 2006), phonological storage deficits associated with dyslexia have been suggested to underlie this poorer learning of novel word forms, as well as pseudoword repetition. In the present study, phonological working memory deficits in the dyslexia risk group were evident in digit span test as well as in a separate behavioral test of repeating variable pseudowords (with up to six syllables). However, during the main experiment the dyslexia risk children showed initially poorer performance but similar improvement in repetition of the recurring pseudowords as the control group, both on whole-word and syllable level. The current results indicate that dyslexia risk children were able to construct phonological memory representations of the new phonological word forms similarly as control children after multiple occurrences of the items. The results do not agree with the view that the underlying cause in dyslexia would lie mainly in impaired implicit learning of phonological representations. Reduced implicit learning has previously been observed in dyslexics for learning of auditory categories (Gabay and Holt, 2015), statistical learning of linguistic regularities (Gabay et al., 2015; Pavildou et al., 2010), and in perceptual-motor tasks (Lum et al., 2013; Menghini et al., 2006; Stoodley et al., 2008). Based on the current results, the hypothesized implicit memory deficit (i.e. less improvement in performance following repetition of the stimulus) in dyslexia does not seem to apply to learning of novel word forms and learning of the motor (pseudoword repetition) task, as similar gains in incidental perceptual-motor learning (improved overt repetition) were observed here for dyslexia risk and control groups.

In contrast to the similar repetition improvement in both groups during the two sessions, group differences emerged in explicit recognition of the recurring word forms on Day 2. Explicit memory encoding and/or retrieval processes (i.e. performance in a task where participants are asked to recognize whether the stimulus has been encountered before) seems to be impaired in the dyslexia risk children compared to controls. The surprise recognition task was administered at the end of the second experimental day, after a consolidation phase of one night's sleep. The results suggest differences in long-term encoding of detailed phonological representations for novel word forms in the dyslexia risk group compared to controls: The word forms might be encoded in long-term memory as less specified in phonological detail and thus less distinguishable from other word forms in a recognition task. This agrees with the hypotheses of generally underspecified lexical phonological representations in dyslexia (e.g.; Snowling, 2000). Typically developing children may form more detailed phonological representations in the long-term lexicon over only two days of exposure and, because of their larger vocabulary knowledge, they may also be able to encode richer representations of the unfamiliar stimuli that include phonological and semantic associations to existing words. A similar explanation has been offered for differences between adults and children in phonological learning: In a previous study with a similar paradigm (Service et al., 2014) recognition and repetition accuracy, used as indices of explicit and implicit memory, showed different patterns of results. Adults and 8-year-old-children differed in recognition accuracy, with better performance in adults, but showed similar improvement in repetition. In our previous study on typically developing 6-to-8-year-old children and adults, the two groups displayed similar repetition improvement (Nora et al., 2012, 2017).

Explicit recognition of the newly learned word forms correlated with reading skills at the 1st grade, suggesting that impairments in explicit memory for novel phonological sequences and reading deficits in dyslexia risk children reflect similar underlying problems. We propose that the underlying problem in both might be the ability to represent spoken word forms, particularly novel word forms, with enough phonological detail to allow their separation from near neighbours and, consequently, to successfully map these phonological sequences to written form. These deficits in lexical learning of novel spoken and written words seem to persist in adults with dyslexia and correlate with reading skills, and they are not fully explained by problems in sublexical phonological skills (Di Betta and Romani, 2006). Indeed, also based on the current results, one bottleneck in dyslexia seems to lie at the lexical level, caused by impairment in forming neural representations for new word forms. Similar conclusions have been recently reached with foreign-language word stimuli and a different paradigm (Ylinen et al., 2019).

On the neural level, sustained responses were observed for meaningless novel word forms, resembling the so-called N400m response identified in adult participants, which reflects online search and rejection of lexical word form candidates (Salmelin, 2007). For pseudowords this activation of the left superior temporal cortex continues until the very end of the word presentation, as a matching word cannot be found in the lexicon and neighbouring words continue to stay activated (Meade et al., 2019). Similarly to the current study, suppression of the sustained responses has been observed for recurring familiar and novel spoken word forms, both in repetition suppression and incidental word form learning paradigms (Helenius et al., 2009, 2014; Nora et al., 2012, 2017, 2015). Our previous studies in adults and children show that the suppression of these temporal sustained responses reflects the online construction of novel phonological word-form-level representation (Nora et al., 2012, 2017, 2015). In previous studies, weaker repetition suppression effects for new and familiar words in bilateral temporal regions have been shown in 9–11-year-old dyslexic and language impaired children and adults compared to controls (Helenius et al., 2009, 2014). Similarly, in the current study the reduction of activation for recurring new word forms was observed both in control participants and dyslexia risk children at 400–1200 ms after word onset, but this effect was stronger for the control group, especially in the left hemisphere.

The temporal effect was observed across both experimental days, also after a consolidation phase. Together, these and the results of previous studies (Nora et al., 2012) indicate, that in typically developing children of this age and adults the left temporal suppression of activation to recurring new word forms reflects the establishment of long-term phonological word form representations. In the current study, weaker (left) temporal suppression in the dyslexia risk group was coupled with weaker explicit memory performance observed in the recognition task (although no direct correlation was observed between the two measures). The current results may point to a possible deficit in processing of word forms in the temporal areas as the cortical basis of impaired phonological representations and impaired language learning in dyslexia.

A right temporal reduction at 400–1200 ms for recurring word forms was observed in both groups. This right-hemispheric effect replicates our previous study with typically developing children and the same paradigm (Nora et al., 2017). In that previous study, however, the

typically developing children were of a somewhat younger age group (on average 7y 2 m; in the current study on average 7y 10 m) and they did not display systematic left temporal learning effects. Also, in that study, the improvement in repetition accuracy correlated with the right temporal suppression; a similar correlation was here observed for the left temporal effect. Here, the dyslexia risk participants displayed a consistent right temporal suppression of activation during word form learning, thus resembling the group of younger children from our previous study (Nora et al., 2017), and seemingly manifesting an "immature" hemispheric balance of phonological learning effects. Indeed, the younger group of children in our previous study also showed worse recognition performance for the word forms compared to adults (Nora et al., 2017), comparable with our dyslexia risk group at a bit older age.

During the early school years, auditory responses in general show large maturational changes that differently affect the two hemispheres (Parviainen et al., 2011, 2019), and the hemispheric balance of phonological processing may also undergo changes. Previous studies suggest that the right hemisphere develops and matures earlier than the left hemisphere (Chi et al., 1977; Dubois et al., 2008). In typically developing children, the auditory responses gain adult-like features sooner in the right than in the left hemisphere (Kotecha et al., 2009; Paetau et al., 1995; Parviainen et al., 2011). Younger children show bilateral activation and phonological learning effects, but there is a shift to left hemispheric dominance as age increases (McNealy et al., 2011; Mills et al., 2005; Szaflarski et al., 2006). A greater right-hemispheric involvement early in development has also been suggested for the reading network, followed by an increasing specialization of the left hemisphere for reading after school entry (Shaywitz et al., 2002; Turkeltaub et al., 2003). Shift to left-hemispheric bias for phonological processing may emerge through development of specific learning mechanisms that predominantly rely on the left hemisphere, i.e. learning based on abstract, categorical phonemic categories (Minagawa-Kawai et al., 2011).

Based on the present findings, we may hypothesize that in dyslexic children the right hemisphere has the ability to respond fairly normally to novel word forms in the early school years, but the left hemisphere gains this ability later than for typically developing children. In our previous study, the right-lateralized learning effects in younger children, compared to left-lateralized learning effects in adults, were taken to indicate less segmental, more holistic representations being formed for the novel word forms (Nora et al., 2017). It has been suggested that right-hemispheric effects in speech processing could be related to reliance on suprasegmental information (prosody, rhythm, stress patterns; features that extend over syllables, words, or phrases), whereas left-hemispheric effects could reflect detailed parsing of words to sequences of phonemes (Abrams et al., 2008; Poeppel, 2003; Vanvooren et al., 2014). Thus, our results might indicate normal (right-hemispheric) suprasegmental processing but impaired (left-hemispheric) phoneme-level processing for novel phonological forms in dyslexia. Abnormal left-hemispheric processing has also been observed in developmental language disorder (de Guibert et al., 2011; Helenius et al., 2009, 2014; Whitehouse and Bishop, 2008), suggesting that it might reflect a more general disruption of phonological processing and detailed encoding of novel phonological representations, and would not be specific to dyslexia.

The current results corroborate previous functional neuroimaging findings showing that dyslexic children and adults display hypoactivation in left hemispheric and overactivation in right-hemispheric temporal areas during lexical decision and phonological working memory tasks (Waldie et al., 2013; Xu et al., 2015). Previous findings also show overall reduced left temporal responses to syllables or sine-wave sounds in dyslexia, indicating that auditory/linguistic processing is impaired in the left hemisphere, possibly contributing to subsequent problems in reading acquisition (Heim and Keil, 2004; Johnson et al., 2013, 2011). An alternative explanation that has been suggested to account for this abnormal hemispheric balance is that it is a consequence of poor phonological and reading skill attainment, rather than its cause. Children in our study had received only about 7–8 months of systematic training in reading skills at the time of the MEG measurement (1st grade spring), but differences in reading scores between the dyslexia risk group and the control group were notable, as the dyslexia risk group consisted of the very poorest learners of letter-to-phoneme correspondences: The dyslexia risk children read 0–12 words in two minutes, whereas the typically reading children already read 19–81 words. Thus, it is possible that the better or poorer attainment of basic reading skills during 1st grade of elementary school may already have had an effect on left-hemispheric phonological processing, and show as group differences between the reading-impaired and typically learning children. Literacy training induces changes in left temporal and frontal speech processing (Dehaene et al., 2010; Monzalvo and Dehaene-Lambertz, 2013), particularly in the detail of lexical phonological representations (Schild et al., 2011). Differences between dyslexic and typically reading children in the cortical implementation of phonological processing, especially in the left-hemispheric areas, may at least partly be a consequence of reading attainment (Bishop, 2013). However, in this study, reading scores were not directly related to the strength of the cortical effects, indicating that the relationship might be more complex.

Furthermore, the reading scores of the dyslexia risk group were clearly below average (−2sd or more) on the 1st grade, but by the 2nd grade spring there was much more variability (from average reading skills to severe reading problems). Thus, the at-risk group consisted of children who showed a substantial risk to reading problems, and were slower in reading acquisition, but not all could be classified as dyslexic later on. Recent findings show that deficits in auditory or phonological processing, reflected also in neurophysiological differences, do not directly predict later dyslexia diagnosis (Vandermosten et al., 2020). These observations agree with the view that multiple deficits underlie dyslexia, including factors that strongly mediate the genetic and environmental influences, and thus phonological processing deficits alone are not sufficient to predict later reading problems (Pennington, 2006). Similarly, the functional brain imaging effects observed in this study and the phonological processing deficiency they are reflecting may well be a predecessor and a predisposing factor for reading problems (rather than their consequence), but do not invariably lead to dyslexia later on.

In the current study, right-hemispheric effects were equally found in the control group. However, greater right frontal activation during reading has predicted better reading gains in dyslexics (Hoeft et al., 2011; Shaywitz et al., 2002), and thus, at least in some dyslexics the more efficient use of a right hemispheric pathway for phonological processing and reading may compensate for deficiencies in the typical left-hemispheric pathways. Previous longitudinal studies question these alternative interpretations, as problems in phonological processing during infancy, reflected in left temporal evoked responses to speech sounds, predict later problems in reading acquisition (Leppänen et al., 2010; Lyytinen et al., 2005). Recent longitudinal work has shown abnormal gyrification and functional connectivity of the left primary auditory cortex in dyslexic children compared to controls both before and after literacy training, indicating that structural differences in the left-hemispheric speech sound processing system precede reading problems (Kuhl et al., 2020).

To summarize, the current study is the first to relate the impaired cortical responsiveness in dyslexic children to the learning of word-form level phonological forms. Deficient learning of novel word forms in children with familial risk for dyslexia was reflected as poorer performance in the recognition task, as well as abnormally weak or inconsistent suppression of left temporal cortical activation for recurring phonological word forms. More longitudinal studies on the cortical correlates of phonological processing and learning are needed to determine whether the observed lack of cortical responsiveness in at-risk children reflects a disruption of processing, a maturational lag, or possibly a consequence of poorer reading acquisition.

Declaration of Competing Interest

The authors declare no competing financial interests. The rights of the commercial version of the learning game used in this work belong to GraphoGame, which is an independent company. HL and the Niilo Mäki Institute are loosely involved in advertising the non-commercial versions of the game, but are not financially involved in the company.

Data and code availability statement

Ethical restrictions imposed by the hospital's research ethics committee prevent the authors from making brain imaging data publicly available without restrictions, as this data cannot be fully anonymized. However, the relevant summary tables of the data are available from the authors upon reasonable request and with permission of the hospital's research ethics committee, for researchers aiming to reproduce the results. The code for conducting the analysis is available from the authors upon request.

Credit authorship contribution statement

A. Nora: Conceptualization, Methodology, Software, Investigation, Formal analysis, Visualization, Writing - original draft, Writing - review & editing, Project administration. **H. Renvall:** Conceptualization, Investigation, Formal analysis, Writing - review & editing. **M. Ronimus:** Investigation, Formal analysis, Writing - review & editing. **J. Kere:** Conceptualization, Resources, Writing - review & editing, Supervision, Funding acquisition. **H. Lyytinen:** Conceptualization, Resources, Writing - review & editing, Supervision, Funding acquisition. **R. Salmelin:** Conceptualization, Methodology, Resources, Writing - review & editing, Supervision, Funding acquisition.

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Ethics statement

This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. It was reviewed by the ethical board of the Central Finland Health Care District. Written informed consent was obtained from the guardians of the child participants. In addition, oral consent was obtained from the participating children.

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