Cerebral Cortex September 2014;24:2489–2501
doi:10.1093/cercor/bht104
Advance Access publication April 18, 2013

Altered Neuronal Response During Rapid Auditory Processing and Its Relation to Phonological Processing in Prereading Children at Familial Risk for Dyslexia

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Developmental dyslexia (DD) is a learning disability affecting 5–17% of children. Although researchers agree that DD is characterized by deficient phonological processing (PP), its cause is debated. It has been suggested that altered rapid auditory processing (RAP) may lead to deficient PP in DD and studies have shown deficient RAP in individuals with DD. Functional neuroimaging (fMRI) studies have implicated hypoactivations in left prefrontal brain regions during RAP in individuals with DD. When and how these neuronal alterations evolve remains unknown. In this article, we investigate functional networks during RAP in 28 children with ($n = 14$) and without ($n = 14$) a familial risk for DD before reading onset (mean: 5.6 years). Results reveal functional alterations in left-hemispheric prefrontal regions during RAP in prereading children at risk for DD, similar to findings in individuals with DD. Furthermore, activation during RAP in left prefrontal regions positively correlates with prereading measures of PP and with neuronal activation during PP in posterior dorsal and ventral brain areas. Our results suggest that neuronal differences during RAP predate reading instruction and thus are not due to experience-dependent brain changes resulting from DD itself and that there is a functional relationship between neuronal networks for RAP and PP within the prereading brain.

Keywords: developmental disorder, functional MRI, learning disability, pediatric neuroimaging, reading disability

Introduction

Developmental dyslexia (DD) is a language-based learning disability with known neurological origin (Galaburda et al. 2006), affecting ~5–17% of all children (Shaywitz 1998). It is a specific reading disability characterized by difficulties with speed and accuracy of word decoding, language comprehension, and spelling (Siegel 2006). Cognitive difficulties may further include speech perception, the accurate representation and manipulation of speech sounds, problems with language, memory or letter sound knowledge. In some cases, it is further characterized by difficulties with rapid automatized naming (RAN; Siegel 2006; O'Brien et al. 2012). These difficulties are not due to lack of exposure to reading instruction (Lyon et al. 2003) and are independent from individual's intelligence quotient (IQ) (Seigel 1989; Ferrer et al. 2010). Epidemiologic longitudinal studies indicate that DD constitutes a persistent condition which cannot be attributed to a transient developmental delay (Shaywitz and Shaywitz 2005). To date, the earliest that DD can reliably be diagnosed is in second or third grade (British Dyslexia Association 2012) and most children who receive a diagnosis exhibit enduring reading impairments throughout adolescence (Flowers 1994; Lyon 1995) and into adulthood (Felton et al. 1990; Vogel and Adelman 1992).

Genetic and family studies strongly suggest a genetic basis for DD (e.g., Childs and Finucci 1983; Pennington 1991); however, no single-gene model can account for the phenotype observed. Longitudinal and crosssectional studies from several research projects indicate that up to 50% of all children with a familial risk for DD will also develop reading problems (Elbro et al. 1998; Scarborough 1998; Gallagher et al. 2000; Pennington and Lefly 2001; Snowling et al. 2007; Eklund et al. 2013). Similarly, there is a smaller portion (~5–10%) of children that will develop reading problems despite a low or absent familial risk factors (e.g., Scarborough 1998). As many as 10 regions of chromosomes have been implicated in DD (e.g., DYX1C1 on 15q, KIAA0319 and DCDC2 on 6p22, and ROBO1 on 13q; for a review, see Gibson and Gruen 2008). The majority of these genes (e.g., KIAA0319, DCDC2, and DYX1C1) have shown to be crucial for neuronal migration and development of the cerebral neocortex (Wang et al. 2006). Rodent studies support the notion that neuronal migration issues may be a causal factor in the deficits observed in DD, including rapid spectrotemporal auditory processing problems (e.g., Fitch et al. 1994). Inducing neuronal migration anomalies in rats leads to significant auditory processing impairments (Fitch et al. 1994), comparable to those seen in children with language disabilities (Tallal and Piercy 1973a, 1973b). Only a few studies, have yet investigated the preliterate brain of typical or atypical developing children (e.g., Pugh et al. 2012). However, studying young children with a familial risk for dyslexia, offers an unique chance to investigate early neural, behavioral, and genetic determinants of DD.

Across languages consensus exists that DD is a specific language disorder with a characterized weakness in phonological processing (PP; e.g., Vellutino 1979; Goswami 2000). Pure PP theories, however, fail to explain widespread evidence of associated deficits in the visual (e.g., Eden, VanMeter, Rumsey, Maisog et al. 1996; Eden, VanMeter, Rumsey, Zeffiro 1996; Grinter et al. 2010; Lipowska et al. 2011), auditory (e.g., Hari and Renvall 2001; Gaab, Gabrieli, Deutsch et al. 2007; Hornickel et al. 2009, 2012; Wright and Conlon 2009; Goswami, Wang et al. 2011; Stefanics et al. 2011), and motor domains (Ramus 2003; Yang and Hong-Yan 2011). Up to 50% of all individuals with DD are reported to also be affected by core sensory processing impairments (Ramus 2003). Some researchers have therefore argued that the perceptual and phonological difficulties observed in DD may be secondary to a more fundamental perceptual deficit (e.g., Ramus et al. 2003; Tallal 2004; Goswami 2011) such as difficulties in

rapid auditory or spectrotemporal processing (McArthur and Bishop 2001; Tallal 2004; Goswami 2011; Diaz et al. 2012).

Rapid auditory processing (RAP) difficulties have been reported in up to 63% of all individuals with DD (Ramus et al. 2003). These difficulties can be observed during tasks of rapid temporal processing, gap detection, recognition of frequency and amplitude modulations, elevated frequency discrimination, and auditory stream segregation (Tallal 1980, 2004; Ramus 2003; Abrams et al. 2006; Tallal and Gaab 2006; Wright and Conlon 2009; Goswami, Fosker et al. 2011; Goswami, Wang et al. 2011; Hornickel et al. 2012). For example, compared with typical reading controls, individuals with dyslexia commonly show difficulties discriminating between consonant–vowel pairs (e.g., ba/da) that mainly differ in the first 40 ms, but not between syllables incorporating longer duration acoustic differences (Tallal and Piercy 1974; Reed 1989). Furthermore, children with DD are challenged when presented with amplitude modulations similar to those seen at the syllable level of speech (Talcott et al. 2000; Goswami et al. 2002; Goswami, Fosker et al. 2011). Goswami et al. (2002) used multiple regression analyses on results from 72 children and observed a significant relation between beat detection and phonological awareness. Auditory processing abilities not only differentiate children with DD from typical reading controls, but also distinguish between children with superior and inferior reading abilities (Goswami et al. 2002). The relationship between reading ability and the timing of subcortical auditory processing has previously been described to represent a continuum, with poor readers having delayed and good readers having early subcortical auditory timing (Banai et al. 2009). However, it is to note that even though ample evidence for sensorimotor deficits in DD exists, some studies, have failed to replicate findings of auditory processing difficulties in DD or found these only in some individuals with DD (France et al. 2002; Breier et al. 2003; Ramus 2003; Gibson et al. 2006) or could not find evidence for a link between rapid auditory and PP deficits (Georgiou et al. 2010; Willburger and Landerl 2010).

Early language difficulties have been firmly associated with later reading disorders (Beitchman et al. 1986; Scarborough 1990, 1998; Stanovich and Siegel 1994). Beyond various linguistic impairments (e.g., syntactic awareness, language comprehension, or speech perception), RAP, and phonological abilities in infants and young children have shown to predict later reading ability (e.g., Benaisch and Tallal 2002; Lyytinen et al. 2004; Tsao et al. 2004; Benasich et al. 2006; Rvachew and Grawburg 2006). Longitudinal work comparing infants and young children with familial risk for DD to typically developing controls shows that differences in categorizing speech sounds already exists in infancy (6 months) and persists until adulthood (Richardson et al. 2003). For example, in a 3-year-long longitudinal study, Huss et al. (2010) show that accurate perception of amplitude envelope rise time predicts phonological awareness and reading development in children ages 8–13 years. Accounting for up to 60% of the variance in reading ability, these findings connect metrical and basic auditory rise time processing, providing a link between primary sensory impairments in auditory processing and development of literacy skills (Huss et al. 2010).

Most neuroimaging research in DD has focused on the investigation of reading and reading-related variables fundamental for the characteristics seen in DD (e.g., PP skills). Numerous functional neuroimaging (fMRI) studies in typical children and adults have implicated left-hemispheric brain network during reading and reading-related tasks, such as PP. One of the most consistent and well-replicated findings in DD is a hypoactivation of this left-hemispheric network during reading, including temporoparietal, occipitotemporal, and inferior frontal brain regions (e.g., for reviews, see Temple 2002; Gabrieli 2009). Neuronal differences have furthermore been supported, by reports of structural atypicalities in left-hemispheric posterior brain regions (Eckert et al. 2005; Kronbichler et al. 2008; Pernet et al. 2009; Linkersdorfer et al. 2012) and reduced functional connectivity (Horwitz et al. 1998; Hampson et al. 2004). Additionally, early studies in prereading and young children at risk for reading failure reiterate the importance of left-hemispheric posterior networks, which later become crucial for skilled reading (Maurer et al. 2007; Specht et al. 2009; Brem et al. 2010; Raschle et al. 2011; Raschle, Zuk, Gaab 2012a; Raschle, Zuk, Ortiz-Mantilla et al. 2012b). However, the interplay between observed sensory deficits in some individuals with DD and the well-replicated phonological impairments has not been investigated in the brain.

Ultimately, although neurological impairments have been repeatedly linked to DD, the nature of the precise neural phenotype remains debated (Ramus 2003; Demonet et al. 2004). A second line of neuroimaging research has focused on basic sensory and sensorimotor processing difficulties observed in DD (e.g., McArthur and Bishop 2001; Ramus et al. 2003; Goswami 2011). For example, research studies using fMRI have reported altered brain activation in individuals with DD in left prefrontal brain regions during experimental modulations of speech rate (Ruff et al. 2002) or RAP (Temple et al. 2000; Gaab, Gabrieli, Deutsch et al. 2007). The left prefrontal cortex has furthermore been associated with rapid but not slow auditory processing abilities in 2 fMRI studies assessing children (Gaab et al. 2007) and adults (Temple et al. 2000) with and without a diagnosis of DD. Both studies performed whole-brain fMRI while participants listened to nonlinguistic acoustic stimuli, incorporating initial rapid or slowed frequency transitions (mirroring the spectrotemporal structure of consonant–vowel–consonant speech syllables). In both studies, typical developing children (average age 10.5 years) and adults, left-hemispheric prefrontal brain regions were activated when comparing rapid with slowed transitions, while the same activation pattern is absent in individuals with DD (Temple et al. 2000; Gaab, Gabrieli, Deutsch, et al. 2007). Additionally, preliminary evidence points towards a possible remediation effect, implied by an increase of left prefrontal activity after training (Temple et al. 2000; Gaab, Gabrieli, Deutsch et al. 2007). Functional MRI studies about auditory processing deficits in DD have furthermore been complemented by electrophysiological evidence. Using electroencephalography and magnetoencephalography, differences in spectotemporal auditory processing have been found in children and adults with a diagnosis of DD (Heim et al. 2003a, 2003b).

The extent to which structural and functional brain differences seen in DD are related to the cause or the consequence of the disability itself is uncertain since most previous research has focused on children and adults with years of reading instruction. However, structural and fMRI results from preliterate and young children at familial risk for DD have

provided first evidence for structural and functional brain alterations associated with reading and language development, similar to those seen in older children and adults with DD (e.g., Maurer et al. 2009; Specht et al. 2009; Raschle et al. 2011; Raschle, Zuk, Gaab 2012a; Raschle, Zuk, Ortiz-Mantilla et al. 2012b). In the current study, we aim to assess the neuronal basis of RAP in prereading children with a familial risk for DD. We will employ the same nonlinguistic auditory stimuli as previously described in 2 studies of school-aged children and adults with DD (Temple et al. 2000; Gaab, Gabrieli, Deutsch et al. 2007). We hypothesize that children with a familial risk for DD compared with typically developing controls, already show alterations in left prefrontal brain regions during the processing of rapid compared with slow changes in sounds. Furthermore, we aim to connect previous findings of reduced neuronal activation in preliterate children at familial risk for DD during PP (Raschle, Zuk, Gaab 2012a; Raschle, Zuk, Ortiz-Mantilla et al. 2012b) to the neuronal correlates of RAP.

Materials and Methods

Subjects

Twenty-eight healthy, native English-speaking children with a familial risk for DD (FHD+/$n = 14$; mean age = 69.05 ± 4.98 months) and without a familial risk for DD (FHD−/$n = 14$; mean age = 67.71 ± 7.04 months) took part in the current study. Twenty-two children are right handed (9 FHD+/13 FHD−), 4 children have not indicated a preference yet (ambidextrous; 3 FHD+/1 FHD−), and 2 children (2 FHD−) are left handed. fMRI analyses were performed with and without inclusion of the 2 left-handed children. However, no difference in outcome was observed. Consequent analyses were thus based on the whole group. Children with a familial risk for DD (FHD+) have at least one first-degree relative with a clinical diagnosis of DD. Those in the control group (no familial risk; FHD−) have no first-degree relative with a clinical diagnosis of DD or reading disability. All participants are part of an ongoing longitudinal study at Boston Children's Hospital which aims to examine behavioral and neural premarkers of DD in preschoolers and beginning readers with and without a familial risk for dyslexia (Boston Longitudinal Study of Dyslexia, BOLD). Participating families are invited each year for 2 visits, 1 behavioral standardized testing session and 1 neuroimaging session for 4 consecutive years starting in preschool. Subjects included in the current article are drawn from year 1 of this longitudinal dataset. None of the children enrolled in this study have a history of neurological or psychological disorder, head injury, poor vision, and poor hearing.

During an initial screening (telephone or email), parents were asked about their child's prereading status. Only children who were not yet reading and whose caregivers planned to have them enter kindergarten in the same year were invited to take part in the study. To further ensure prereading status, the word ID subtest of the Woodcock Reading Mastery Test (Woodcock 1987) was administered to all children. Twenty-one children (11 FHD+/10 FHD−) did not recognize any isolated sight words, 3 children (2 FHD+/1 FHD−) recognized 1 or 2, 3 children (1 FHD+/2 FHD−) recognized between 3 and 5 words and one child recognized 9 words (1 FHD−). All children were tested between May and November of their kindergarten entry year. Group characteristics are in line with similar longitudinal studies on early childhood development showing, for example, that by kindergarten entry only 2% of children in the United States of America are able to identify sight words and only 1% recognizes words in context (Denton et al. 2000; Morris and Bloodgood 2003). This study was approved by the local ethics committee at Boston Children's Hospital. Verbal assent and informed consent were obtained from each child and guardian, respectively.

Behavioral Group Characteristics and Demographics

Children completed standardized assessments examining language and prereading skills such as expressive and receptive vocabulary (Clinical Evaluation of Language Fundamentals (CELF Preschool 2nd edition; (Semel et al. 1986)), PP (Comprehensive Test of Phonological Processing (CTOPP (Wagner et al. 1999)), the Verb Agreement and Tense Test (VATT; (van der Lely 2000)), and RAN (Rapid Automatized Naming Test; (Wolf and Denckla 2005)). Additionally, participating families were given a socioeconomic background questionnaire (questions adapted from the MacArthur Research Network: http://www.macses.ucsf.edu/Default.htm; for a complete overview of socioeconomic status questions, see Supplementary Material 1) and a home literacy questionnaire (based on Denney et al. 2001; as cited in Katzir et al. 2009; see Supplementary Material 2). The 2 groups of children do not significantly differ in gender (FHD+: 3 females/11 males and FHD−: 7 females/7 males), age (mean age during neuroimaging; FHD+: 70.7 months/FHD−: 69.2 months; $P = 0.490$), nonverbal IQ (KBIT-2; FHD+ mean score: 100.7/FHD− mean score: 100.2; $P = 0.893$), and socioeconomic background (e.g., parental education or total family income; $P < 0.05$). However, even though FHD+ and FHD− children do not significantly differ in gender, there are more boys than girls in the group of children at familial risk for DD. Post hoc analyses have been performed to rule out an effect of gender on brain activation.

fMRI—Task Procedure

Prior to neuroimaging, a 45-min preparation session was conducted in a mock scanner area (see also Raschle et al. 2009 and Raschle, Zuk, Gaab 2012a). This session involved extensive training to familiarize each child with the task instructions and stimuli prior to the experiment. The neuroimaging session included a total of 3 fMRI tasks as well as structural image acquisition. Two fMRI experiments are part of the present analysis and further described here. The neuroimaging session lasted about 1.5 h including breaks, however total scan time per child was no more than 40 min maxima. Whole-brain imaging was performed on 28 children during a RAP task. Twenty-three children also completed a PP task (first sound matching). Due to the participants' age, all tasks were divided into 2 runs with a total duration of 5–6 min per run. The order of experiments and runs were pseudo-randomized across participants.

RAP Task

The stimuli and task were adapted from Temple et al. (2000) and have been described previously (Temple et al. 2000; Gaab, Gabrieli, Deutsch et al. 2007). Experimental stimuli lasting 600 ms were nonlinguistic with a spectrotemporal structure similar to that of consonant–vowel–consonant speech syllables. All stimuli were designed to contain either very rapid frequency changes (within 40 ms) or slowed frequency transitions (extended transition of 200 ms). Stimuli incorporating both rapid and slowed transitions included high (250 Hz F0) and low (125 HZ F0) pitched stimuli. A behavioral interleaved gradient imaging design (Hall et al. 1999; Gaab et al. 2007a, 2007b, 2008) was employed allowing stimuli to be presented without interference from the MR scanner background noise. One single high- or low-pitched sound lasting 600 ms was presented every 2850 ms, while image acquisition accounted for 1995 ms. The 600-ms tones were randomly presented (jittered) within the 855-ms time window. Stimuli were presented in 8 blocks of each type (rapid frequency transition, slowed frequency transition, or rest), with 8 items per block (total of 8 blocks with tones incorporating rapid frequency transition, 8 blocks with slowed frequency transitions and 8 rest blocks). In each block, 50% of the stimuli were high pitched and 50% were low pitched; presented in a randomized order. A 2850-ms cue was used before the start of every experimental or rest block. Participants were asked to indicate the pitch (high/low) of each stimulus by button press. An alien-themed cover story was used to motivate participants and to conduct the experiment in a child-friendly and age-appropriate way (Raschle et al. 2009). During the rest condition, a fixation cross was presented and participants were instructed to stay very still without pressing any buttons.

PP Task

The stimuli and task have been described previously (for details, see Raschle, Zuk, Gaab 2012a). All children listened to 2 consecutively presented common object-words, spoken in a male or female voice, accompanied by corresponding pictures. During the experimental condition (first sound matching; FSM) children indicated via button press whether the first sound of the 2 presented object-words matched. During the control condition (voice matching; VM) participants were to decide whether it was the same voice (same gender) presenting the 2 object-words or not. Experimental and control task were matched with a rest condition (fixation cross). Each trial lasted for 6 s: the 2 object-words were presented for 2 s each, following by a question mark presented for 2 s. This setup allowed for presentation of the 2 words without interference from the MR scanner in a behavioral interleaved gradient design (Hall et al. 1999; Gaab et al. 2007a, 2007b, 2008). A block design was employed to incorporate a total of 7 blocks (4 trials in each block) of experimental and control trials. The whole experiment consisted of 2 separate runs, to accommodate the younger participants, lasting around 5–6 min each.

In-Scanner Performance

Button presses and reaction times (RTs) were recorded during in-scanner performance for all participants. During the RAP task, children were instructed to indicate the pitch (high/low) of the presented stimuli as quickly and accurately as possible after stimulus presentation. Children were allowed to correct their responses until the beginning of the next stimulus presentation (maximum correction time = 2 s; ending at the time of the start of a consecutive trial). To ensure that all participants were engaged in the task, children with more than 25% missed trials were excluded from the imaging analyses. Pitch-identification and RT were compared between children with and without a familial risk for DD using independent sample *t*-tests using SPSS software. Due to a technical problem, 1 FHD+ and 2 FHD− children had no in-scanner data recorded for RAP. All 3 children were still included in the imaging analyses as their performance during the training session indicated that the tasks were well understood. For the PP task, FSM scores, VM scores, and RT were compared between children with and without a familial risk for DD. Due to a technical problem, 1 FHD+ had no in-scanner data recorded for the PP task and 1 FHD+ child had only data for 1 run (FSM). Both children were included in the imaging analyses as their performance during the training session indicated that the tasks were well understood.

fMRI—Acquisition and Analyses

Each experimental run included the acquisition of 112 functional whole-brain images for the RAP task and 60 for the PP task. Images were acquired with a 32-slice echo planar imaging-interleaved sequence on a SIEMENS 3T Trio MR scanner, including the following specifications: TR 2850 ms (RAP task)/6000 ms (PP task); TA 1995 ms; TE 30 ms; flip angle 90°; field of view 194 mm; voxel size 3 × 3 × 4 mm; slice thickness 4 mm. Before the start of the first block, additional functional images were obtained and later discarded to allow for T_1 equilibration effects.

Image processing and analyses were carried out using SPM5 (www.fil.ion.ucl.ac.uk/spm) executed in MATLAB (Mathworks, Natick, MA, USA). To adjust for movement artifacts within the acquired fMRI time series, we first realigned all images using a least squares approach with reference to the first image (after discarding the first images to allow for T_1 equilibration effects). Next, all images were spatially normalized into standard space, as defined by the ICBM, NIH-20 project (Talairach and Tournoux 1998; Ashburner and Friston 2005) and finally smoothed with an 8-mm full-width at half-maximum isotropic kernel to remove noise and effects due to residual differences in functional and structural anatomy during inter-subject averaging (www.fil.ion.ucl.ac.uk/spm/doc/spm5_manual.pdf).

Due to the age of the participants, a rigorous procedure for artifact detection was chosen. Particularly, to visualize motion, plot potential movement artifacts and review analysis masks of each subject, we used the art-imaging toolbox (http://www.nitrc.org/projects/artifact_detect). Upon visual inspection of all raw images, the art-imaging toolbox was used to plot differences in motion between consecutive images and to review artifactual time points: First, we identified all images that exceeded a movement threshold of 3 mm and a rotation threshold of 0.05 mm. Then, we visually inspected every image exceeding the said threshold and those images containing artifacts (e.g., missing voxels, stripes, ghosting, or intensity differences) were discarded from further analyses. There were no significant differences in the number of omitted scans per group ($P > 0.5$). Additionally, the art-imaging toolbox was used to create an explicit mask, excluding the identified artifactual time points, and to save movement regressors. Movement regressors were modeled as cofounds within the general linear model and explicit masking was performed during each subject's first-level analysis to assure inclusion of each voxel of the analysis mask.

The general linear approach in SPM5 was used to analyze the data in a block design for each subject. Contrast images for experimental > control condition (RAP task: "Fast Transition (FT) > Slow Transition (ST)"/PP task: "FSM > VM") were obtained. Finally, second-level analyses using 1 and 2 sample *t*-tests were performed in order to examine functional differences during RAP and PP within each group and between children with and without a familial risk for DD. Results are reported at a significance level of $P < 0.005$, uncorrected; extent threshold of 50 voxels for each group separately and for those regions that showed significantly more activation in FHD− compared with FHD+ children.

Region of Interest Analyses

Two main regions of interest (ROIs) analyses were performed, to (I) assess the relationship between the neural activation during RAP and standardized assessments of PP; and (II) further investigate the relationship between brain activation during both rapid auditory and PP.

ROI Analyses—Part (I)

The goal of this ROI analysis was to examine the relationship between weighted parameter estimates in brain regions observed in the current group of participants and their behavioral prereading scores for PP (CTOPP blending). Functional ROIs were based on the second-level group comparison (FHD+<FHD−) during RAP (FT>ST). The mean parameter estimates during RAP in left-hemispheric prefrontal ROI were extracted from each participant's first-level analysis and correlated with their prereading measures (PP based on CTOPP blending).

ROI Analyses—Part (II)

To further examine the relationship between neuronal activation during RAP and neuronal activation PP, we performed a separate ROI analysis using independent anatomical ROIs, 1 set for each task (named RAP ROIs and PP ROIs). Two studies comparing children and adults with and without a diagnosis of DD, using the same RAP task employed here, have demonstrated the involvement of left inferior frontal brain regions during RAP (Temple et al. 2000; Gaab, Gabrieli, Deutsch et al. 2007). Therefore, we defined 2 left-hemispheric frontal brain ROIs (RAP ROI*s* BA9 and 46: left middle/superior frontal gyri) using the Wake Forest University (WFU) PickAtlas toolbox (Maldjian et al. 2003; Maldjian et al. 2004) in SPM5. The mean parameter estimates during RAP (FT>ST) were extracted from the first-level T-contrast of each participant. In a second step, PP ROIs were defined based on ample evidence of neuronal dysfunction (hypoactivation) in left temporoparietal and occipitotemporal brain regions during reading and reading-related tasks in individuals with DD (for reviews, see McCandliss and Noble 2003; Schlaggar and McCandliss 2007; Gabrieli 2009). Therefore, 3 left-hemispheric posterior ROIs were defined (*PP ROIs* BA37, BA40, and a BA41/42/22: occipitotemporal and parietotemporal) using the WFU PickAtlas toolbox (Maldjian, Laurienti, Kraft et al. 2003; Maldjian, Laurienti and Burdette 2004) in SPM5. The mean parameter estimates were extracted from the first-level T-contrast of our PP experiment (FSM>VM). Correlational analyses were then used to relate mean parameter estimates within the 2 RAP and the 3 PP ROIs using SPSS software package, version 19.0

(SPSS, Inc. (1999) SPSS Base 10.0 for Windows User's Guide. SPSS, Inc., Chicago, IL, USA).

Results

Demographics and Behavioral Group Characteristics

Demographics and behavioral group characteristics for all 28 participants are provided in Table 1. Children with a familial risk for DD (FHD+) scored significantly lower than children without a familial risk for DD (FHD−) on standardized assessments of expressive language skills (CELF Expressive Language ($t_{(26)} = -2.119$; $P = 0.044$)) and RAN ($t_{(25)} = -3.313$; $P = 0.003$). No differences were observed in age (age at imaging session, $t_{(26)} = 0.700$; $P = 0.490$/age at psychometric session, $t_{(26)} = 0.580$; $P = 0.567$), verbal ($t_{(26)} = 0.266$; $P = 0.792$) or nonverbal IQ ($t_{(26)} = -0.279$; $P = 0.783$), or socioeconomic status (e.g., parental education or income, $P > 0.05$; Table 1).

Table 1
Participant demographics and behavioral group characteristics

	FHD+	FHD−	*P*-values Sig. 2-tailed
	Mean ± SD	Mean ± SD	FHD+ vs. FHD−
n	14	14	
Age (in months/psychometrics session)	69.05 ± 4.98	67.71 ± 7.04	0.567
Age (in months/imaging session)	70.69 ± 4.76	69.16 ± 6.64	0.490
Core language	104.71 ± 10.43	111.00 ± 9.78	0.112
Receptive language	106.14 ± 13.83	109.86 ± 11.66	0.449
Expressive language	101.86 ± 11.11	110.71 ± 11.01	0.044*
Language content[a]	101.31 ± 10.79	108.67 ± 11.22	0.108
Language structure	105.14 ± 11.99	111.14 ± 9.81	0.159
CTOPP			
Elision	9.14 ± 1.88	10.64 ± 2.68	0.098
Blending[b]	10.46 ± 1.90	11.36 ± 1.39	0.172
Nonword repetition[b]	9.54 ± 2.47	9.86 ± 2.25	0.729
RAN			
Objects[c]	89.93 ± 11.27	104.46 ± 11.52	0.003**
VATT			
Inflection[d]	27.00 ± 5.05	24.00 ± 9.87	0.368
Repetition[d]	36.00 ± 4.02	38.60 ± 1.26	0.064
KBIT			
Verbal ability[c]	111.5 ± 9.64	110.43 ± 11.56	0.792
Nonverbal ability[c]	100.71 ± 11.43	101.93 ± 11.64	0.783
	Mean ± SD	Mean ± SD	Sig. 2-tailed (independent samples *t*-test)
In-scanner performance (raw scores; maxima = 128)			
RAP[a](pitch-discrimination)			
Correct	86.46 ± 21.93	99.17 ± 25.86	0.197
Incorrect	28.61 ± 14.96	21.00 ± 23.61	0.341
RT (ms)	1125 ± 212.34	1028.97 ± 184.70	0.238
	Mean rank	Mean rank	Sig. 2-tailed (Mann–Whitney)
Socioeconomic status parental education[e]	11.59	14.11	0.387
Income (total family income for last 12 months)[f]	12.79	13.19	0.882

Note:
Measures (standard scores are reported).
[a]13 FHD+/12 FHD− (3 children did not finish all testing).
[b]13 FHD+/14 FHD− (1 child did not finish all testing).
[c]14 FHD+/13 FHD− (1 child did not finish all testing).
[d]12 FHD+/10 FHD− (6 children did not finish all testing).
[e]Parental Education scores are calculated according to the 7-point Hollingshead Index Educational Factor Scale, summed for husband and wife and divided by 2.
[f]Scale where 1 = 0–5000$, 2 = 5000–11 999$, 3 = 12 000–15 999$, 4 = 16 000–24 999$, 5 = 25 000–34 999$, 6 = 35 000–49 900$, 7 = 50 000–74 999$, 8 = 75 000–99 999$, 9 = 100E000+ $, 10 = do not know, 11 = no response.
*$P < 0.05$; **$P < 0.01$; 2-tailed *t*-test; all other *t*-tests nonsignificant at threshold of $P = 0.05$.

In-Scanner Performance—Results

RAP Task

There were no differences in pitch-discrimination ($P = 0.197$) or RT ($P = 0.238$) between children with or without a familial risk for DD (FHD+ mean raw score for pitch-discrimination: 86.46 ± 21.93, RT = 1126 ms/FHD− mean raw score for pitch-discrimination: 99.16 ± 25.90, RT = 1029 ms; Table 1).

Phonological Processing Task

Children with a familial risk for DD (FHD+; mean = 16.60 [$N_{max} = 28$]) were significantly less accurate on FSM than children without a familial risk (FHD−; mean = 21.83; $P = 0.015$). There was no performance difference on VM and RT did not differ between groups on either experimental or control task ($P > 0.05$).

fMRI Results

RAP Task

Whole-brain analysis revealed 2 brain regions in children without a familial risk for DD that were more active during rapid compared with slowed auditory processing (FT > ST; Table 2, Fig. 1*b*). These regions included the inferior/middle frontal and precentral/middle frontal gyrus. Children with a familial risk for DD showed no difference in brain activation during the processing of rapid compared with slowed stimuli (Table 2, Fig. 1*a*). A direct comparison between children with and without a familial risk for DD (FHD+<FHD−) during blocks of fast compared with slow stimuli (FT>ST) revealed differences in left-hemispheric frontal brain areas (superior/medial, inferior/middle and precentral/middle gyrus) as well as in the left cerebellum/fusiform gyrus and right precentral/middle frontal gyrus (Table 2, Fig. 1*c*). The opposite contrast (FHD+>FHD−) did not yield any significant voxels. Furthermore, to rule out gender effects, we performed a ROI analysis for the neuronal activation in the left prefrontal ROI (inferior/middle, superior/medial, and precentral/middle frontal gyrus) for males only. Results (FHD−>FHD+) reveal significant differences in neuronal activation during RAP in the inferior/middle frontal and precentral/middle frontal gyrus as previously reported in the mixed group.

PP Task

In a smaller group of 23 children (10 FHD+/13 FHD−), previous findings of hypoactivations in children with, compared

Table 2
Brain activations for rapid versus slow stimuli (FT>ST) for children with (FHD+) and without (FHD−) a familial risk for DD

Region	Brodmann area	*x*	*y*	*z*	*Z*	Size, voxels
Prereading children without a familial risk for dyslexia (FHD−/*n* = 14)						
Frontal lobe						
Inferior/middle frontal gyrus (L)	9	−52	12	32	3.95	52
Precentral/middle frontal gyrus (L)	3/4/6	−50	−12	48	3.90	145
Prereading children with a familial risk for dyslexia (FHD+/*n* = 14)						
No brain activation at $P = 0.005$, uc ($k = 50$)						
Group difference (children with a familial risk for dyslexia < children without a familial risk)						
Frontal lobe						
Superior/medial frontal gyrus (L)	9/10	−2	58	20	3.82	147
Inferior/middle frontal gyrus (L)	9/45/46	−54	12	30	3.97	136
Precentral/middle frontal gyrus (L)	9/45/46	−44	−8	50	3.48	93
Precentral/middle frontal gyrus (R)	6	22	−18	64	3.25	51
Other						
Cerebellum/fusiform gyrus (L)	19	−24	−82	−26	3.64	65

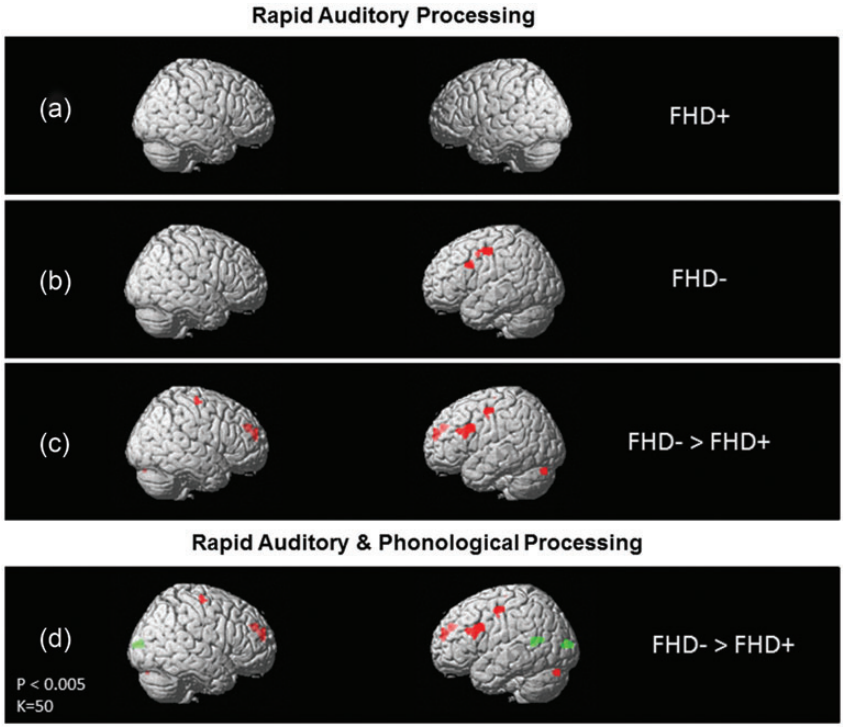

Figure 1. Statistical parametric maps showing brain activation for rapid versus slow acoustic stimuli (FT > ST) in children with (FHD+(a)) and without (FHD− (b)) a familial risk for DD. Group differences reveal that FHD+ children show a disruption in neural response to rapid compared with slow acoustic information in left frontal brain regions when compared with FHD− children (c). (d) incorporates group differences (FHD−>FHD+) during rapid auditory (in red) and phonological processing (in green).

with without, a familial risk for DD in left-hemispheric posterior reading networks were confirmed (Raschle, Zuk, Gaab 2012a). Group differences indicate a disrupted neural response during PP in FHD+ children within left middle occipital gyrus/cuneus ($x = -18$, $y = -92$, $z = 8$) and left superior temporal gyrus ($x = -26$, $y = -58$, $z = 16$). Figure 1*d* incorporates the results of group differences (FHD−>FHD+) in neuronal activation during both, rapid auditory (in red) and PP (in green). These tasks have been conducted in randomized sequential order, but are both rendered on the same brain for displaying purposes.

Region of Interest Analyses—Results

*ROI Analyses—Part (**I**)*

To assess the relationship of neuronal activity during RAP and standardized behavioral assessments of PP, mean parameter estimates were extracted for RAP (FT>ST) based on ROIs defined by our second-level group differences (FHD+<FHD−). Neuronal activation within left-hemispheric prefrontal ROIs was correlated with standardized assessments of PP (CTOPP blending). Table 3 gives an overview of the results and demonstrates that neuronal activation during RAP in left precentral/middle frontal gyrus positively correlates with phonological skills ($P = 0.007$).

*ROI Analyses—Part (**II**)*

To further assess the neuronal relationship between RAP and PP, additional ROI analyses were conducted. Two independent left-hemispheric RAP ROIs and 3 independent occipitotemporal and parietotemporal PP ROIs were used to extract mean parameter estimates for RAP (FT>ST) and PP (FSM>VM), respectively. The neuronal activation during RAP within specified RAP ROIs was then compared with neuronal activation during PP within specified PP ROIs through correlational analysis. Within the whole group of participants, neuronal activation during RAP in left middle frontal gyrus (BA9) positively correlated with neuronal activation during PP in parietotemporal (BA22/41/42; $P = 0.038$) and occipitotemporal areas of the brain (BA37; $P = 0.005$; see Table 4).

Table 3
Overview of correlational analysis results, demonstrating a positive correlation between the neuronal activation during RAP in left precentral/middle frontal gyrus and phonological skills ($P = 0.007$)

		Pearson correlations between RAP and phonological processing (CTOPP blending)		
		RAP ROIs (left hemisphere)		
		Superior/medial frontal gyrus (*P*-values)	Inferior/middle frontal gyrus (*P*-values)	Precentral/middle frontal gyrus (*P*-values)
Phonological processing	CTOPP blending	−0.049 (0.807)	0.045 (0.825)	0.508* (0.007)

Note: *Correlation is significant at the 0.01 level (2-tailed).

Discussion

The presented results demonstrate that prereading children with a familial risk for DD already show a neuronal disruption of left prefrontal brain regions during rapid spectrotemporal processing similar to that seen in older children and adults with a diagnosis of DD (Temple et al. 2000; Gaab, Gabrieli, Deutsch et al. 2007). This atypical activation pattern was

Table 4
Correlational analysis between neuronal activation during RAP and PP

		Pearson correlations between RAP and PP ROI	
		RAP ROIs (left hemisphere)	
		Brodmann area 9 (*P*-values)	Brodmann area 46 (*P*-values)
PP ROIs (left hemisphere)	Brodmann area 22/41/42	0.435* (0.038)	0.174 (0.426)
	Brodmann area 40	0.243 (0.264)	0.225 (0.303)
	Brodmann area 37	0.561** (0.005)	0.207 (0.343)

Note: *Correlation is significant at the 0.05 level (2-tailed).
**Correlation is significant at the 0.01 level (2-tailed).

observed despite the covert nature of the task employed; participants were asked to indicate the pitch of the tones, but neuronal response to blocks of tones with altered initial transitions (rapid or slowed) was measured. Furthermore, neuronal activation during RAP within left prefrontal brain regions positively correlates with behavioral standardized PP skills. We here also confirm previous findings of a disrupted neural response to PP in left-hemispheric posterior reading networks in prereading children with a familial risk for DD in a subsample of children published in Raschle, Zuk, Gaab (2012a). Correlational analyses indicate a link between neuronal activation patterns during rapid auditory and neuronal activation patterns during PP. Finally, children at familial risk for DD score significantly lower on standardized tests of expressive language skills and RAN. No differences in IQ, home literacy environment, or socioeconomic status were observed. In line with our previous publications (Raschle et al. 2011; Raschle, Zuk, Gaab 2012a), we suggest that behavioral and neuronal differences characteristic of individuals with DD may already be present at birth or develop within the first few years of life. Furthermore, neuronal activation in prefrontal brain regions during RAP seems to be associated with neuronal activation during PP in left-hemispheric posterior brain regions. Since all children in the present study were prereaders at the time of testing, the observed differences cannot be due to any effects related to reading instruction or reading failure per se.

Our results demonstrate an early neuronal disruption in prefrontal brain regions during RAP in prereading children at risk for DD. Various neuroimaging studies have implicated left prefrontal brain regions during language and auditory processing tasks in typical reading children and adults (e.g., Gabrieli et al. 1998; Price 1998; Pugh et al. 2001, 2012), when comparing those with reading disabilities to typical readers (Cao et al. 2006; Hoeft et al. 2006; Booth et al. 2007; Gaab, Gabrieli, Deutsch, et al. 2007; Kovelman et al. 2011) or good with poor beginning readers (Bach et al. 2010). Along with the basal ganglia, the left dorsal inferior frontal gyrus has been described as part of the anterior reading circuit associated with higher-level phonological recoding in mature readers (Pugh et al. 2001; Booth et al. 2007). Neuronal activation within the left prefrontal brain region has been described during PP or awareness (Devlin et al. 2003; Kovelman et al. 2011), letter substitution tasks (Bach et al. 2010), RAP (Temple et al. 2000; Gaab, Gabrieli, Deutsch et al. 2007), phoneme memory tasks (Beneventi et al. 2010), and semantic analysis (Gabrieli et al. 1998). Studies with and without participants with reading disabilities have specifically implicated left dorsolateral prefrontal brain regions during the processing of transient acoustic features, such as the manipulation of rapidly changing speech and nonspeech sounds (Belin et al. 1998; Temple et al. 2000; Poldrack et al. 2001; Temple 2002; Gaab, Gabrieli, Deutsch et al. 2007). For example, by using the exact same stimuli as in the current publication, a disrupted response to rapid acoustic stimuli has been demonstrated in children and adults with DD, when compared with typical reading controls (Temple et al. 2000; Gaab, Gabrieli, Deutsch et al. 2007). Interestingly, the neuronal alterations seen in children with DD was shown to be partly ameliorated through remediation and led to improved language and reading abilities (Gaab, Gabrieli, Deutsch et al. 2007).

Furthermore, we here demonstrate a link between the neuronal activation during RAP in preliterate children at risk for DD and behavioral assessments of prereading skills. The mean parameter estimates during RAP positively correlates with PP skills (CTOPP blending). Behavioral studies investigating RAP and PP abilities have both shown to predict later language skills and development (Juel 1988; Scarborough et al. 1991; Benaisch and Tallal 2002; Choudhury et al. 2007). Our findings could indicate that RAP skills may be involved in the development of prereading skills, such as PP abilities but a causal conclusion cannot be drawn without longitudinal analyses. However, this would be in line with ample behavioral evidence implicating auditory processing difficulties in developmental language disorders (e.g., Tallal and Piercy 1973; Elliott et al. 1989; Wright et al. 1997). However, it is notable that there have also been ample findings that failed to replicate an association between rapid auditory and PP deficits or have not replicated auditory deficits in DD (France et al. 2002; Breier et al. 2003; Georgiou et al. 2010; Willburger and Landerl 2010). Again, other studies have found a link between rapid auditory and PP in DD, but only in a subset of children or adults with reading disabilities (Ramus 2003; Gibson et al. 2006). However, it is important to note that there were no significant differences in PP between the 2 groups and significant group differences were only observed for RAN and expressive language skills. Interestingly, mean standardized scores for RAN in FHD+ as a group were below the mean of the norming sample (mean: 89.93 ± 11.27 for FHD+) whereas standardized scores for expressive language were right at the mean of the norming sample (mean: 101.86 ± 11.11 for FHD+). This raises the question whether the FHD+ children can be considered at risk for DD based on their behavioral scores which is important for the interpretation of our results. It has been suggested that phonological awareness and naming speed variables contribute uniquely to different aspects of reading (Wolf and Bowers 1999) suggesting the presence of 2 single-deficit and 1 double-deficit subtype with more pervasive and severe impairments in both PP and naming speed. Furthermore, several studies have shown that RAN is one of the key predictors of reading disability in preschool (Badian 1994; Puolakanaho et al. 2007; 2008) and in one of our previous studies, we could show that it positively correlates with gray matter indices in left temporoparietal and occipital-temporal regions prior to reading onset. It remains unclear which of the children here studied will receive a diagnosis of DD in elementary school and whether these children (and how many) will show a single-deficit in RAN, as decribed by Wolf and Bowers (1999), or not but our current results in a relative small sample suggets that

FHD+ children with an isolated RAN deficit in preschool also show the characteristic brain deficits in posterior temporoparietal and occipitotemporal regions during PP and left prefrontal regions during RAP. Furthermore, the groups differ in expressive language scores and deficits in expressive language skills have been show to be a predictor of later reading disability (e.g., Scarborough 1990, 1998; Stanovich and Siegel 1994). However, we do not think that our FHD+ group can be considered impaired in expressive language or even qualify for a diagnosis of specific language imapirment at this point, but our longitudinal study design will allow us to observe the developmental trajectories of expressive language oever time and how it relates to brain activation in the observed key regions.

During PP, similar activation patterns as previously described in Raschle, Zuk, Gaab (2012a) were observed in our smaller sample which consists of 19 children from Raschle, Zuk, Gaab (2012a) and 4 new children (3 FHD+/1 FHD−). Neuroimaging data implicates a left-hemispheric specialized reading network in older children and adults (Pugh et al. 2001), which is disrupted in individuals with DD (Temple et al. 2001; Shaywitz et al. 2002; Maurer et al. 2007; Blau et al. 2010). Our findings are in line with research suggesting an early specialization of the reading network in young children (Gaillard et al. 2003; Vaessen and Blomert 2010) and a disruption of its main components in children at risk for DD (even preliterate; e.g., Simos et al. 2000; Maurer et al. 2007, 2009; Specht et al. 2009; Brem et al. 2010; Raschle et al. 2011; Raschle, Zuk, Gaab 2012a), similar to adult studies in DD.

It has been shown previously that regions within the left inferior frontal cortex of the brain maybe similarly sensitive to transient measures of acoustic features of speech and those requiring PP abilities (Poldrack et al. 2001). However, it is to note that a direct involvement of left prefrontal brain regions during PP (neuronal activation in left prefrontal cortex during PP) was not seen in the current sample or within a previously published group of children with or without a familial risk for dyslexia (Raschle, Zuk, Gaab 2012a). This may be explained by various findings of a developmental component on neuronal activation within inferior frontal brain regions during reading-related task, observable by activation increases in this region with age (Turkeltaub et al. 2003; Brown et al. 2005; Bitan, Cheon, Lu, Burman and Booth 2007; Bitan, Cheon, Lu, Burman, Gitelman et al. 2009). The young age of the participants studied here, may thus explain the missing involvement of the left prefrontal cortex during PP. Enhanced left inferior frontal gyrus activation during PP in adults with DD compared with controls is oftentimes interpreted representing as compensatory mechanisms in individuals who struggle to read. Compensation is hereby reflected by greater reliance on articulatory processes when PP is disrupted (e.g., Shaywitz et al. 1998; Brunswick et al. 1999; MacSweeney et al. 2009; Richlan et al. 2009), leading to overactivation in DD compared with typical reading subjects in left inferior frontal gyrus. However, all the children in the current sample were still preliterate at the time of testing and compensatory mechanisms are unlikely in place yet. Our findings may reflect an early engagement of left inferior frontal brain regions during RAP, while the importance of this region for PP tasks is not yet developed in preliterate children, independent of familial risk for reading disabilities. We thus suggest that within the left prefrontal cortex the basic auditory mechanisms for processing rapid spectrotemporal features of sounds are already developed in preliterate typically developing children, but dysfunctional in preliterate children at risk for dyslexia. For both, children with and without a familial risk for reading failure, this brain region is not yet employed in prereading tasks, such as PP. Longitudinal studies integrating neuroimaging and behavioral findings, ideally from a very young age on, will be needed to investigate how this brain region develops and to see whether phonological and RAP are independent components or not.

A Link Between Neuronal Activation During Rapid Auditory and Phonological Processing?

The current findings may indicate a potential link between the neural systems during phonological and RAP in the prereading brain. The correlational analysis demonstrated a link between neuronal activation during RAP in left prefrontal brain regions and neuronal activation during PP in posterior parietotemporal and occipitotemporal areas of the brain. While the prefrontal cortex has been implicated during higher level phonological recoding, the posterior dorsal and ventral brain regions are especially linked to graphem-phoneme mapping, letter identification and fluent reading (Pugh et al. 2000). In particular, the left occipitotemporal brain area has been suggested to be seat of the visual word form area, a brain region critical for visual word processing (McCandliss et al. 2003). The importance of this brain region in the prereading brain has been implicated by various neuroimaging studies (e.g., van Atteveldt et al. 2004; Maurer et al. 2007; Specht et al. 2009; Brem et al. 2010). For example, Brem et al. (2010) observed that occipitotemporal print sensitivity develops during the earliest phase of reading acquisition in childhood, suggesting that a crucial part of the later reading network first adopts a role in mapping print and sound (Brem et al. 2010). Parietotemporal brain regions have been found to be particularly crucial for the integration of letter and speech sounds (van Atteveldt et al. 2004) and are activated during neuroimaging tasks of reading (for reviews, see Pugh et al. 2001; Schlaggar and McCandliss 2007). We here demonstrated a correlation between the neuronal activation during RAP in left prefrontal brain regions and PP in posterior areas of the brain. These findings may be interpreted as initial evidence that RAP and phonological abilities required to learn to read is influential to each other during reading acquisition. Because reading acquisition is highly dependent on fine-grained auditory processing skills, it has been reiterated in the literature that improving the neural response to sound processing is likely linked to enhanced reading skills (for reviews, see, e.g., Hornickel et al. 2012; Tallal 2012).

However, some precautions need to be noted. Our findings are in line with results by Pugh et al. (2012) who observed shared brain pathways and thus a link between temporal auditory and PP and underline the importance between sound processing and reading acquisition (Hornickel et al. 2012; Tallal 2012). However, in agreement with Pugh et al. (2012) and others before (Ramus et al. 2006), the current results cannot be interpreted as a causal relationship between rapid auditory or PP. The differences seen in this group of preliterate children may be simply explained by common cortical and subcortical networks that are less optimally organized in children and adults with reading disabilities or young

children at risk for such (Pugh et al. 2012; Ramus et al. 2006). Longitudinal studies integrating neuroimaging and behavioral findings, ideally from a very young age on, will be needed.

The Many Faces of DD

Our current and previous findings speak for a range of functional (Raschle, Zuk, Gaab 2012a) and structural (Raschle et al. 2011) alterations, which are already observed in prereading children with a familial risk for DD. DD is a language-based learning disability with a core deficit in PP. However, DD is often accompanied by various perceptual deficits, including those involving visual (Eden, VanMeter, Rumsey, Maisog et al. 1996; Eden, VanMeter, Rumsey, Zeffiro 1996; Grinter et al. 2010; Lipowska et al. 2011), auditory (Gaab, Gabrieli, Deutsch et al. 2007; Stefanics et al. 2011), and motor abilities (Stoodley et al. 2006; Brookes et al. 2010). Auditory processing deficits are among the most commonly observed deficits in DD next to PP issues. For example, by reviewing previous studies including individual subject data, Ramus et al. (2003) concluded that 39% of individuals with dyslexia also displayed an auditory deficit. But, even though auditory impairments are often observed in individuals with DD, they are not present in every individual with a clinical diagnosis of DD. Due to the lack of auditory processing impairment in some individuals with DD it has been argued that the auditory processing deficits cannot be causal to the disability itself (White et al. 2006). These and similar findings have driven the idea of different subtypes of DD (e.g., Heim et al. 2008), covering the wide range of individuals with and without auditory processing difficulties or similar sensorimotor challenges. Our results may be interpreted as evidence for the presence of neuronal deficits of rapid auditory and PP in prereading children at risk for DD and may suggest a connection of these. However, without a continuing investigation using longitudinal designs, it cannot yet answer the question about the causality of either one of these deficits in shaping the development in reading failure.

By investigating young children with a familial risk for DD, our study results offer a chance to better understand neural premarkers of DD. To date, there is a line of research investigating early neuroimaging markers of later reading ability. Most of this research derives from electrophysiological studies, using event-related potential measures to improve our understanding of reading development (e.g., Molfese, Molfese and Modgline 2001; Molfese, Modglin and Molfese 2003; Maurer, Bucher, Brem and Brandeis 2003; Maurer, Bucher, Brem, Benz et al. 2009; Guttorm, Leppanen, Poikkeus et al. 2005; Guttorm, Leppanen, Hamalainen et al. 2010). However, some studies have successfully begun to incorporate the use of (f)MRI for the means of predicting reading outcome in developmental samples with and without familial risk for DD (e.g., Specht et al. 2009; Hoeft et al. 2011). For example, Hoeft et al. (2011) conducted a prospective longitudinal study in older children aged 11–14 years over the course of 2.5 years to examine the potential of fMRI or diffusion tensor imaging to predict reading improvement in DD (Hoeft et al. 2011). Initial evidence suggests that a combination of neurophysiological and behavioral measures may increase the accuracy of prediction over a single measure alone (Maurer et al. 2009; Hoeft et al. 2011). It remains to be investigated, whether the present findings of left prefrontal hypoactivations in prereading children at risk for DD may be used for the early identification of children at risk for DD and whether prereading children may already benefit from remediation as shown in 10-year-old children (Gaab, Gabrieli, Deutsch et al. 2007). An early identification of children at risk for developmental disabilities, such as DD, is crucial for the development, evaluation, and implementation of early remediation programs. Overall, an early identification and remediation of reading disabilities may reduce social, psychological, and clinical challenges associated with the progress of developmental disabilities (McNorgan et al. 2011).

Even though our data are evidence for the presence of neuronal deficits of rapid auditory and PP in prereading children at risk for DD and suggest a connection of these, there are some important limitations to note. It has been reported that 30–64% of children with a parent or first-degree relative with reading difficulties will develop difficulties themselves (Gilger et al. 1992; Schulte-Korne et al. 1996; Pennington and Lefly 2001). We cannot be certain about whom exactly or how many participants, will develop a reading disability ultimately and/or receive a clinical diagnosis of DD. Follow-up and large-scale longitudinal studies will be required to assess these questions further. However, findings of various neuronal and behavioral alterations in children with a familial risk for DD compared with typically developing controls fit the idea of a more comprehensive model of DD (e.g., Goswami 2011). Another potential caveat is the fact that previous studies indicate that not all individuals with DD do present difficulties in RAP (Ramus 2003; Gibson et al. 2006; Georgiou et al. 2010; Willburger and Landerl 2010). Longitudinal designs and follow-up assessments on the children tested here may shed more light on these questions.

Furthermore, it is important to note that our results may have been influenced by environmental variables such as home literacy or socioeconomic status. Although there are no significant differences observed in these variables between the groups in our current sample, there are some marginal trends suggesting for instance that the quality of the home literacy environment in the FHD− group may be slightly better than in the FHD+ group. It remains unclear whether this has any influence on brain activation in the key regions observed in the current study but future studies need to investigate the relationship between environmental variables important for reading development and neural deficits characteristic for DD.

Conclusion

In this article, we demonstrate differences in rapid auditory and PP in prereading children with, compared with without, a familial risk of DD and offer initial evidence for a potential link between rapid auditory and PP skills prior to reading acquisition. The current study is a first step toward broadening our knowledge about the neural phenotype, and thus core characteristics, of preliterate children at risk for DD. Future studies employing longitudinal designs should be used to investigate the developmental trajectories of the neural disruption in DD and to determine whether these markers may be used for early identification of children at risk for DD. The identification of very young children and/or infants at risk for reading disability coupled with the onset of early remediation

may induce more beneficial maturational trajectories (Dekker and Karmiloff-Smith 2011).

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/.

Funding

This work was supported by the Eunice Kennedy Shriver National Institute of Child Health & Human Development (1R01HD065762-01/02 to N.G.); Charles H. Hood Foundation (to N.G.); Boston Children's Hospital Pilot Grant (to N.G.); the Swiss National Foundation (to N.M.R); and the Janggen-Pöhn Stiftung (to N.M.R.).

Notes

We thank all participating families. *Conflict of Interest*: None declared.

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