Reduced Learning of Sound Categories in Dyslexia Is Associated with Reduced Regularity-Induced Auditory Cortex Adaptation

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A main characteristic of dyslexia is poor use of sound categories. We now studied within-session learning of new sound categories in dyslexia, behaviorally and neurally, using fMRI. Human participants (males and females) with and without dyslexia were asked to discriminate which of two serially-presented tones had a higher pitch. The task was administered in two protocols, with and without a repeated reference frequency. The reference condition introduces regularity, and enhances frequency sensitivity in typically developing (TD) individuals. Enhanced sensitivity facilitates the formation of “high” and “low” pitch categories above and below this reference, respectively. We found that in TDs, learning was paralleled by a gradual decrease in activation of the primary auditory cortex (PAC), and reduced activation of the superior temporal gyrus (STG) and left posterior parietal cortex (PPC), which are important for using sensory history. No such sensitivity was found among individuals with dyslexia (IDDs). Rather, IDDs showed reduced behavioral learning of stimulus regularities and no regularity-associated adaptation in the auditory cortex or in higher-level regions. We propose that IDDs’ reduced cortical adaptation, associated with reduced behavioral learning of sound regularities, underlies their impoverished use of stimulus history, and consequently impedes their formation of rich sound categories.

Key words: auditory cortex; dyslexia; frequency discrimination; perceptual learning; statistical regularities

Significance Statement

Reading difficulties in dyslexia are often attributed to poor use of phonological categories. To test whether poor category use could result from poor learning of new sound categories in general, we administered an auditory discrimination task that examined the learning of new pitch categories above and below a repeated reference sound. Individuals with dyslexia (IDDs) learned categories slower than typically developing (TD) individuals. TD individuals showed adaptation to the repeated sounds that paralleled the category learning in their primary auditory cortex (PAC) and other higher-level regions. In dyslexia, no brain region showed such adaptation. We suggest that poor learning of sound statistics in sensory regions may underlie the poor representations of both speech and nonspeech categories in dyslexia.

Introduction

Developmental dyslexia is defined as a persistent impairment in acquiring reading skills, which is not accounted for by low IQ, a lack of educational opportunities, or acquired brain damage (World Health Organization, 2008). In addition to reading difficulties, individuals with dyslexia (IDDs) commonly have difficulties in phonological awareness and verbal short-term memory (Vellutino et al., 2004). In addition, IDDs often perform more poorly in nonlinguistic perceptual tasks (Ahissar et al., 2000; Ramus et al., 2003; Sperling et al., 2005).

The “anchoring deficit” hypothesis (Ahissar et al., 2006; Ahissar, 2007) posits that IDDs’ difficulties result from poorer use of stimulus regularities. This hypothesis was initially based on the observation that in both two-tone frequency discrimination and speech perception, introducing simple regularities through repeated sounds was less beneficial to IDDs than to typically developing (TD) individuals. Subsequent studies showed that IDDs’ advantage from regularity within short (~1–3 s) intervals was adequate, yet it decayed more quickly than TDs’ (Jaffe-Dax et al., 2017; Lieder et al., 2019). Related work showed that IDDs’ impaired use of regularities applies to both structured
(repeated stimulus structure, as in morphology) and unstructured (stimulus prevalence) repetitions, in both linguistic (Kimel and Ahissar, 2020) and nonlinguistic (Daikhin et al., 2017) contexts. IDDs’ faster decay of benefits from regularities is expected to yield poorer acquisition of categorical representations (Banai and Ahissar, 2018), as observed in several studies (Chandrasekaran et al., 2009; Perrachione et al., 2011; Jones et al., 2018).

The neural mechanism underlying impoverished categorical representations of sounds in IDDs is not well-understood. The auditory cortex has been studied extensively in works exploring the adequacy of phonological representations in IDDs, with mixed results. Using fMRI, Boets et al. (2013) found adequate bilateral phonological representations in IDDs’ auditory cortices. They suggested that the phonological difficulties stem from poor connectivity between the posterior and frontal regions (the “connectivity hypothesis”; Boets, 2014; Ramus, 2014). By contrast, Perrachione et al. (2016) found reduced adaptation (i.e., repetition-induced reduction in activation) to the repetition of visual and auditory stimuli in stimulus-specific cortical areas. Jaffe-Dax et al. (2018) characterized the dynamics of adaptation to tones in IDDs and found shorter adaptation compared with TDs in the left primary auditory cortex (PAC), the left superior temporal cortex, and the right insular cortex. A similar general tendency was found in all activated regions. MEG studies that have tested adaptation to word and pseudo-word repetitions also reported weaker reductions in the bilateral temporal regions of IDDs (Helenius et al., 2009), and in left temporal areas of children at risk for dyslexia (Nora et al., 2021). This was interpreted as indicating impaired short-term maintenance of phonological representations in the left hemisphere of IDDs.

Here, we ask whether IDDs’ atypical adaptation in the auditory cortex is associated with, and perhaps underlies, poorer learning of stimulus regularities, as suggested by the anchoring hypothesis. We used frequency discrimination with and without learning of stimulus regularities, as suggested by the anchoring hypothesis. We hypothesized that TDs would benefit more from the regularity than IDDs. Assuming an association between reduced benefits from regularity and reduced stimulus-specific adaptation (Lu et al., 1992; Jaffe-Dax et al., 2017), we further hypothesized that TDs would show larger adaptation in the reference condition compared with IDDs, and that the dynamics of neural adaptation would parallel behavioral improvement.

**Materials and Methods**

**Participants**

Forty-three native Hebrew speakers (23 IDDs and 20 TDs) were recruited through ads posted at the Hebrew University of Jerusalem and several other colleges in Jerusalem. The sample size was determined based on a previous behavioral study, in which an effect size of $d \approx 1$ was found between TDs and IDDs in an auditory discrimination task with a reference protocol similar to that used here (Oganian and Ahissar, 2012). To detect an effect of this size with a power of 80%, ~20 participants in each group are needed. We did not have a specific prediction for the neural effect size, but previous studies which tested the specificity (Perrachione et al., 2016) and dynamics (Jaffe-Dax et al., 2018) of neural adaptation in adult TDs and IDDs assessed ~20 participants in each group and found significant group differences. Hence, we assumed that this sample size would be sufficient here as well. Participants were asked to complete a questionnaire on their learning and reading background (including previous diagnoses), musical background, and medical conditions, if any. The initial exclusion criteria were hearing problems, psychiatric medications other than attention deficit medication, and musical background exceeding two years of playing an instrument (i.e., minimal, since pitch sensitivity is known to increase with musical training; Michely et al., 2006; Parbery-Clark et al., 2011; Oganian and Ahissar, 2012). IDDs were included if they were diagnosed by authorized clinicians as having a specific reading disability, and TDs were included based on a self-reported history of no reading or learning difficulties. Participants who met these criteria were invited to an initial screening session to evaluate their reading, working memory, and nonverbal reasoning skills (described below). The group means are shown in Table 1 and individual data are shown in Figure 1. All remaining participants passed our inclusion criteria: (1) They scored at least 10 in the Block Design task (the Hebrew version of WAIS-III; Wechsler, 1997), which measures visuo-spatial reasoning skills, indicating that their reading disability was specific. (2) Their reading related skills matched the expected from their group according to the reading-evaluation $z$ score calculated for each participant. This score was the mean of the pseudo-word and paragraph reading, spelling, and spoonerism (all measures were normalized based on TD performance). F = female participants; WAIS = Wechsler adult intelligence scale; ns = not statistically significant, **p < 0.01, ***p < 0.001 in a Mann–Whitney U test between the groups. For individual data, see Figure 1.

**Table 1. Scores in cognitive assessments**

<table>
<thead>
<tr>
<th>Score</th>
<th>TDs (mean (SD))</th>
<th>IDDs (mean (SD))</th>
<th>Group difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>27.3 (4.3)</td>
<td>26.4 (4.6)</td>
<td>0.21, ns</td>
</tr>
<tr>
<td>General cognitive tests</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(scaled WAIS score)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Block design</td>
<td>14.1 (2.1)</td>
<td>14 (2.1)</td>
<td>0.04, ns</td>
</tr>
<tr>
<td>Digit span</td>
<td>11.3 (3)</td>
<td>7.7 (2.4)</td>
<td>0.68***</td>
</tr>
<tr>
<td>Reading rate (items/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pseudo-word reading rate</td>
<td>70.6 (22)</td>
<td>30.1 (10.7)</td>
<td>0.89***</td>
</tr>
<tr>
<td>Paragraph reading rate</td>
<td>147.1 (19.4)</td>
<td>94.5 (19.5)</td>
<td>0.96***</td>
</tr>
<tr>
<td>Reading accuracy (% correct)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pseudo-word reading accuracy</td>
<td>90.2 (12)</td>
<td>64.1 (14.3)</td>
<td>0.87***</td>
</tr>
<tr>
<td>Paragraph reading accuracy</td>
<td>98.1 (1.6)</td>
<td>95 (2.3)</td>
<td>0.73***</td>
</tr>
<tr>
<td>Phonological awareness</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Spoonerism rate (items/min)</td>
<td>11.2 (4.3)</td>
<td>5.3 (1.58)</td>
<td>0.93***</td>
</tr>
<tr>
<td>Spoonerism accuracy (% correct)</td>
<td>90 (8.1)</td>
<td>74.1 (18)</td>
<td>0.62***</td>
</tr>
<tr>
<td>Spelling</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Spelling rate (items/min)</td>
<td>84.4 (12.2)</td>
<td>41.3 (15.8)</td>
<td>0.95***</td>
</tr>
<tr>
<td>Spelling accuracy (% correct)</td>
<td>99.8 (0.9)</td>
<td>95.6 (7.6)</td>
<td>0.44***</td>
</tr>
<tr>
<td>Summary $z$ score</td>
<td>0 (0.6)</td>
<td>-2.63 (1.8)</td>
<td>1***</td>
</tr>
</tbody>
</table>

**Table 1. Scores in cognitive assessments**

Mean, SD and Cliff’s $\delta$ for the measures of cognitive skills after excluding the two IDDs who performed poorly in two-tone discrimination. Cliff’s $\delta$ is a nonparametric effect size of the overlap between two sample distributions, which ranges (in absolute value) from 0 (stochastic equality) to 1 (nonoverlapping distributions). The summary $z$ score is the mean $z$ score of accuracy and rate of pseudo-word and paragraph reading, spelling, and spoonerism (all measures were normalized based on TD performance). F = female participants; WAIS = Wechsler adult intelligence scale; ns = not statistically significant, **p < 0.01, ***p < 0.001 in a Mann–Whitney U test between the groups. For individual data, see Figure 1.
Committee of the Psychology Department of the Hebrew University and the Helsinki Ethics Committee of Hadassah Hospital, Jerusalem, Israel.

Cognitive assessments in the screening session
1. Nonverbal reasoning was measured with the Block Design visuospatial reasoning task (the Hebrew version of WAIS-III; Wechsler, 1997).
2. Short-term verbal memory was measured using the standard Digit Span task, consisting of the Digit Forward and Backward subtests (the Hebrew version of WAIS-III; Wechsler, 1997).
3. Phonological decoding was assessed using a list of 24 pseudo-words in Hebrew characters with diacritics (Deutsch and Bentin, 1996). Participants were instructed to read the words aloud, as quickly and accurately as possible.
4. Fluent reading was assessed by reading a four-paragraph academic-level text (adapted from Ben-Yehudah et al., 2001). Participants were instructed to read the text aloud, as quickly and accurately as possible, but slow enough to be able to answer a simple content question at the end.
5. Phonological awareness was assessed using the spoonerism task, in which participants heard 20 two-word expressions in Hebrew, and were asked to repeat them vocally (Ben-Yehudah et al., 2001; Ben-Yehudah and Ahissar, 2004).
6. Spelling skills were measured with a task in which participants were presented with 26 written word pairs, each composed of a real word and a homophone that contains a spelling error (Ben-Yehudah et al., 2001). Participants were requested to mark the correctly spelled word as quickly as possible.

In all phonological and reading tasks, both accuracy and rate were scored. The groups differed significantly in all reading, spelling, and phonological tasks and in the Digit Span task (Gallagher et al., 2000). Yet, there was no difference in age or nonverbal reasoning skills (Table 1).

Experimental procedure
The two-tone frequency discrimination procedure was based on the protocol administered by Daikhin and Ahissar (2015), with changes to the frequency differences, so that the two conditions (described below) would yield similar performance levels in the TD group. Participants were presented with pairs of pure tones at a comfortable intensity level, and were asked to decide which tone was higher by pressing one of two buttons on a response device. All participants, including the two who were left-handed, were asked to respond with their right hand. All trials had the following temporal sequence: each trial began with 120 ms of silence followed by a 50-ms-long tone, a silent interval of 530 ms, and then a second 50-ms tone. Each trial was 2000 ms long, leaving the participants 1250 ms to respond after the second tone. This limit is much longer than the mean reaction time (RT) of ~500 ± 20 ms previously reported in this task (Daikhin and Ahissar, 2015). No feedback was given. Two experimental conditions were used: (1) a no-reference condition, in which no tone was consistently repeated between consecutive trials. The first tone was chosen from a frequency range of 800–1250 Hz, and the second tone was chosen according to the sequence of frequency differences (Fig. 2, black line); (2) a reference condition, in which the first tone was always 1000 Hz, and the second tone was chosen according to the reference condition (Fig. 2, gray line). These sequences were the mean of adaptive protocols, designed to converge at 80% correct, administered as a pilot to an unrelated group of TDs. As in Daikhin and Ahissar (2015), we aimed to match the level of difficulty of the two conditions. However, since the participants in that study performed the reference condition with greater success compared with the no-reference condition, we administered another pilot in which similar accuracy was achieved in the two conditions. The resulting sequences began with initially large (50%) frequency differences, which gradually decreased, reaching ~11% in the no-reference condition and ~2.5% in the reference condition (in Daikhin and Ahissar, the tone differences reached ~17% in the no-reference condition and ~5% in the reference condition). The stimulus sequences presented to the two groups were the same and were not adaptive on an individual basis. The aimed level of difficulty was such that TDs’ expected accuracy would be similar in the two conditions. The choice of same stimuli for TDs and IDDs despite the expected differences in accuracy was designed to ensure that any BOLD differences were not the direct result of acoustic differences.

A single fMRI run was administered, which contained 15 blocks of each condition. Each block consisted of 12 trials, yielding 180 trials per
condition. Three blocks of the same condition (trials) were presented sequentially, followed by a trial of the other condition, in an interleaved manner. The condition presented first (reference or no-reference) was counterbalanced across participants. The run began with a 30-s rest period, followed by 24× blocks with a rest period of 12 s between blocks. Before entering the scanner, participants completed a short version of the behavioral protocol that they subsequently performed during scanning. Participants were asked to keep their eyes closed throughout the run. The experiment was programmed and administered using E-prime 2.0 (Schneider et al., 2012). The stimuli were presented via MRI-compatible insert earphones (Sensimetrics S14). RT and accuracy were measured while the participants performed the task.

Behavioral data analysis
All statistical analyses were performed using R version 4.0.2 (R Core Team, 2020). Nonparametric two-tailed tests were used to test within-group (Wilcoxon signed ranks test) and between group (Mann–Whitney U test) differences in accuracy and RT. Trials without a recorded response were considered incorrect trials for the analysis of accuracy, and were removed from the RT analysis. RT was analyzed separately for correct and incorrect responses.

Since the frequency differences were larger in the no-reference condition, comparing mean accuracies between these conditions does not reflect the benefits of using a reference. Accuracy in the physically more difficult reference condition can be lower than in the no-reference condition even when sensitivity is enhanced by the reference. To compare frequency sensitivities in each of the two conditions between groups, we therefore modeled participants’ responses to the two experimental conditions, the no-reference and reference; i.e., the frequency difference in each trial and its effect on the binary response, while accounting for the fact that trials were nested within participants, using random effects for participants. To this end, we modeled the percent frequency difference, the condition (reference or no-reference), the group (TD or IDD), and all the interactions between these predictors as fixed effects. As random effects, we included a by-participant random intercept and random slopes for frequency difference, condition and the interaction between them. To examine the evolution of the effect during the course of the experiment, we ran the same model separately for the initial (first trial) and subsequent (trials 2–5) stages of each condition in the experiment, as well as an additional model on all the trials which extended the original one by adding the stage of the experiment and all relevant interactions as fixed effects. In all models, the random effects were chosen according to the maximal random structure that converged and was justified by the design (Barr et al., 2013). Trials without a response were removed from this analysis. Frequency differences were scaled and centered before they were entered into the models. Categorical variables were deviation-coded. This modeling allowed us to calculate the significance of the fixed effects and their interaction.

In order to visualize the individual interaction effects between frequency difference and condition in both analyses, we ran similar models without the fixed effects of group and experimental stage, for all the trials, and then separately for the first trial and for trials 2–5 in each condition, and extracted the unscaled and exponentiated random slopes of the interaction between frequency difference and condition.

fMRI data acquisition
Scanning was performed using a 3-T scanner (Magneto Skyra, Siemens) and a 32-channel head coil, at the ELSC Neuroimaging Unit (ENU). At the beginning of the scan session, high-resolution T1-weighted magnetization-prepared rapid acquisition gradient-echo (MPRAGE) images were acquired (1×1×1 mm resolution), followed by functional scans. Functional T2*-weighted MRI protocols were based on a multislice gradient echoplanar imaging (multiband parallel imaging with acceleration factor 3; Moeller et al., 2010). Scanning parameters were: TR = 1.2 s, TE = 30 ms, voxel resolution: 3×3×3 mm, flip angle: 8°, field of view = 192 mm, and acceleration factor = 3. Whole-brain coverage for the functional data were obtained using 51 slices with a thickness of 3 mm. A total of 925 functional volumes were acquired. The functional scanning was oriented according to the AC-PC plane.

fMRI data analysis
Preprocessing
The quality of the functional images was assessed using MRIQC (v0.15.2;rc1; Esteban et al., 2017). MRIQC extracts image quality metrics (IQMs) and generates visual reports at the individual and group level. Data from one IDD were marked as an outlier because of high movement, and this participant was excluded from further analyses (mean framewise displacement of 0.39 mm, exceeding 2.5 SDs from the mean across all participants; see detailed explanation of this measurement of head motion below). After removing this dataset, there was no significant difference between the groups in mean framewise displacement (TDs: mean ± SD = 0.17 ± 0.06 mm; IDDs: mean ± SD = 0.18 ± 0.05 mm, t(38) = −0.72, p = 0.48), nor in other IQMs, such as dvars_std, aor, aqi, and smr. See the MRIQC documentation for information about these IQMs.

The imaging data were preprocessed and analyzed using SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/) and MATLAB 2018b. Functional images were realigned to the first scan by rigid body transformations to correct for head motion. Structural T1 images were co-registered to the mean functional images, and then the gray and white matter were segmented from the co-registered T1 images. The resulting parameter maps of the deformation fields were used to normalize the functional and T1 images to the standard anatomic Montreal Neurologic Institute (MNI) template using the original voxel size resolution. Finally, the functional data were smoothed with an 8-mm full-width at half-maxima (FWHM) Gaussian kernel.

For the first level analysis, individual contrast images were estimated for each participant using a general linear model (GLM). A hemodynamic response function (HRF) with a time to response peak of 5 s and a time to undershoot peak of 15 s was chosen to model the BOLD response, to match the default parameters in the BrainVoyager QX program used by Daikhin and Ahissar (2015). To assess the differential response to the two experimental conditions, the no-reference and reference conditions were first modeled as regressors of interest, and the rest periods were modeled implicitly as a silent baseline. The data were later remodeled to test for changes during the course of the experiment, with a different regressor for the first trial and for trials 2–5 in each condition.
condition, thus resulting in four regressors of interest. Another modeling was conducted to test within-triad changes in each condition, with a different regressor for each of the three blocks within a triad in each of the two conditions, resulting in six regressors of interest. In all the analyses, a high-pass filter of 128 s was implemented and the six realignment parameters were used as nuisance regressors. To further account for head motion, realignment estimates were used to calculate framewise displacement (FD) for each volume. FD was computed for each volume as the sum of the absolute values of the derivatives of the six realignment parameters (Power et al., 2012). Volumes with FD > 0.9 mm were censored and excluded from further analysis by including a regressor of no interest for each censored volume (Siegel et al., 2014). The average percent of censored volumes (out of 925 total volumes) was small in both groups (TDs: mean ± SD = 0.42 ± 0.72%; IDDs: mean ± SD = 1.14 ± 1.86%), and the group difference was not significant (Mann–Whitney U test: U = 150, p = 0.17). Contrast images were created for the comparison between the two conditions (no-reference minus reference). In addition, to assess sensitivity to regularity across same-type trials, a contrast of the first minus third block in each triad was created for each condition. We also created contrast maps for task-related activity (no-reference plus reference vs implicit baseline) to test for possible differences between the groups.

Region of interest (ROI) analysis
ROI analysis on β estimates was conducted using the marshall toolbox for SPM (Brett et al., 2002). Mean contrast estimates of interest were extracted from an ROI of the PAC in each hemisphere. This ROI was a combination of subregions TE1.1, TE1.0, and TE1.2 in Heschl’s gyrus (HG) based on human postmortem histology (Morosan et al., 2001), published as three ROIs in MNI coordinates (Norman-Haignere et al., 2013). These three subregions comprised our PAC ROI in each hemisphere. We used a Wilcoxon signed ranks test on the contrast values of each ROI to examine within-group effects, and a Mann–Whitney U test to test the differences between the groups, all two-tailed.

To identify the temporal dynamics of the response, we extracted the average time courses of the normalized BOLD signal from the ROI in each hemisphere. We used the first-level procedure described above, with the same high-pass filter and nuisance regressors, but without a regressor of interest and without serial correlation. Temporal residuals were unscaled and spatially averaged across each ROI. For each experimental block, a window of 32 time points was extracted, starting two TRs before block onset and ending 10 TRs after the end of the block. In order to normalize the signal, we subtracted from each time course the mean value of TRs – 2, –1, and 0 of the block, divided each time point by this mean, and then multiplied by 100. The resulting time course was averaged once over all blocks of the same condition (for the condition analysis) and once over all blocks of the relative position in triads of the same condition. Statistical analysis of differences between conditions was performed using cluster-based permutation tests (Maris and Oostenveld, 2007) implemented in the permute function for MATLAB (Gerber, 2021). To identify significant clusters, paired t tests were calculated at each time point with a statistical threshold of p < 0.05, two-tailed. The sum of the t-scores in each cluster of significant time points was compared with those obtained over 10,000 permutations. A p-value of 0.05 was then used to determine the significant clusters.

Whole-brain analysis
In addition to the hypothesis-driven ROI approach, we conducted an exploratory whole-brain analysis. Individual contrast images were entered into a one-sample t test separately for TDs and IDDs. In addition, a two-sample t test was conducted to obtain a group comparison (TDs vs IDDs) on the contrast values.

The individual mean FD was controlled as a covariate in all the second-level whole-brain analyses. The results were corrected for multiple comparisons using a cluster size limitation with an initial threshold of p < 0.001 in the within-group analyses and p < 0.005 in the between-group analyses, and a minimal cluster size which was calculated in SPM12 based on a 0.05 FWE-correction. Individual contrast estimates, used for illustrative purposes, were extracted using marshall from each cluster identified in the whole-brain analyses, and averaged across the cluster voxels. To label the brain areas, we used the Anatomical Automatic Labeling (AAL) atlas in SPM12 (Tzourio-Mazoyer et al., 2002).

Results
Behavioral results
TDs benefit more than IDDs from stimulus regularity
The overall accuracy of TDs (mean ± SD = 84.6 ± 11%) was significantly higher than that of IDDs (mean ± SD = 75.5 ± 9.5%; Mann–Whitney U test: U = 316, p = 0.006), in line with previous studies (Oganian and Ahissar, 2012). Importantly, the pattern of performance in the two conditions differed between the two groups (Fig. 3). TDs benefited more than IDDs from the reference-containing condition. Both groups performed the no-reference better than the reference condition (TDs: mean ± SD = 86.6 ± 9.8% vs 82.6 ± 12.1%, Wilcoxon signed ranks test: z = 2.31, p = 0.02; IDDs: mean ± SD = 80.4 ± 7.9% vs 70.6 ± 8.6%, Wilcoxon signed ranks test: z = 3.29, p = 0.001; Fig. 3A), which had a substantially smaller frequency difference between the tones in each trial (see Materials and Methods). However, the difference in accuracy between the two conditions was significantly larger in the dyslexia group (a significant condition × group interaction, Mann–Whitney U test on the differences: U = 127, p = 0.031).

Because of the smaller absolute frequency differences between the tones in the reference condition, performance accuracy does not directly reveal frequency sensitivity. To calculate sensitivity, we used a mixed-effects logistic regression model on the categorical response in each trial (for a full description of the model, see Materials and Methods). As expected, there was a significant interaction between frequency difference, condition and group
Based on previous findings relating neural differences between groups (Mann–Whitney U = 3.51, p = 0.015). As shown in Figure 3B, this interaction indicates that TDs’ reference-related enhancement of frequency sensitivity was significantly larger than IDDs’. Participants’ frequency sensitivity was defined as the increase in the odds of responding that the second tone was higher per unit increase in frequency difference (second tone minus the first). Each dot in Figure 3B denotes the ratio of the frequency sensitivity in the reference condition to that in the no-reference condition of a single participant; 1 indicates no difference in sensitivity, and values larger than 1 indicate increased sensitivity in the reference condition. Most participants in both groups benefitted from the reference condition (TDs: mean ± SD = 1.67 ± 0.52; IDDs: mean ± SD = 1.24 ± 0.17), as manifested in the significant interaction between frequency difference and condition (β = −2.12, z = −8.76, p < 0.001). Interestingly, the variability of condition enhancement in the dyslexia group was substantially smaller, reflecting the finding that none of the IDDs derived large benefits from the reference condition, whereas in TDs, the magnitude of benefits was quite variable. As expected, there was a significant effect for frequency difference (β = 4.06, z = 12.97, p < 0.001; the effect of the magnitude and direction of the difference between tones on responses) and for the interaction between frequency difference and group (β = 1.18, z = 3.77, p < 0.001; better sensitivity of TDs across conditions).

Participants were not asked to be quick, and the RTs did not differ significantly between the two groups either for correct (TDs: mean ± SD = 506 ± 82 ms; IDDs: mean ± SD = 531 ± 74 ms; Mann–Whitney U test: U = 168, p = 0.279) or incorrect responses (TDs: mean ± SD = 617 ± 84 ms; IDDs: mean ± SD = 598 ± 94 ms; Mann–Whitney U test: U = 253, p = 0.268). The percentage of trials without a response was small in both groups (TDs: mean ± SD = 2.97 ± 4.23%; IDDs: mean ± SD = 4.1 ± 6.17%) and did not differ significantly between groups (Mann–Whitney U test: U = 165.5, p = 0.249).

Imaging results

In dyslexia, the PAC showed regularity-induced adaptation Based on previous findings relating neural differences between individuals with and without dyslexia to stimulus-specific sensory areas (Perrachione et al., 2016; Jaffe-Dax et al., 2018), we conducted an ROI analysis of the no-reference minus reference contrast of β estimates on bilateral ROIs of the PAC (Fig. 4A) asking whether we could detect group differences as early as the PAC. For TDs, greater activity in the no-reference compared with the reference condition was found in both the right (mean contrast ± SD = 0.22 ± 0.21, Wilcoxon signed ranks test: z = 3.51, p < 0.001) and the left PAC (mean contrast ± SD = 0.2 ± 0.23, Wilcoxon signed ranks test: z = 3.06, p = 0.001; Fig. 4B). No significant difference between conditions was found for the dyslexia group in either ROI (mean contrast ± SD right = 0.03 ± 0.23, Wilcoxon signed ranks test: z = 1.12, p = 0.277; mean contrast ± SD left = 0.03 ± 0.22, Wilcoxon signed ranks test: z = 0.71, p = 0.498). Importantly, there was a significant difference between the contrast β estimates of the two groups in the right PAC (Mann–Whitney U test: U = 289, p = 0.015). The same trend was observed in the left PAC, but was only marginally significant (Mann–Whitney U test: U = 269, p = 0.06).

The above observation of a group difference in PAC sensitivity to regularity was based on preprocessing with standard 8-mm FWHM smoothing. Since such smoothing might have led to apparent PAC sensitivity which actually stemmed from neighboring auditory regions, we repeated this analysis with a smaller smoothing kernel of 4 mm. We found very similar results, with the same significant effects, suggesting a genuine reduction in PAC sensitivity in dyslexia. This observation does not mean that this reduction applied to all TD participants, or that it was specific to the PAC, as detailed below (see the section “Whole-brain analyses of sensitivity to regularity revealed different patterns of activity in TDs and IDDs”).

The difference between TDs and IDDs in β estimates stemmed from reduced activation in the reference condition (adaptation) in TDs, which was evident in the right PAC throughout most of the experimental block (TRs 6–19 and 21–26; Fig. 4D). In the left PAC, the difference only reached significance in a cluster at the beginning of the block, around the peak responses (TRs 6–10; Fig. 4C), IDDs showed similar response magnitudes in the two conditions throughout the block (Fig. 4C D).

Behaviorally, the reference condition was especially difficult for IDDs (Fig. 3). Therefore, our observation of no regularity-induced adaptation in their PAC might have resulted from their additional effort, which increased their BOLD signal, and consequently masked their adaptation. To test this alternative (adaptation + effort) account, we compared only the subgroup of TDs whose performance in the reference condition was similar to that of IDDs, by performing a median split analysis on the TD group, based on their accuracy in the reference condition. This split resulted in two subgroups: 10 participants with accuracy below the median (poor performers of the reference condition) and 10 participants with accuracy above the median (good performers; Fig. 5A). Accuracy in the reference condition of the TD poor performers did not differ from that of IDDs (TD poor performers: mean ± SD = 72.11 ± 7.17%; IDDs: mean ± SD = 70.63 ± 8.57%; Mann–Whitney U test: U = 114, p = 0.72). Nevertheless, the average no-reference minus reference contrast was very similar in the two TD subgroups, both in the right ROI (TD poor performers: mean ± SD = 0.24 ± 0.26; TD good performers: mean ± SD = 0.2 ± 0.16; Mann–Whitney U test: U = 51, p = 0.97) and in the left ROI (TD poor performers: mean ± SD = 0.19 ± 0.28; TD good performers: mean ± SD = 0.19 ± 0.17; Mann–Whitney U test: U = 53, p = 0.85; Fig. 5B). Despite having only 10 participants in each TD subgroup, in the right ROI, there was still significantly greater activity in the no-reference than in the reference condition of both poor (Wilcoxon signed ranks test: z = 2.4, p = 0.014) and good TD performers (Wilcoxon signed ranks test: z = 2.6, p = 0.006). The difference in contrast values between TDs and IDDs in the right ROI was significant for good performers (Mann–Whitney U test: U = 148, p = 0.035), and marginally significant for poor performers (Mann–Whitney U test: U = 141, p = 0.074). In the left ROI, it was marginally significant for good performers (Mann–Whitney U test: U = 144, p = 0.055), and not significant for poor performers (Mann–Whitney U test: U = 126, p = 0.267). Overall, this control analysis demonstrated that the neural effect was a robust property of TDs, found across participants with various levels of accuracy. The cross-participant consistency in TDs’ regularity-induced adaptation thus rules out behavioral difficulty as an explanatory variable, and suggests that the observed difference in neural adaptation may have been indicative of a basic mechanistic, neural difference between the groups rather than a manifestation of behavioral differences whose neural source is elsewhere.

Together, these results suggest that the detection of the reference tone in TDs was associated with adaptation in the PAC, an effect that was more robust in the right hemisphere, perhaps because of its predominance in sensitivity to pitch (Hyde et al.,
In line with the reduced behavioral benefit in IDDs, auditory areas were similarly active with and without a reference tone.

Parallel behavioral learning and adaptation across triads in the primary auditory ROI

If the group difference in the PAC was related to the behavioral difference between TDs and IDDs in detection of regularity, we should see the two effects evolve simultaneously. To test this supposition, we used the fact that the pattern of regularity introduced in the experiment was new to our participants. It takes several trials for TD participants to implicitly detect and behaviorally benefit from the reference tone (Nahum et al., 2010). Therefore, we did not expect to see either a behavioral or a neural difference between the groups at the beginning of the experiment. In order to have enough data for a reliable estimation of the effect, we considered the first three consecutive blocks (triad) in each condition as representing the beginning of the experiment, and compared both behavior and the BOLD response in these triads to the remaining triads of the experiment (triads 2–5 in each condition).

To test the behavioral effect of learning, we again used a mixed-effects logistic regression model, with the addition of a
Figure 5. A median split of the TD group, based on accuracy in the reference condition, shows similar regularity-induced adaptation in the two subgroups. A, Distribution of behavioral accuracy in the reference condition among TDs (blue) and IDDs (red). TDs with accuracy above the median (good performers, N = 10) are denoted by squares and TDs with lower accuracy (poor performers, N = 10) are denoted by triangles. Note that the differences in minus reference contrast in the left and right ROIs of TDs (in blue, contrast for the first triad and triads 2–5 in the left and right ROIs of TDs (in red, N = 20) and IDDs (in red, N = 20). As in A, good TD performers are denoted by squares and poorer performers are denoted by triangles. Note that the differences in $\beta$ values of the two TD subgroups are similar. Data points are the same as those shown in Figure 4B. Values were jittered horizontally for display purposes. Horizontal lines denote the means. Error bars denote the SEM.

Figure 6. Behavioral learning of the reference between the first and subsequent trials is evident both behaviorally and in regularity-induced adaptation in the PAC. A, Mean differences in (exponentiated) random slopes of the interaction between frequency sensitivity and condition in the behavior of TDs (in blue, N = 20) and IDDs (in red, N = 20) in the first triad and triads 2–5. Error bars denote the SEM. The group $\times$ experimental stage $\times$ condition $\times$ frequency difference interaction was significant ($p < 0.001$), reflecting a larger increase in frequency sensitivity because of the introduction of the reference from the first triad to triads 2–5 in TDs compared with IDDs. B, Mean differences in $\beta$ values for the no-reference minus reference contrast in the left and right PAC ROIs of TDs (in blue, N = 20) and IDDs (in red, N = 20). As in A, good TD performers are denoted by squares and poorer performers are denoted by triangles. Note that the differences in $\beta$ values of the two TD subgroups are similar. Data points are the same as those shown in Figure 4B. Values were jittered horizontally for display purposes. Horizontal lines denote the means. Error bars denote the SEM.

To examine whether the neural effect showed similar dynamics, we modeled the fMRI data with separate regressors for the first triad and triads 2–5 in each condition and tested for differences in activity between the two conditions in the PAC (Fig. 6B). A trend similar to the behavioral effect was observed: in both groups, the interference between the two conditions was low and similar in the first triad in both hemispheres. In triads 2–5, the average contrast tended to increase only for TDs (right: mean change $\pm$ SD: 0.23 $\pm$ 0.66, Wilcoxon signed ranks test: $z = 1.72$, $p = 0.09$; left: mean change $\pm$ SD: 0.19 $\pm$ 0.77, Wilcoxon signed ranks test: $z = 1.53$, $p = 0.132$) whereas no positive change was detected for IDDs (right: mean change $\pm$ SD: $-0.1 \pm 0.4$, Wilcoxon signed ranks test: $z = -1.16$, $p = 0.261$; left: mean change $\pm$ SD: $-0.06 \pm 0.43$, Wilcoxon signed ranks test: $z = -0.971$, $p = 0.349$), with the interaction between experimental stage and group nearly reaching significance in a two-tailed test (Mann–Whitney U test on the differences, right: $U = 270$, $p = 0.06$; Left: $U = 272$, $p = 0.052$). These results support the interpretation that the different patterns of adaptation in the auditory cortex of the two groups reflected the different patterns of behavioral learning of the auditory regularity in this task.

Within-triad adaptation in the primary auditory ROI
As a final investigation of the auditory ROI, we tested the changes in brain activity that occurred at shorter time scales within each experimental condition. The experiment was designed with a structure of interleaved triads of blocks; namely, there were three consecutive blocks (triads) of a single condition, followed by three blocks of the other condition, and so forth. However, there was no explicit sign that marked this transition for the participants. Thus, they had to re-adjust to the regularity at the beginning of each reference trial. We hence examined whether this re-learning process would be manifested in the activation of the auditory cortex as adaptation from the first to the third block of each triad (following Daikhin and Ahissar, 2015). We further asked whether such a difference would only be manifested in the TD group. As shown in Figure 7, the BOLD activity revealed a greater reduction in activity in the third block of the reference condition in TDs compared with the three other block types: no-reference first and third and reference first. To test the significance of the effect, we assessed the following contrast: the difference in $\beta$ values between the first and third block in the reference compared with the no-reference condition. There was a significant difference for TDs in both the right (mean contrast $\pm$ SD: 0.25 $\pm$ 0.49, Wilcoxon signed ranks test: $z = 2.13$, $p = 0.032$) and left (mean contrast $\pm$ SD: 0.14 $\pm$ 0.52, Wilcoxon signed ranks test: $z = 1.58$, $p = 0.056$). Figure 7A shows that the activity differences between the first and third block were reduced in IDDs compared with the three other conditions, and were statistically significant in the right (mean contrast $\pm$ SD: 0.25 $\pm$ 0.49, Wilcoxon signed ranks test: $z = 2.13$, $p = 0.032$) and left (mean contrast $\pm$ SD: 0.14 $\pm$ 0.52, Wilcoxon signed ranks test: $z = 1.58$, $p = 0.056$).
and left (mean contrast ± SD: 0.24 ± 0.51, Wilcoxon signed ranks test: z = 2.13, p = 0.033) primary auditory ROIs. This difference was not significant in IDDs (right: mean contrast ± SD: 0.07 ± 0.56, Wilcoxon signed ranks test: z = 0.82, p = 0.43; left: mean contrast ± SD: 0.08 ± 0.57, Wilcoxon signed ranks test: z = 0.635, p = 0.546). The block × condition × group interaction did not reach significance (right: Mann–Whitney U test: U = 237, p = 0.327; left: Mann–Whitney U test: U = 242, p = 0.265). It should be noted that using a different analysis, of the average normalized BOLD time courses (across TRs 0–20 of the block) instead of the β values, this interaction was significant in the right hemisphere (right: Mann–Whitney U test: U = 281,
p = 0.028; left: Mann-Whitney U test: U = 232, p = 0.247). This suggests that there was possibly a group effect here, but it was weak and less reliable. Nevertheless, this analysis showed within-triad, cross-block reference-induced adaptation, only in TDs.

Whole-brain analyses of sensitivity to regularity revealed different patterns of activity in TDs and IDDs

Following the hypothesis-driven analysis of the ROIs in the PAC, we asked whether other brain areas were sensitive to frequency regularities. In addition, having found that the auditory cortex of IDDs did not show adaptation because of frequency regularity, we reasoned that this reduced sensitivity could be associated with broader modifications in the pattern of brain activation, which might be an outcome of the PAC’s reduced sensitivity. Because we had no specific hypothesis as to other regions that could show reduced sensitivity, we conducted an exploratory whole-brain analysis to determine which areas were more highly activated in the no-reference condition, and which were more activated in the reference condition. We examined each group separately and then tested for differences between the two groups.

In TDs, greater activation in the no-reference condition compared with the reference condition was found in four clusters, three of which were located in the lateral temporal lobe. These clusters were composed mostly of the bilateral superior temporal gyrus (STG), extending into the temporal pole (TP), the middle temporal gyrus (MTG), the supramarginal gyrus (SMG) and the Rolandic operculum (ROL), and in the right hemisphere also into HG. A fourth cluster of significant activation was found in a parietal area in the left hemisphere, in voxels which are part of the inferior parietal lobule (IPL), post-central gyrus (PoG), and superior parietal lobule (SPL; Fig. 8A, C; Table 2). There were no areas where the opposite direction of the contrast was significant. Namely, for TDs no region was significantly more highly activated in the reference condition. These results suggest that the adaptation effect that was found in the ROI analysis of TDs’ PAC extends to vast areas in the bilateral STG, and includes left posterior parietal regions. It was suggested that these parietal regions may be associated with the use of stimulus regularities for perceptual judgment in both humans (Daikhin and Ahissar, 2015) and mice (Akrami et al., 2018).

Figure 8. Whole-brain analysis reveals regularity-induced adaptation in TDs’ bilateral STG and left IPL. In IDDs it reveals an increase in activation in the reference compared with the no-reference condition in parts of the DMN. Whole-brain analysis of the contrast between the two conditions. A. Areas that were significantly more active in the no-reference than in the reference condition. Clusters are shown only for TDs (N = 20), since no clusters were found in IDDs. B. Areas that were significantly more active in the reference than in the no-reference condition. Clusters are shown only for IDDs (N = 20), since no clusters were found in TDs. In A, B, significant t values are presented using a red-yellow color scale on 3D renderings of cortical gray matter (Cortex_2044 template in SPM12). The maps were created using an initial cluster-defining threshold of p = 0.001, and a subsequent cluster-size threshold of 104 (in A) and 102 (in B), resulting in 0.05 FWE-corrected clusters. Additional information on the clusters appears in Table 2. C. Individual differences in mean β values for the no-reference minus reference contrast obtained from each cluster in the whole-brain analysis in A. D. Individual differences in mean β values for the no-reference minus reference contrast obtained from each cluster in the whole-brain analysis in B. In C, D, TDs are shown in blue and IDDs in red. Values were jittered horizontally for display purposes. Horizontal lines denote the means. Error bars denote the SEM.
Table 1. Gray matter regions with significant contrasts in the whole-brain analyses

<table>
<thead>
<tr>
<th>Regions</th>
<th>MNI coordinates</th>
<th>Peak z value</th>
<th>Number of voxels</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. TD: no-reference &gt; reference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R superior temporal gyrus, temporal pole (superior temporal gyrus), supramarginal gyrus, Heschl’s gyrus, middle temporal gyrus, Rolandic operculum</td>
<td>$57 - 4 - 7$</td>
<td>4.97</td>
<td>911</td>
</tr>
<tr>
<td>L inferior parietal lobule, postcentral gyrus, superior parietal lobule</td>
<td>$-30 - 37 44$</td>
<td>4.91</td>
<td>222</td>
</tr>
<tr>
<td>L superior temporal gyrus, Rolandic operculum, temporal pole (superior temporal gyrus), middle temporal gyrus</td>
<td>$-60 - 1 - 1$</td>
<td>4.19</td>
<td>108</td>
</tr>
<tr>
<td>L superior temporal gyrus, middle temporal gyrus, supramarginal gyrus</td>
<td>$-63 - 34 8$</td>
<td>3.81</td>
<td>114</td>
</tr>
<tr>
<td>B. Dyslexia: reference &gt; no-reference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L inferior frontal gyrus (orbital part), insula</td>
<td>$-30 26 - 19$</td>
<td>4.24</td>
<td>122</td>
</tr>
<tr>
<td>Bilateral anterior cingulate gyrus, superior frontal gyrus (including medial part)</td>
<td>$-15 59 8$</td>
<td>4.23</td>
<td>394</td>
</tr>
<tr>
<td>L middle temporal gyrus</td>
<td>$-48 - 7 - 19$</td>
<td>3.73</td>
<td>122</td>
</tr>
<tr>
<td>C. TD &gt; dyslexia: no-reference – reference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R superior temporal gyrus, middle temporal gyrus, hippocampus, postcentral gyrus, parahippocampal gyrus, temporal pole (superior temporal gyrus), Rolandic operculum, precentral gyrus, temporal pole (middle temporal gyrus), amygdala, inferior temporal gyrus, supramarginal gyrus, insula</td>
<td>$18 - 16 - 19$</td>
<td>4.52</td>
<td>1332</td>
</tr>
<tr>
<td>L middle temporal gyrus, hippocampus, inferior frontal gyrus (orbital part), lingual gyrus, temporal gyrus (middle temporal and superior temporal gyrus), fusiform gyrus, superior temporal gyrus, amygdala, inferior temporal gyrus, inferior frontal gyrus (triangular part), thalamus</td>
<td>$-54 - 7 - 28$</td>
<td>3.98</td>
<td>940</td>
</tr>
<tr>
<td>Bilateral precuneus, median cingulate and paracingulate gyri, posterior cingulate gyrus, calcarine fissure, cuneus</td>
<td>$-9 - 49 20$</td>
<td>3.55</td>
<td>675</td>
</tr>
</tbody>
</table>

Peak z values and MNI coordinates for the significant clusters (initial threshold $p < 0.001$ in the within-group analyses and $p < 0.005$ in the between-groups analyses, 0.05 FWE cluster-corrected) in the whole-brain analyses of the contrast between the no-reference and reference conditions for each group separately and for the comparison between the two groups. For labeling we used the AAL atlas in SPM12.

In contrast to TDs, in the dyslexia group there were no significant areas with greater activation in the no-reference compared with the reference condition. The conditions may not have differed in perceived regularity, so that the reference condition was simply more difficult, given its substantially smaller frequency difference. When inspecting the opposite contrast, we found several clusters that were significantly more active in the reference than in the no-reference condition (Fig. 8B,D; Table 2). These included a bilateral fronto-medial cluster in the anterior cingulate gyrus (ACG) and superior frontal gyrus (SFG; including medial part), a left cluster in the MTG, and a left inferior-frontal cluster encompassing the left inferior frontal gyrus (IFG; orbital part) and insula. The ACG, SFG and the lateral temporal cortex are all known to be part of the default-mode network (DMN), which was originally identified based on a consistent decrease in activity during tasks compared with nontask states (Shulman et al., 1997; Raichle et al., 2001; Buckner et al., 2008). Using a more lenient cluster-defining threshold of $p = 0.005$, additional areas reached significance, including the left hippocampus, bilateral medial frontal gyrus and middle frontal gyrus (MFG), and a bilateral cluster in the precuneus and median cingulate and paracingulate gyri (MCG). These areas are also considered to be part of the DMN, suggesting that the network was sensitive to the difference between the two conditions in the dyslexia group.

The two groups demonstrated different, condition-dependent patterns of brain activity, associated with different sensitivities to pitch regularities. In order to directly assess the significance of these group differences, we conducted a whole-brain independent-samples $t$ test on the no-reference minus reference contrast maps of the two groups. We found a significant effect of larger contrast values in TDs compared with IDDs in several ventral-posterior areas, as shown in Figure 9 and Table 2. This effect was identified in three clusters: two large, mostly temporal clusters, which encompass areas in the lateral temporal lobe (bilateral STG, MTG, inferior temporal gyrus, and the TP) and in the medial temporal lobe (bilateral hippocampus and amygdala). The cluster in the left hemisphere extended to neighboring visual areas ( fusiform gyrus and lingual gyrus), the IFG (orbital part) and the thalamus. The right cluster extended to the parahippocampal gyrus (PHG) and lateral fronto-parietal areas [PoG, precentral gyrus (PrG), ROL, insula, and SMG]. A third cluster was found in posterior medial areas including the bilateral precuneus, MCG, posterior cingulate gyrus (PCG), calcarine fissure and cuneus. These clusters include parts of the bilateral temporal areas which were found in the main analysis of TDs, and also areas in the DMN, most of which were identified in the analysis of IDDs. Using a stricter initial cluster-defining threshold of $p = 0.001$, significant clusters remained in bilateral MTG and STG and the right TP. There were no areas where the opposite direction of the test (IDDs > TDs) was significant. There was also no significant group difference in the basic task minus rest contrast.

In summary, the main differences between the groups in activity associated with frequency discrimination with and without a reference tone were in: (1) the STG and surrounding sensory regions, which were associated with better detection of regularity only in TDs; (2) the DMN, where the two groups showed opposite tendencies, for TDs greater activation in the no-reference compared with the reference condition, whereas IDDs showed greater activation in the reference compared with the no-reference condition, yielding significant group differences.

Discussion

Asking whether different dynamics of adaptation in PAC underlies the differences in sensitivity to frequency regularities between TDs and IDDs, we administered a behavioral task while participants were scanned in fMRI. Participants performed a two-tone frequency discrimination task with and without a reference tone. Introducing a reference enhanced TDs’ frequency resolution, which developed over several dozen trials. IDDs’ reference-induced enhancement of frequency resolution was smaller, suggesting that perceptual learning of regularities is impaired in dyslexia. fMRI scans showed regularity-induced adaptation in TDs’ PAC, whose dynamics paralleled their behavioral learning. By contrast, IDDs’ BOLD response did not differ between the two conditions. Whole-brain analysis showed similar effects in TDs’ bilateral STG and surrounding areas, and in a left parietal area,
whereas no region showed reference-induced adaptation in IDDs. These findings link atypical auditory learning of sound categories in dyslexia to atypical adaptation in the PAC and in associated auditory regions.

Auditory cortex sensitivity to statistical regularities, in TDs and IDDs

The sensitivity of the auditory cortex to simple statistical regularities has been systematically observed across species, although most studies have only focused on simpler (zero order) statistics of frequency regularities. In nonhuman animals, stimulus-specific adaptation (SSA), a decrease in the response to frequent versus rare sounds in an oddball paradigm, was observed at the level of single neurons in various regions along the auditory pathways (Ulanovsky et al., 2003; for review, see Khouri and Nelken, 2015). The PAC was also shown to be sensitive to structure (enhanced adaptation to a fixed vs random number of standards preceding each deviant; Yaron et al., 2012).

In humans, the oddball paradigm has been studied in both TDs and IDDs, mostly using EEG and MEG by measuring the mismatch negativity (MMN), the difference between the response to the deviant and the standard sounds. The STG and the auditory cortex are considered main sources of the MMN signal (Garrido et al., 2003; for review, see Khouri and Nelken, 2015). The PAC was also shown to be sensitive to structure (enhanced adaptation to a fixed vs random number of standards preceding each deviant; Yaron et al., 2012).

Both the oddball paradigm and repetition suppression protocol yield fast reduction in the magnitude of the response (adaptation). In such experiments, finer tuning occurs fast and does not allow for online tracking of the learning process. In the current study, we used simple yet unfamiliar pure tones, embedded in an easily detectable structure, without consecutive repetitions. These produced intermediately fast improvement which took dozens of trials to develop. This time constant allowed us to compare the dynamics of performance gain and adaptation in the BOLD response. Although pure tones have the benefit of being novel and thus allowing tracking of fast learning, future studies with linguistic stimuli are needed for generalizing the current observations to linguistic processing.

Figure 9. The DMN and STG of TDs and IDDs show opposite patterns of activation in response to frequency discrimination with and without regularity. Whole-brain analysis of the comparison between the two groups. A, Areas in which the no-reference minus reference contrast was significantly greater for TDs (N = 20) than IDDs (N = 20). Significant t values are presented using a red-yellow color scale on a 3D rendering of cortical gray matter (Cortex_20484 template in SPM12) and template brain slices (mm152_2009bet template in MRIcroGL). The maps were created using an initial cluster-defining threshold of p = 0.005, and a subsequent cluster-size threshold of 313, resulting in 0.05 FWE-corrected clusters. B, Individual differences in mean β values for the no-reference minus reference contrast obtained from each cluster in the whole-brain analysis (blue and red for TDs and IDDs, respectively; see Table 2). Values were jittered horizontally for display purposes. Horizontal lines denote the means. Error bars denote the SEM.
finding that IDDs’ activation in the reference condition did not differ from the no-reference condition may reflect a simultaneous effect of adaptation (decreasing activation) and greater task difficulty (increasing activation) in the reference condition. However, when inspecting a subgroup of TDs with similar accuracy levels in the reference condition as found in IDDs, we still observed adaptation in the reference compared with the no-reference condition (Fig. 5). This suggests that the relatively poor performance of IDDs in the reference condition is not an independent reason for their lack of adaptation in this condition. This analysis also showed that adaptation to the reference was a robust property of TDs, characteristic of both good and poor performers in a condition with structured regularity. This consistency may hint that regularity-induced adaptation is a basic mechanism of TDs and that the subgroup of poor TD performers did not fully behaviorally use their adequate PAC sensitivity to regularities.

Another possible explanation is related to the experimental design. Since the reference and no-reference conditions differed acoustically, the differences in brain activation could theoretically reflect these acoustic differences. Namely, most of the tone pairs in the reference condition were similar in frequency to each other and to 1000 Hz (the reference tone), which perhaps induced greater adaptation than the no-reference condition, as follows. The auditory cortex and STG sensitivities to pitch are manifested in an increased BOLD response with an increased pitch interval, with a right-hemisphere predominance (Hyde et al., 2008; Zatorre et al., 2012). Thus, the larger frequency intervals of the no-reference condition were expected to yield a larger BOLD response, particularly in the right STG, as was the case in the TD group. However, this account predicts larger BOLD signals in the no-reference condition than in the reference condition for the dyslexia group as well, which exhibited an even greater behavioral difference between the two conditions (their performance was well above chance in both). However, the dyslexia group did not evidence this difference in BOLD.

In summary, neither behavioral difficulty nor the size of frequency intervals can explain the differences in PAC sensitivity to regularities found here between TDs and IDDs.

The role of other brain regions in benefitting from the reference

Whole-brain analysis in the dyslexia group found no region which showed adaptation in the reference condition compared with the no-reference condition. By contrast, this same analysis in TDs revealed several regions. In addition to the bilateral temporal clusters, including the STG and the auditory cortex, it found a left parietal cluster, located in parts of the IPL, PoG, and SPL. A left parietal cluster was also found in a similar previous study with TDs, when similar conditions were compared (Daikhin and Ahissar, 2015). A rodent study that temporarily deactivated a similar region (posterior parietal cortex; PPC) of rats performing serial discrimination between two sounds found a reduction in their use of recent sound statistics (Akrami et al., 2018), suggesting that the PPC is critical for the representation and use of prior stimulus information. Taken together, these results suggest that the PPC in dyslexia does not integrate stimulus statistics as in TDs, perhaps as an outcome of atypical adaptation in the PAC and related STG regions.

The PAC might not be the earliest stage in the auditory processing pathways where IDDs’ adaptation to the reference condition is reduced. Previous studies have reported a stronger response to phonological changes versus acoustic changes in TDs’ but not in IDDs’ left medial geniculate body (MGB, the auditory thalamus) in a change detection task (Diaz et al., 2012). Moreover, there is less connectivity between the left MGB and parts of the left secondary auditory cortex (planum temporale) in dyslexia (Tschentscher et al., 2019). Since activity in subcortical regions was not the focus of the current study, we did not aim for high resolution in these regions. Nevertheless, we found a group difference in the pattern of adaptation in the left thalamus as part of a larger, mostly temporal cluster covering regions including the hippocampus, MTG, STG, TP, and IFG.

These accounts do not refute the possibility that reduced adaptation to regularity in dyslexia is a general characteristic of both auditory and nonauditory cortices (and possibly subcortical regions as well), as suggested by studies that have assessed the spatial cortical distribution of adaptation in dyslexia (Perrachione et al., 2016; Jaffe-Dax et al., 2018). An interesting idea for an underlying mechanism, perhaps already at the level of the brainstem, that could explain reduced sensitivity to fine regularities is increased variability in response to stimuli (Hornickel and Kraus, 2013). Such variability would impede the brain’s ability to detect structures and form priors based on fine stimulus differences.

The pattern of DMN activation

Distributed areas, including the bilateral precuneus, MCG, PCG, hippocampus, and lateral temporal cortex, which are considered part of the DMN (Shulman et al., 1997; Raichle et al., 2001; Buckner et al., 2008) showed an opposite pattern of activation in the reference compared with the no-reference condition in the two groups. IDDs showed higher activation in the reference condition, whereas TDs exhibited the opposite tendency (Fig. 9), despite the reference condition being more difficult for both groups (although more so for IDDs). Therefore, task difficulty cannot explain the pattern in both groups. A somewhat modified account, which explains the DMN pattern of both populations, and is also supported by previous studies (Mason et al., 2007; Scheibner et al., 2017) is that reduced task-engagement increases DMN activation. Thus, the acoustically more challenging reference condition engages TDs to a greater extent than the easier no-reference condition. However, for IDDs, who benefit less from the regularities of the reference, this condition was more frustrating and therefore brought about more attentional lapses (Weissman et al., 2006). Recently, it was proposed that the DMN is associated with a broader temporal context (Yeshurun et al., 2021), and may be related to higher-level, more abstract processing of sensory information (Smallwood et al., 2021). According to these accounts, the challenging reference condition may activate higher-level strategies in the dyslexia group, in the absence of sufficiently reliable sensory information. The behavioral data indicate that such putative strategies are not very successful.

In conclusion, we found reduced sensitivity to regularities in dyslexia both behaviorally and neurally, in the PAC. Higher-level brain regions, including the STG and PPC, also showed regularity-induced adaptation in TDs but not in dyslexia. One possible explanation for these results is that reduced sensitivity to stimulus statistics in sensory cortices in dyslexia may lead to atypical adaptation in higher-level cortical regions known to be associated with the learning of stimulus statistics. Overall, the findings suggest that reduced sensory sensitivity to regularities, as manifested in reduced adaptation, may underlie atypical category formation in dyslexia.

References


