

RESEARCH ARTICLE

Neural correlates of sequence learning in children with developmental dyslexia

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Abstract

Developmental Dyslexia (DD) is a condition in which reading accuracy and/or fluency falls substantially below what is expected based on the individuals age, general level of cognitive ability, and educational opportunities. The procedural circuit deficit hypothesis (PDH) proposes that DD may be largely explained in terms of alterations of the cortico-basal ganglia procedural memory system (in particular of the striatum) whereas the (hippocampus-dependent) declarative memory system is intact, and may serve a compensatory role in the condition. The present study was designed to test this hypothesis. Using Magnetic Resonance Imaging, we examined the functional and structural brain correlates of sequence-specific procedural learning (SL) on the serial reaction time task, in 17 children with DD and 18 typically developing (TD) children. The study was performed over 2 days with a 24-h interval between sessions. In line with the PDH, the DD group showed less activation of the striatum during the processing of sequential statistical regularities. These alterations predicted the amount of SL at day 2, which in turn explained variance in children's reading fluency. Additionally, reduced hippocampal activation predicted larger SL gains between day 1 and day 2 in the TD group, but not in the DD group. At the structural level, caudate nucleus volume predicted the amount of acquired SL at day 2 in the TD group, but not in the DD group. The findings encourage further research into factors that promote learning in children with DD, including through compensatory mechanisms.

KEYWORDS

developmental dyslexia, hippocampus, procedural memory, sequence learning, statistical learning, striatum

1 | INTRODUCTION

Developmental Dyslexia (DD) is a condition in which reading accuracy and/or fluency falls substantially below what is expected based on the individuals age, general level of cognitive ability, and educational opportunities (Lyon et al., 2003). The condition is highly heritable (Erbeli et al., 2021), and commonly co-occurs with challenges in other

domains, such as attention (DuPaul et al., 2013), executive functions (Farah et al., 2021), processing speed (McGrath et al., 2011), and language development (Snowling et al., 2021; Torppa et al., 2010).

At the cognitive level, there is a robust association between the reading difficulties in DD and limited phonological ability, in particular with phoneme awareness (i.e., the ability to detect and manipulate the individual sounds—phonemes—of spoken words, Melby-Lervåg

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et al., 2012). According to the phonological deficit hypothesis (Stanovich, 1988; Wagner & Torgesen, 1987), these difficulties are causally related to the reading problems in DD by hindering the development of efficient grapheme–phoneme (letter–sound) mapping. However, although there is strong evidence for a pivotal role of phonological ability in learning to read (Castles et al., 2018), and for challenges in this domain to predict DD (Vellutino et al., 2004), specific phonological challenges do not suffice to account for the reading difficulties associated with the condition, and fails to explain the high prevalence of co-occurring challenges in domains outside of reading (McGrath et al., 2011; Pennington, 2006). Therefore, a more complete understanding of DD may require theoretical models that acknowledge the contribution of nonphonological factors to the reading process, and to the dyslexic phenotype (Peterson & Pennington, 2015).

In the present study, we test the predictions of the procedural circuit deficit hypothesis (PDH; Nicolson & Fawcett, 2007; Ullman et al., 2020) of DD. The PDH takes a neurocognitive rather than purely cognitive approach to account for the pattern of strengths and weaknesses associated with DD, and suggests that the condition may be largely explained by alterations of the cortico-basal ganglia procedural memory system (in particular of the striatum, Ullman et al., 2020). The hippocampus-dependent declarative memory system, by contrast, is posited to be intact, and to potentially serve a compensatory role in the condition (Ullman et al., 2020; Ullman & Pullman, 2015).

The procedural memory system consists of circuits connecting the basal ganglia with associated cortical and subcortical regions, and underlies the implicit acquisition, consolidation and processing of skills and habits (Hélie et al., 2015; Packard & Knowlton, 2002; Squire & Zola, 1996). While previous research largely focused on this system's importance for motor functions, it is now widely acknowledged that it may also support a range of perceptual, cognitive, and linguistic functions, in particular when the information to be processed has a sequential structure (Aldridge & Berridge, 1998; Knowlton et al., 1996; Ullman et al., 2020). The system has been implicated in many of the functions that may be challenging for individuals with DD, including in aspects of phonological processing (Tettamanti et al., 2005; Wang et al., 2019), attention (Rubia et al., 2009), executive functions (Darki et al., 2020), and language learning and processing (Jeon et al., 2014; Karuza et al., 2013; Orpella et al., 2021; Teichmann et al., 2015; Thibault et al., 2021). Against this background, it has been suggested that alterations of the procedural memory system could potentially provide a unifying explanation for the core (i.e., phonological and reading) as well as commonly co-occurring difficulties in this condition (Nicolson & Fawcett, 2007; Ullman et al., 2020).

Learning in the procedural memory system is commonly assessed with the Serial Reaction Time (SRT) task (Nissen & Bullemer, 1987). This task is designed to tap the extraction of sequential statistical regularities in the input, and is closely related to paradigms within the field of statistical learning (Christiansen, 2019; Perruchet & Pacton, 2006). In the SRT task, a visual stimulus appears repeatedly in one of four locations on a computer display, and participants are asked to press one of four buttons that matches the location of the

visual stimulus' position as soon as possible following stimulus onset (Figure 1). In the implicit version of this task, participants are not informed that the stimuli appear according to a fixed sequential structure of statistical regularities. Sequence-specific learning (henceforth SL) on the task (i.e., the implicit extraction of these statistical regularities) is operationalized as the difference in the reaction times of responses made to trials in which the visual stimulus follows the fixed sequence compared with control trials in which the visual stimulus appears randomly in one of the four locations. If knowledge of the sequential structure has been acquired, responses are faster for sequence stimulus presentations compared with random presentations. The sequence-random trial comparison allows for an examination of SL by providing excellent control of possible confounding variables (i.e., more general perceptual and motor learning). SL on the SRT task has been shown to rely heavily on the basal ganglia, including the striatum (Janacsek et al., 2020).

Learning on the SRT task, and in the procedural system more generally, is characterized by a gradual development over time, and studies suggest that the neural correlates of SL vary as a function of practice with the task. While early learning appears to be characterized by a wide-spread activation pattern that includes the medial temporal lobe (hippocampus), in addition to the striatum, studies focusing on later learning and consolidation point to a more limited activation pattern with an increasingly important role for the striatum (Batterink et al., 2019; Doyon et al., 2009; Pinsard et al., 2019; Rieckmann et al., 2010; Simon et al., 2012).

Previous behavioral SL studies using the SRT task, as well as studies using other statistical learning paradigms, have yielded mixed results in individuals with DD. While some studies have shown impaired learning in DD (e.g., Gabay et al., 2015; Howard Jr. et al., 2006; Jimenez-Fernandez et al., 2011; Lum et al., 2013; van Witteloostuijn et al., 2017), others have reported null results (e.g., Deroost et al., 2010; Kelly et al., 2002; Roodenrys & Dunn, 2008; Russeler et al., 2006; van Witteloostuijn et al., 2019). It has been suggested that some of this inconsistency may be explained by differences in the specific sequential structures, as well as by the time interval, under study (e.g., Orban et al., 2008). When learning has been studied beyond a single practice session, it has been found that intact initial learning on day 1 may be followed by impaired overnight consolidation/retention in children with DD compared with typically developing children (Hedenius et al., 2021).

Of particular importance for the present study, inherent differences in experimental design could allow (declarative) compensatory mechanisms to mask procedural deficits to different degrees, as long as the paradigm is strictly behavioral. In line with this notion, Rieckmann et al. (2010) found that elderly participants showed intact SL at the behavioral level, compared with younger adults, by relying on medial temporal lobe activation to compensate for striatal alterations. The authors found that, with extended practice, SL was associated with activation increases in the striatum and activation decreases in the medial temporal lobe in younger adults. In older adults, by contrast, SL was positively related to activation increases not only in the striatum, but also in the medial temporal lobe. Similar compensatory patterns have also been observed in patient groups afflicted with striatal pathology (e.g., Moody et al., 2004).

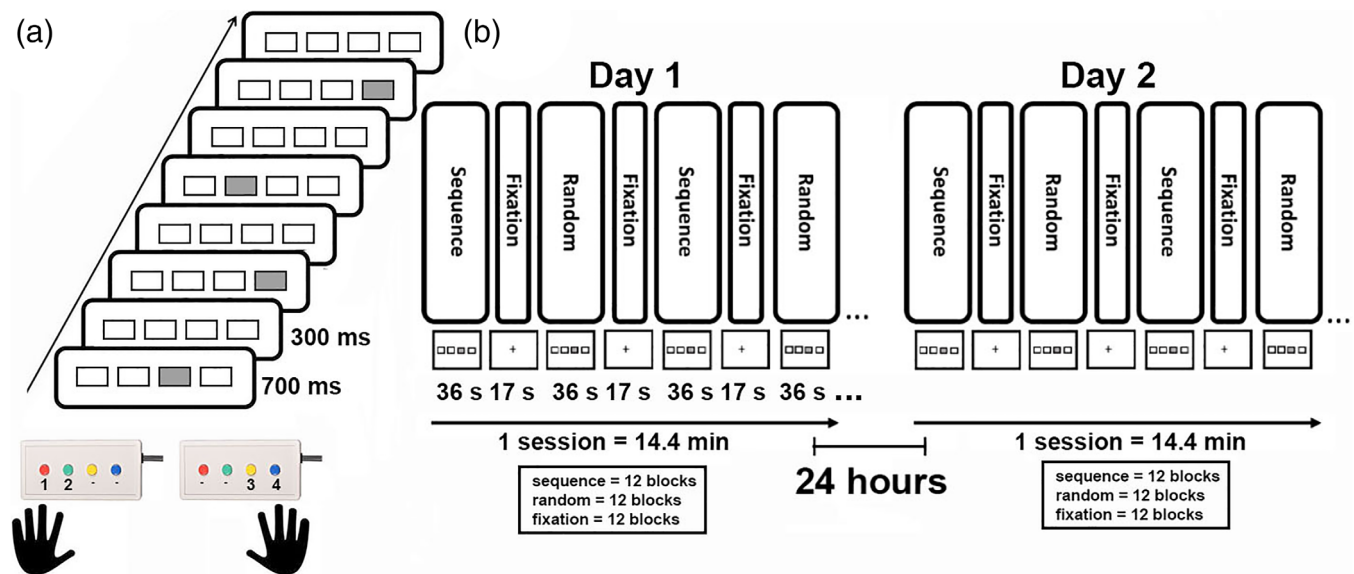


FIGURE 1 (a) A schematic of the serial reaction time task used in the study. (b) Study design

To date, very few studies have examined the neural correlates of SL in DD. We are aware of only two studies examining the functional (Menghini et al., 2006) and structural (Menghini et al., 2008) correlates of learning on the SRT task in a group of adults with DD compared with typical control participants. At the behavioral and functional levels, they found impaired learning in the DD group together with group differences in the activation patterns of the supplementary motor area, inferior parietal areas and cerebellum. At the anatomical level, learning was found to correlate with the volume of a pre-defined area of the superior parietal lobule in the TD group, but not in the DD group. Importantly, this study did not isolate SL from more general visuo-motor learning on the task (Janacek et al., 2020). Therefore, the observed activation pattern likely reflects a broader set of task related cognitive processes, in addition to SL. Thus, despite a relatively large number of studies aiming to characterize SL in DD at the behavioral level, there is still a complete lack of studies examining its functional and structural correlates. Additionally, although some previous studies have shown associations between SL on the SRT task and individual differences in reading proficiency (e.g., Hedenius et al., 2013, 2021), the brain level mechanisms underlying this association remain unexplored.

1.1 | The present study: Aim and predictions

The aim of the present study was to test the predictions of the PDH by examining the functional and structural correlates of SL in children with DD compared with typically developing (TD) children using magnetic resonance imaging (MRI). In order to cover learning beyond an initial learning session the study was performed over 2 days with a 24-h inter-session interval. A majority of the children (DD $n = 13/17$; TD $n = 13/18$) had previously participated in a behavioral study of sequence learning and consolidation on the ASRT task (Hedenius et al., 2021).

The PDH predicts that any task that relies on the striatum should be problematic in DD. Therefore, we predicted that, at the behavioral level, children with DD would show poorer performance on the SRT task, either across the task as whole (e.g., Lum et al., 2013) or at day 2 (Hedenius et al., 2021). At the functional level, we expected differences in the within-groups correlations between SL and blood-oxygen-level-dependent (BOLD) signal in pre-defined regions of interest (hippocampus [HC]/striatum) with evidence for compensatory reliance on HC activation for learning in the DD group compared with the TD group (Rieckmann et al., 2010; Ullman & Pullman, 2015). Specifically, we predicted that in the TD children, early learning (here defined as SL day 1) would be associated with both striatal and hippocampal activation, with increased reliance on the striatum, and decreased reliance on the HC, in later learning (SL day 2). For the DD group, we predicted that difficulties associated with striatal learning would lead to continued reliance on the HC also later in learning (Rieckmann et al., 2010; Ullman & Pullman, 2015). At the structural level, we expected group differences in the striatum as well as differences in the within-group correlations between SL and HC/striatal grey matter (GM) volumes, with greater SL in the DD and TD groups being associated with greater HC and striatal volume, respectively (Erickson et al., 2010). Finally, we aimed at exploring the link between potential striatal alterations, SL challenges, and individual differences in reading proficiency.

2 | METHODS

2.1 | Behavioral methods

2.1.1 | Ethics statement

The study met the ethical requirements of the Declaration of Helsinki, and was approved by the ethical review board of Uppsala, Sweden. All parents or legal guardians gave written informed

consent, and all children gave informed written assent, before participation.

2.1.2 | Participants

Seventeen children with DD and 18 TD children participated in the study. The groups did not differ with respect to age (9–13 years), sex, performance IQ (PIQ), or a language composite score based on vocabulary and syntactic comprehension. There were significant group differences with respect to word reading, reading fluency, spelling, and phoneme awareness (see Table 1). All children were mono-lingual Swedish speaking, with equivalent exposure to English as a second language in school.

All children were part of a larger behavioral study focusing on learning and memory in children with reading difficulties (the REMEMBR project), and the reading and cognitive tests reported in Table 1 were part of a larger test battery performed within this project. These tests were administered on a separate occasion within 6 months prior to participation in the present study.

Within the REMEMBR project, participants with DD were recruited from speech and language therapy clinics in the Stockholm-Uppsala area in Sweden. Inclusion criteria for the present study were a clinical diagnosis of dyslexia from a certified speech and language therapist, and a word reading score < 15th percentile on a standardized Swedish word reading test (Elwér et al., 2011). Exclusion criteria for the DD group were PIQ scores < 80 (Wechsler, 2003a), any other known comorbid neuropsychiatric condition (as reported by parents) and a language composite stanine score < 3 (see Methods). These inclusion/exclusion criteria are consistent with the Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM-5; American

Psychiatric Association, 2013) as well as with previously published studies on DD (e.g., Knoop-van Campen et al., 2018; Segers & Verhoeven, 2018).

TD children were recruited from schools in the same area. Inclusion criteria for the present study were normal language, reading and writing development as reported by parents. Exclusion criteria were any known neurodevelopmental condition (as reported by parents), PIQ scores < 80 (Wechsler, 2003a), word reading, nonword reading, or spelling scores (Elwér et al., 2011) < the 20th percentile, or a language composite stanine score < 3.

Possible unrecognized ADHD was ruled out using the “executive functions” subdomain in the Five-to-Fifteen (FTF) parent questionnaire (Kadesjö et al., 2004). The FTF targets ADHD symptoms, and its common co-morbidities, in children and adolescents between 5 and 15 years of age. It has been shown to be a reliable and valid screening instrument that correlates significantly with other ADHD questionnaires, as well as performance-based measures (Bohlin & Janols, 2004; Lind et al., 2010). No child in the sample had significant ADHD symptoms.

2.1.3 | Reading and cognitive tests

The cognitive and reading-related measures used to characterize the groups were chosen based on their relatively high reliability and validity (Swedish Agency for Health Technology Assessment and Assessment of Social Services, 2014). Reliability estimates were acceptable to excellent for all measures (internal consistency and/or test-retest reliabilities of .74–.97), with the exception of the phonological awareness test which lacks such information (see below).

Variable	DD (n = 17)		TD (n = 18)		Comparison	
	M	SD	M	SD	t	p
Age	12.3	0.78	12.1	1.5	0.59	.557
Sex (F/M)	7/10		10/8		$\chi^2 = 0.72$.395
PIQ	101.5	11.7	108.3	14.6	1.51	.141
Nonword read	7.2	5.2	63.6	23.3	9.45	<.001
Word read	6.3	2.9	64.2	22.1	9.56	<.001
Read fluency	1.9	0.8	4.9	1.5	7.11	<.001
Spelling	10.9	8.6	74.5	20.8	11.23	<.001
PA	17.5	7.3	35.7	9.3	6.26	<.001
LangComp	6.1	1.2	5.8	1.2	0.88	.385

TABLE 1 Participant characteristics

Note: DD, Children with Developmental Dyslexia; TD, Typically developing children; PIQ, scores from WISC-IV performance IQ subtests (Wechsler, 2003a); Nonword read, percentile scores from the nonword reading subtest from LäST (Elwér et al., 2011); Word read, percentile scores from the word reading subtest from LäST; Spelling, percentile scores from the spelling subtest from LäST; Read fluency, stanine scores from the reading fluency subtest from DLS ([Diagnostic Reading and Spelling test], Järpsten & Taube, 2010); PA, raw scores from the Paulin phoneme awareness test (Andersson & Berggren, 2013); LangComp, a composite score based on stanine scores from DLS vocabulary subtest (Järpsten & Taube, 2010) and the Test for Reception of Grammar-2 (TROG-2, Bishop, 2009).

Word reading

The phonemic decoding and sight word recognition efficiency subtests from Läst (Elwér et al., 2011), which is a Swedish version of the Test of Word Reading Efficiency (TOWRE, (Torgesen et al., 1999), were used to assess word reading skills. The phonemic decoding (nonword) subtest assesses the ability to translate letters to sounds and words, and the word recognition (real word) subtest assesses orthographic decoding skills, that is, the ability to recognize a word as fast as possible (Torgesen et al., 1999). In both subtests, children were given 45 s in which to read as many nonwords/real words as possible from the provided lists. Two equivalent forms of the test, forms A and B, were used for both the phonemic decoding and the word recognition subtests. That is, participants were given two equivalent lists for phonemic decoding/nonword reading, and two equivalent lists for word recognition, each with a 45 s time limit. The test score for each subtest was the total sum of successfully read nonwords and words.

Reading fluency

The ability to read with speed, accuracy and preserved text comprehension is called reading fluency (Wagner, 2011). This capacity is thought to tap the degree of automatization of reading skills since intact text comprehension requires that sufficient attentional resources may be used to process the content of what is read. Reading fluency was assessed with the reading fluency subtest of the Diagnostic Reading and Spelling Test (DLS, Järpsten & Taube, 2010). This is a standardized Swedish reading test with Stanine norms for ages 9 to 13. On the DLS reading fluency test, participants read a continuous text with 36 blanks where words were missing. Next to the blanks were three suggested words, and the participants were instructed to underline the word that was most suitable in the context. After 4 min, the task was interrupted. The test score was the number of correctly underlined words within the 4-min time limit. The reading fluency test was not used to categorize children into TD and DD groups, but was included to allow for an examination of the relationship between procedural memory and reading skill as a continuous variable.

Phoneme awareness

The Paulin's Test of Phonological Awareness (Andersson & Berggren, 2013) was applied. The test has a maximum score of 50 and consists of five parts; phoneme deletion, deletion of a sequence of phonemes, reversed phoneme sequences in words, reversed phoneme sequences in nonwords, and spoonerisms (Chard & Dickson, 1999). Reliability estimates are lacking for this test. However, the five tasks included in this test have previously been found reliable in assessing phonological awareness, as well as in identifying students with dyslexia (see Andersson & Berggren, 2013; Preston & Edwards, 2007; Wilson & Lesaux, 2001).

Language composite score

A composite language score based on the vocabulary subtest from the DLS (Järpsten & Taube, 2010), and the Swedish version of the Test for Reception of Grammar-2 (TROG-2, Bishop, 2009), was used to estimate broader language ability. The DLS vocabulary subtest is a

multiple-choice test in which participants are presented with a target word, and asked to indicate which, of four alternatives, is the synonym of the target word. The target items, as well as the four alternatives for each item, were read aloud to the participants. The test comprises 40 words, and the maximum score is 40. TROG-2 is a multiple-choice sentence picture-matching task. Participants listened to a target sentence read by an experimenter and were asked to identify, from a choice of four, the picture that corresponded to the heard sentence. Items were presented in 20 blocks, each with four items focusing on a particular grammatical structure. Participants were required to pass all four items within each block and testing was discontinued after five failed consecutive blocks. The maximum score was 20. Because norms for the DLS vocabulary subtest is available in stanine scores only, TROG-2 percentile scores were converted to stanine before an average score of the two tests were calculated for each participant. There were no group differences in either of the component parts of the language composite score (DLS vocabulary: DD mean = 6.4, SD = 1.9; TD mean = 6.0, SD = 1.8, $t = 0.59$, $p = .560$; TROG-2: DD mean = 5.9, SD = 1.3; TD mean = 5.6, SD = 0.8, $t = 0.90$, $p = .372$).

Performance IQ

Nonverbal IQ was assessed with the performance IQ subtests from the Wechsler Intelligence Scale for Children (WISC-IV; Wechsler, 2003a); matrices, block design and picture categories.

2.1.4 | Stimuli and procedure

The serial reaction time task

Four squares were presented horizontally in the center of a computer screen. Each square position corresponded to one of four buttons, in order from left to right. Participants were instructed to press the corresponding button using the index and middle finger of each hand as quickly and accurately as possible when a white square turned gray (Figure 1a). Response accuracy and reaction times (RT) were recorded with two MRI-compatible response boxes, one for each hand. Button presses were recorded using E-prime 2.0 (Psychology Software Tools, Inc., 2002). A blocked fMRI design was used, and the task was administered in two sessions (from here on referred to as day 1 and day 2), with a 24-h inter-session-interval (Figure 1b). Each session included 24 blocks. Each block consisted of 36 trials, and each trial lasted 700 ms with a 300 ms inter-stimulus interval. In half of the blocks, and unknown to the participants, the trials followed a fixed second-order 12-item sequence with positions from left (1) to right (4) of 1-2-1-4-2-3-4-1-3-2-4-3 (Schendan et al., 2003). In the remaining blocks, trials were presented in a pseudo-random order with the constraint that two consecutive trials were not the same. Sequence and random blocks were alternated, and each block was separated by a 17-s fixation period. Error trials or omissions were excluded from analysis and median response times were used to minimize the influence of outlier responses.

For each participant, we calculated the median RT for the random and sequence blocks of each session, separately. General skill learning was defined as the sequence-independent RT decrease that occurs as a result of practice with the task and was calculated from the average RT across sequence and random trials. Sequence-specific learning (SL) was operationalized as the median RT difference, for each session, between random and sequence blocks. Because longer average response times will lead to a numerically larger difference between sequence and random blocks (and thus erroneously to more “learning” in the slower group), we followed the procedure outlined in Hedenius et al. (2011) to calculate a normalized measure of SL. This measure was obtained by dividing the difference between the median RTs for the random and sequence blocks, in each session, by the average median RT across both random and sequence blocks, for that same session (i.e., $[\text{median RT for random blocks in session X} - \text{median RT for sequence blocks in session X}] / ([\text{median RT for random blocks in session X} + \text{median RT for sequence blocks in session X}] / 2)$).

The primary SRT dependent variables were (i) the average normalized RT difference between sequence and random trials on day 2 (henceforth SL day 2), reflecting the overall learning outcome, and (ii) the difference in SL between day 1 and day 2 (henceforth SL change), reflecting the amount of learning from day 1 to day 2. For both measures, larger numbers reflect more SL.

Procedure

Children were accompanied to the MRI-center by a caregiver, and welcomed by two trained experimenters. On each day, children completed two consecutive sessions of the SRT task while undergoing MR scanning. On day 1, children were first familiarized with the scanning procedure using a mock scanner. In addition, a SRT task practice session was performed prior to scanning, in which children completed 24 blocks of the task later used in the scanner on a personal desktop computer. The data from the practice session was not analyzed but simply served the purpose of ensuring that all children understood the task. On day 2, the children performed the within-scanner SRT task only. The accompanying caregiver was present in the scanner room during scanning on both days.

2.2 | MRI methods

2.2.1 | Functional MRI acquisition

Participants were scanned with a 32-channel phased array receiving head coil (Discovery MR750 3.0 T scanner, General Electric). Functional data were acquired in a blocked fMRI design, using a gradient echo-planar imaging (EPI) sequence (FOV = 22 cm, acquisition matrix 72×72 and slice thickness 3 mm—with additional zero-filling the matrix was filled to 128×128 with voxel size $1.7 \times 1.7 \times 3 \text{ mm}^3$ —flip angle 75° , TR = 2000 ms, TE = 30 ms, total accelerated ($R = 2$) EPI readout duration = 16.4 ms, 42 axial slices acquired in an interleaved bottom/up order). For each of the four blocks, 170 images were acquired with a scanning time of 5 min and 40 s each. To allow

for progressive saturation of the MR signal, five dummy scans were collected, and discarded prior to experimental image acquisition. The scanner task was presented on a projector, seen through a mirror mounted on the head coil. T1-weighted 3D spoiled gradient recalled (SPGR) images were also obtained with $0.94 \times 0.94 \times 1 \text{ mm}^3$ voxel size (TR: 7.908 ms, TE: 3.06 ms, field of view: 24 cm, 176 axial slices, flip angle of 12°).

2.2.2 | Functional MRI preprocessing

All fMRI data were preprocessed using the statistical parametric mapping software SPM12 (Wellcome Trust Centre for Neuroimaging, <http://www.fil.ion.ucl.ac.uk/spm/>) implemented in Matlab (R2017b; The Mathworks, Inc.). Preprocessing comprised realignment and unwarp, slice timing correction to the first slice, and co-registration of the individual T1 image to the mean functional image. Following co-registration, the T1 image was segmented into grey matter and white matter, and the Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) toolbox (Ashburner, 2007) was used to create a custom group template from the segmented GM and white matter images. In addition, deformations from the group-specific template to each of the participant-specific GM and white matter images were computed (i.e., flow fields). Finally, the co-registered fMRI images were nonlinearly normalized, participant by participant, to the sample-specific template using the flow fields, affine aligned into the MNI template, and finally smoothed using an 8 mm FWHM Gaussian kernel. The final voxel size was $2 \times 2 \times 2 \text{ mm}$.

2.2.3 | Regions-of-interest analyses

The regions-of interest (ROI) analyses were performed on anatomically as well as functionally defined ROIs. Based on the well-established role of the striatum in SL and the specific hypotheses of the PDH regarding the role of these structures in dyslexia (see Section 1), all analyses were performed on these six ROIs: left caudate nucleus (CN), right CN, left putamen, right putamen, left HC and right HC. The anatomically defined ROIs were defined using automated anatomical labeling (AAL) as implemented in WFU Pickatlas. The functional ROIs were defined from the voxels that showed increased activation in the sequence condition compared with the random condition across all participants at a family-wise error (FWE) corrected threshold of $p < .05$ ($k > 5$ voxels). All voxels within the significant cluster formed the basis for creating a binary ROI. The binary ROI was used to extract the average BOLD signal from all voxels included in the ROI. BOLD signal was extracted and analyzed using the Marsbar toolbox (<http://marsbar.sourceforge.net/>). Mean BOLD parameter estimate value was extracted from each condition for each participant.

2.2.4 | Voxel-based morphometry

Analyses of GM brain volume were performed using voxel-based morphometry (VBM). The T1-weighted MR images were segmented into

GM, white matter, and cerebrospinal fluid using the unified segmentation approach (Ashburner & Friston, 2005) in SPM12 implemented in Matlab (R2017b; The Mathworks, Inc). The “light cleanup” option was used to remove odd voxels from the segments. The GM images were further analyzed using DARTEL in SPM12. The GM segments were imported into DARTEL space, and a customized GM template was created including participant-specific flow fields containing the individual spatial normalization parameters (diffeomorphic nonlinear image registration). By incorporating the affine transformation of the DARTEL template to Montreal Neurological Institute (MNI) space, the GM segments were further warped into standard MNI space. To preserve local-tissue volumes, the normalized GM volumes were modulated by scaling them with Jacobian determinants from the registration step. Volumes were smoothed with an isotropic full-width at half maximum Gaussian kernel of 8 mm.

We defined six masks of left and right CN, putamen, and HC as ROIs, which were used to extract normalized volumes from each individual's smoothed images. The masks were based on the WFU Pickatlas AAL. We then visually inspected the fit of each mask to the mean GM mask and optimized each mask's fit in terms of clear separations between masks. The resulting masks were then used to extract mean regional volumes for each participant. All variables displayed acceptable skewness and kurtosis (Kline, 2005).

2.3 | Statistical analyses

2.3.1 | Whole-brain and ROI analyses of sequence-specific brain activation across all children

Two runs of 170 volumes each were acquired for fMRI analyses during day 1 and day 2 (680 volumes in total). BOLD signal change for each of the conditions was analyzed using the general linear model approach implemented in SPM12. A block-design matrix including all conditions of interest was specified using the canonical hemodynamic response function. In addition, six motion parameters were modeled as covariates. The onset of each run was set to the first stimulus in each condition. The resulting individual contrast images were submitted to a second-level analysis. The first and second run for each of the 2 days were modeled separately.

First, the overall pattern of brain activation across all participants was established in order to examine the validity of the SRT task for testing the predictions of the PDH in children. The main dependent variables used in the fMRI analyses were (i) the sequence > random BOLD signal difference on day 2, and (ii) the change in the sequence > random BOLD signal difference between day 1 and day 2.

To estimate BOLD signal changes related to SL, three separate analytic approaches were utilized. First, activation related to task condition, independent of the amount of SL, was examined by contrasting sequence and random task blocks (sequence > random). This analysis was performed over both days and across all

participants in order to identify task-related brain areas, and also to define functional regions-of-interest (ROIs) associated with the task. For the functional ROIs, given the predictions from the PDH, we were focusing on regions within the striatum (CN and putamen) and the HC. Second, we examined whether task-related activation differed between days and group (TD vs. DD) using (i) whole-brain voxel-based analyses, (ii) region-specific analyses using functional ROIs from step one (described above), and (iii) region-specific analyses using anatomical ROIs derived from the anatomical automatic labeling (aal) atlas. Third, in order to examine activation related to SL, individual performance scores were used as regressors in the model. SL was correlated with the corresponding sequence > random BOLD signal difference on day 2 using the multiple regression option in SPM12. These results reflect brain activation that significantly correlates with SL day 2. The same approach was used for investigating correlations between SL change and the change in the sequence > random BOLD signal difference between day 1 and day 2. In addition to this whole-brain voxel-based approach, and similar to step two, we also performed region-specific analyses using both functional and anatomical ROIs.

At the whole brain level, we set a peak-level family-wise error (FWE) corrected threshold of $p < .05$ ($k > 5$ voxels) for the SPM analyses. For ROI analyses (i.e., CN, putamen and HC), we used an uncorrected threshold of $p < .001$ at the peak-level, which we proceeded to follow-up with small-volume corrections by applying the mask of the ROI, assessing significance at a p value $< .05$, FWE corrected. No further corrections for multiple comparisons were performed across the different levels (i.e., whole-brain and ROI-based) analysis.

2.3.2 | Prediction 1. Group differences in behavioral SL

The prediction of a group difference in behavioral SL was examined with a mixed-design 2 (between-participants; group: DD vs. TD) \times 2 (within-participants; session: day 1 vs. day 2) ANOVA with the normalized RT difference between sequence and random events as the dependent variable.

2.3.3 | Prediction 2. Group differences in the functional neuroanatomy of SL

Group differences in the activation patterns related to task condition was examined by adding group as a predictor in the regression model contrasting sequence and random blocks (described in Section 2.3.1). Group differences in the associations between the sequence > random BOLD signal difference and behavioral SL, across the whole brain and in the ROIs, were examined using within-groups analyses following the steps outlined in Section 2.3.1. The difference between the within-group correlations was tested for significance using the Fisher r -to- z transformation.

2.3.4 | Prediction 3. Group differences in the structural neuroanatomy of SL

For the VBM analyses, total intracranial volume (TIV), age and sex were included as covariates in all analyses (Ramus et al., 2018). Two analyses were performed. First, we tested the prediction of anatomical alterations of the striatum, and intact HC, in the DD group compared with the TD group, using a repeated-measures analysis of variance (ANOVA) where hemisphere (left/right) and ROI were included as separate factors. Second, we investigated group differences in the associations between the GM volume of the anatomically defined ROIs and (i) SL day 2 and (ii) SL change. The difference between the within-group correlations was tested for significance using the Fisher *r*-to-*z* transformation.

2.3.5 | The brain—SL—reading link

Potential links between the striatum, SL, and reading ability was tested with a mediation analysis using the PROCESS macro for SPSS (Hayes, 2013), with 95% confidence intervals, and the number of bootstrap estimates set to 5000. This analysis was used to test the hypothesis that any predictive effect of striatal alterations on reading would be at least partly mediated by SL difficulties. The independent variable in this analysis was the day 2 sequence > random BOLD signal difference in the striatum (i.e., the mean sequence > random BOLD signal difference of the bilateral CN and bilateral putamen). The dependent variable was the children's reading fluency scores, and the mediator was SL day 2. Thus, the direct pathway in the model assessed the direct effect of day 2 sequence > random BOLD signal difference in the striatum on children's reading fluency scores. The indirect pathway assessed the effect of day 2 sequence > random BOLD signal difference in the striatum on children's reading fluency scores via SL day 2. Note that, in contrast to traditional methods of mediation analysis (Baron & Kenny, 1986), more modern theories do not require that the individual paths in the model are significant in order for a mediation model to be valid (e.g., Hayes, 2013; Hayes & Rockwood, 2017; MacKinnon et al., 2007).

3 | RESULTS

3.1 | Behavioral results

3.1.1 | General skill learning

No significant group differences were observed for overall accuracy (DD Mean = 89.5%, *SD* = 7.1%; TD Mean = 91.8%, *SD* = 6.3%, $t(33) = 0.99$, $p = .327$) or response speed (DD Mean = 385, *SD* = 45; TD Mean = 351, *SD* = 68, $t(34) = 1.73$, $p = .092$). The degree of general skill learning across sessions (i.e., the sequence-independent RT decrease with practice) was also similar in the two groups. The 2 (between-participants; group: DD vs. TD) \times 2 (within-participants; session: day 1 vs. day 2) ANOVA, with average RT as the dependent

variable, produced a significant main effect of day ($F(33) = 28.2$, $p < .001$, $\eta_p^2 = .460$), with significantly lower RTs across all children on day 2 compared with day 1 (day 1 Mean = 378, *SD* = 62; day 2 Mean = 360, *SD* = 64, $t(35) = 4.65$, $p < .001$), and no group \times session interaction ($F(33) = 1.85$, $p = .183$, $\eta_p^2 = .053$).

3.1.2 | Sequence-specific learning (SL)

The 2 (between-participants; group: DD vs. TD) \times 2 (within-participants; day 1 vs. day 2) factorial ANOVA revealed a large effect of group ($F(33) = 7.97$, $p = .008$, $\eta_p^2 = .195$) with poorer performance in the DD group compared with the TD group on both days (Figure 2). Additionally, there was a significant main effect of day ($F(33) = 6.19$, $p = .018$, $\eta_p^2 = .158$) reflecting an increase in SL from day 1 to day 2 across both groups (SL day 1 mean = 0.081, *SD* = 0.049; SL day 2 mean = 0.101, *SD* = 0.059). The increase in SL between day 1 and day 2 (SL change) was significant in the TD group ($t(17) = 2.38$, $p = .029$) but not in the DD group ($t(16) = 1.14$, $p = .270$); however, the group \times day interaction was not significant ($F(33) = .760$, $p = .389$, $\eta_p^2 = .023$).

3.2 | Functional and structural MRI results

3.2.1 | Functional neuroanatomy of SL across all participants

A whole-brain condition-based analysis (sequence > random) performed across both days, demonstrated activation in the parietal cortex, thalamus, medial prefrontal cortex (PFC), posterior cingulate gyrus, putamen, bilateral CN, HC, cerebellum, and precentral gyrus (Figure 3). Most of these regions were significantly activated both at day 1 and day 2 (Appendix S1). Activated areas within the predefined ROIs (HC and striatum) are presented in Table 2.

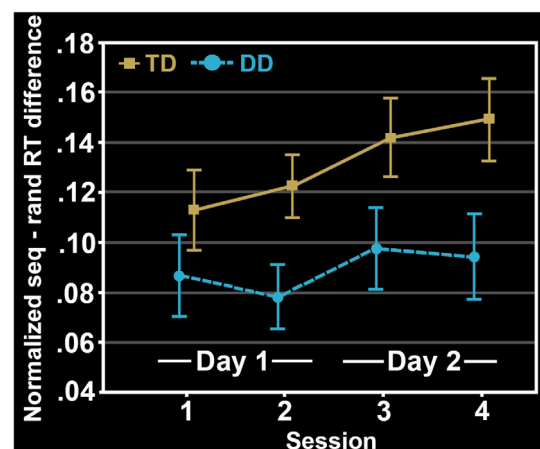


FIGURE 2 Sequence-specific learning (SL) across day 1 and day 2 displayed by groups. In order to provide a more fine-grained view of learning, the data for each day is divided into two runs with each run consisting of 12 blocks

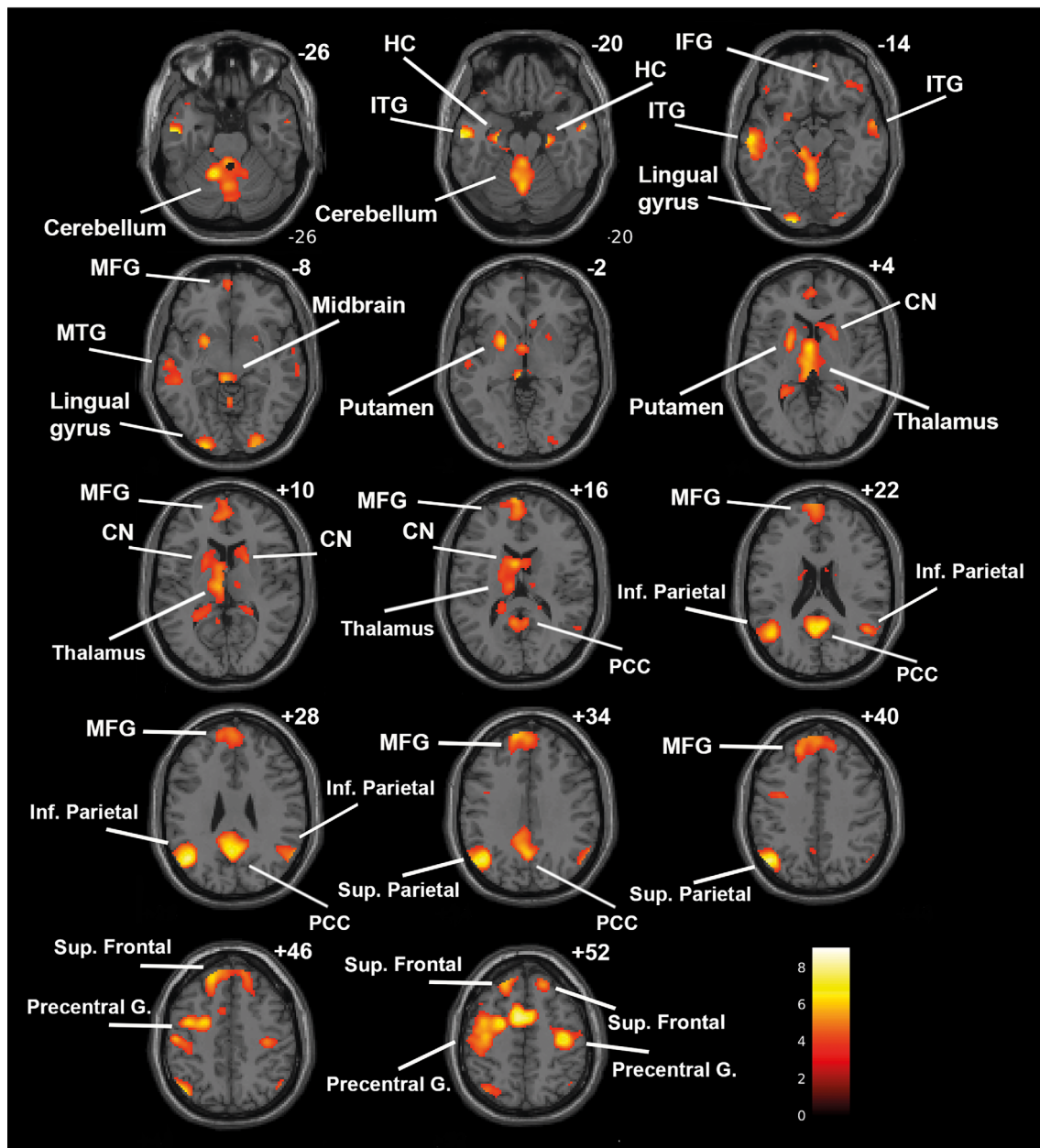


FIGURE 3 Brain activation associated with sequence-specific learning (SL). Results are displayed at a corrected threshold of $p^{\text{FWE}} < .05$. All results are reported in MNI space. Activation is shown on transverse sections of the brain

Correlation analyses between sequence > random activation differences and SL day 2

A whole-brain analysis showed that BOLD activation (sequence > random at day 2) in the right CN ($x, y, z = 8, 18, -4$) was significantly and positively associated with SL day 2. Follow-up ROI analyses using the functionally defined regions from the sequence > random contrast ($x, y, z = -20, 10, 12$; Table 2) showed a significant positive correlation between SL day 2 and task-related BOLD activation (sequence > random) at day 2 in the left CN ($r = .441, p = .008$; Figure 4a). None of the other functionally defined ROIs showed significant SL day 2–BOLD correlations (all $ps > .1$). Analyses using anatomically defined ROIs showed positive correlations between SL day 2 and task-related

BOLD activation in both left and right CN (Figure 4b and 4c; left CN: $r = .473, p = .004$; right CN: $r = .442, p = .008$).

Whole-brain analyses between the day-to-day change in the sequence > random BOLD signal difference and SL change

This analysis showed a negative correlation between SL change and the day-to-day change in the sequence > random BOLD signal difference in the right HC ($z, y, z = 28, -10, -24$; $t = 3.32$, size = 424 mm^3). That is, a larger amount of SL change was related to a reduction in HC activation between day 1 and day 2. No significant clusters were found for a positive correlation with SL change. ROI analyses (functional and anatomical) showed no significant correlations.

TABLE 2 MNI coordinates for areas within predefined regions-of-interest that showed increased activation for sequence > random

Anatomical localization	x	y	z	mm ³	t
Day 1					
L Caudate Nucleus	-6	2	8	292	5.26
R Caudate Nucleus	10	6	16	313	4.87
L Putamen	-20	4	4	310	5.57
R Putamen	24	8	-6	115	4.25
L Hippocampus	-24	-14	-22	69	5.97
R Hippocampus	26	-18	-18	50	6.21
Day 2					
L Caudate Nucleus	-18	8	16	119	4.04
R Caudate Nucleus	20	16	8	44	4.13
L Putamen	-22	4	0	102	4.47
R Putamen	22	14	6	46	4.08
L Hippocampus	-26	-16	-22	27	4.87
R Hippocampus	24	-14	-20	32	4.61
Day 1 and day 2 combined					
L Caudate Nucleus	-20	10	12	440	5.30
<i>L Caudate Nucleus</i>	-8	4	18		4.50
R Caudate Nucleus	20	16	6	435	5.02
<i>R Caudate Nucleus</i>	20	10	12		4.56
<i>R Caudate Nucleus</i>	8	22	0		4.24
L Putamen	-22	4	0	469	6.61
R Putamen	20	10	8	191	5.11
L Hippocampus	-24	-16	-22	116	7.08
L medial temporal	-20	-40	8		4.28
R Hippocampus	26	-16	-20	67	5.75

Note: Coordinates in italics refer to sub-peaks of activation.

3.2.2 | Group differences in the functional neuroanatomy of SL

Condition-based (sequence > random) contrast

Entering group as a predictor in the whole-brain condition-based analysis described in Section 3.2.1, showed that the DD children had a smaller sequence > random difference, compared with the TD children, in the right CN ($p^{(FWE)SVC} < .05$; Figure 4d; $x, y, z = 10, 12, 8$). Exploratory analyses using a more liberal threshold ($p < .001^{uncorrected}$) showed a reduced sequence > random activation difference also in the right PFC ($x, y, z = 36, 52, 16$; $t = 3.88$, cluster volume = 8200 mm³), thalamus ($x, y, z = -16, -18, -6$; $t = 3.86$; cluster volume = 1912 mm³) and right motor cortex ($x, y, z = 42, 10, 56$; $t = 3.85$; cluster volume = 2208 mm³) in the DD group compared with the TD group. No significant voxels were found for the reverse contrast (DD > TD).

Correlation analyses between sequence > random activation differences and SL day 2

No significant group differences were observed for the associations between the BOLD (sequence > random) difference in the CN ($x, y,$

$z = 8, 18, -4$) and SL day 2 (all $ps > .09$). This pattern held for the whole-brain analyses as well as for the functionally and anatomically defined ROI analyses.

Correlations between the day-to-day change in the sequence > random BOLD signal difference and SL change

Group differences in the association between SL change and decreasing hippocampal activity was examined using the functional and anatomical ROIs. For the anatomically defined ROI, the within-groups correlations were found to differ significantly (Figure 5; left HC: $z = -1.73, p = .042$; right HC: $z = -2.2, p = .014$). Within the TD group there was a significant negative correlation between SL change and the day-to-day change in BOLD activation in both the left and right HC (Figure 5; left HC: $r = -.511, p = .036$; right HC: $r = -.584, p = .014$), showing that reduced hippocampal activation from day 1 to day 2 was related to better SL. No significant correlations were found in the DD group (Figure 5; left HC: $r = .077, p = .695$; right HC: $r = .147, p = .495$).

3.2.3 | Group differences in the structural neuroanatomy of SL

Examining structural group differences in the striatum

A 2 (hemisphere: left/right) \times 3 (ROI: CN/putamen/HC) \times 2 (group: TD/DD) repeated-measures ANOVA showed no significant main effects or interactions (all $ps > .05$). Independent follow-up analyses targeting the striatum (CN and putamen) and HC, showed a significant difference between the TD and DD groups in the left CN (Figure 6a; $F(34) = 6.32, p = .017, \eta_p^2 = .161$). No other group differences were observed (all $ps > .1$).

Correlation analyses between ROI volume and SL day 2

Correlation analyses between SL day 2 and the volume of the three ROIs were performed within each group. In the TD group, there was a significant correlation between SL day 2 and CN volume (Figure 6b; left CN: $r = .507, p = .032$; right CN: $r = .575, p = .013$). In the DD group, these correlations were both nonsignificant (Figure 6b; left CN: $r = .12, p = .647$; right CN: $r = -.083, p = .751$). The difference between groups for these associations was not significant for the left CN ($z = 1.18, p = .119$), but for the right CN ($z = 1.99, p = .023$). No other correlations were significant (all $ps > .1$).

Correlation analyses between ROI volume and SL change

Correlation analyses of the association between SL change and the volume of the three ROIs revealed a significant correlation between SL change and left CN volume in the TD group (Figure 6c; $r = .541, p = .019$). In the DD group, there was a nonsignificant negative correlation between SL change and left CN volume ($r = -.157, p = .517$). The difference between groups for these associations was significant ($z = 2.66, p = .004$). Additionally, there was a significant correlation in the DD group between right HC and SL change (Figure 6c; $r = .594, p = .012$). No such association was found in the TD group (Figure 6c;

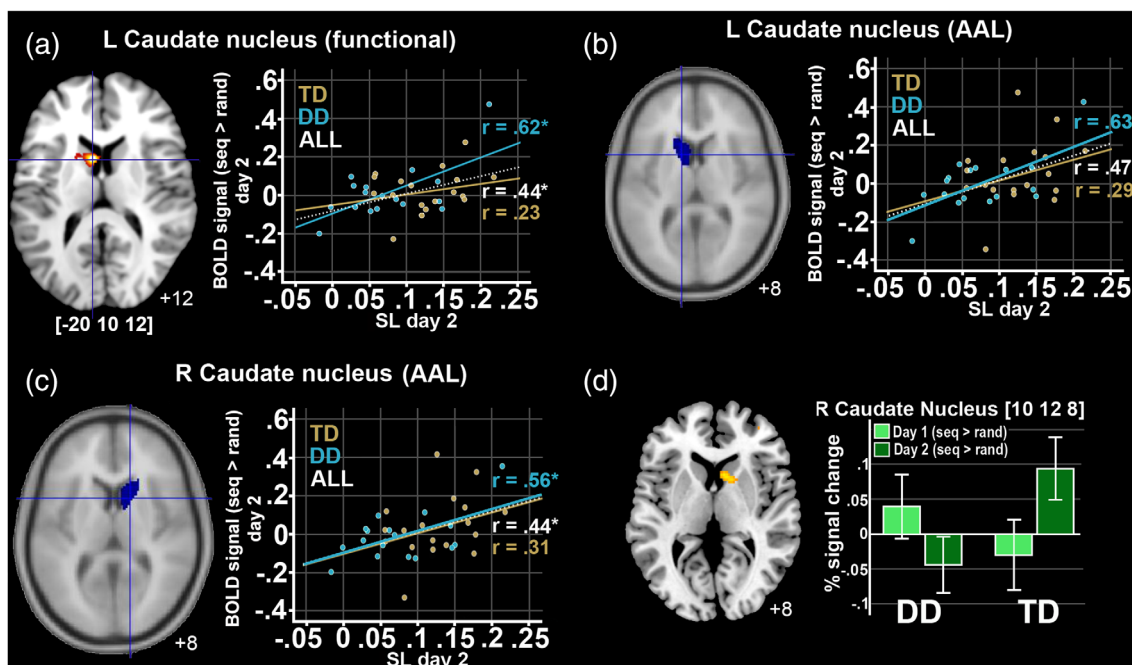


FIGURE 4 (a) A significant positive association between sequence-specific (sequence > random) BOLD-signal on day 2 and behavioral sequence-specific learning day 2 (SL day 2) in left CN [x, y, z = -20, 10, 12] was found across all participants as well as within the DD group. (b) A significant positive association between sequence-specific (sequence > random) BOLD signal on day 2 and behavioral sequence-specific learning day 2 (SL day 2) was found in left CN across all participants as well as within the DD group for anatomically defined ROIs. (c) A significant positive association between sequence-specific (sequence > random) BOLD signal on day 2 and behavioral sequence-specific learning day 2 (SL day 2) was also found in the right CN across all participants as well as within the DD group for anatomically defined ROIs (d) Activation in the right CN for sequence-specific learning (SL) across day 1 and day 2 for TD and DD children. DD children had significantly less activation compared to the TD children as indicated by the group by day interaction

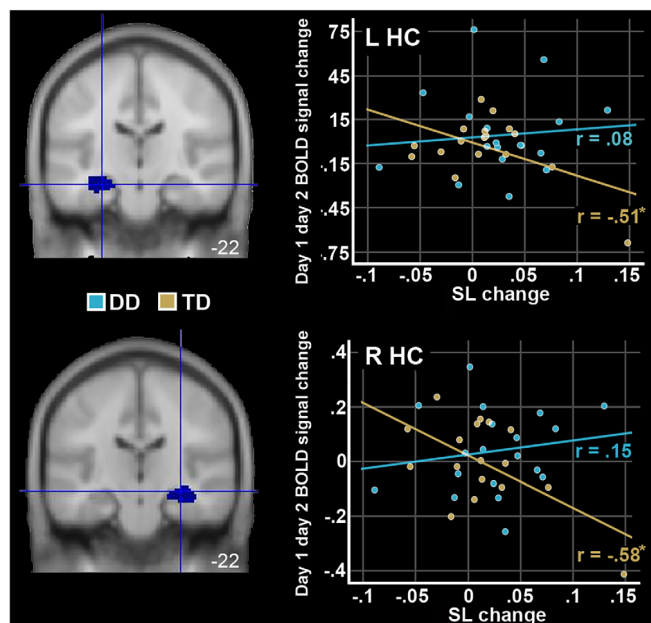


FIGURE 5 Associations between sequence-specific BOLD-signal on day 2 and sequence-specific learning day 2 (SL day 2) in the anatomically defined ROIs of left and right HC. A significant negative association was demonstrated in the TD group but not in the DD group

$r = .158, p = .531$). The difference between groups for these associations did not, however, reach significance ($z = 1.41, p = .079$).

3.2.4 | The brain–SL–reading link

The results of the mediation analysis showed that the amount of sequence-specific striatal activity did not have a significant direct effect on reading fluency ($b = -3.19, 95\% \text{ CI}, -7.88 \text{ to } 1.51$). However, the indirect effect, via SL, was significant ($b = 2.44, 95\% \text{ CI}, .451 \text{ to } 6.06$). As shown in Figure 7, striatal sequence-specific activity predicted SL ($b = .171, 95\% \text{ CI}, .046 \text{ to } 2.97$) which in turn predicted reading fluency ($b = 15.64, 95\% \text{ CI}, 4.81 \text{ to } 26.47$). This means that a change with one unit in striatal activation will lead to a change in reading fluency that is equal to the product of the striatum–SL effect and the SL–reading fluency effect (Hayes & Rockwood, 2017).

4 | DISCUSSION

This study aimed at testing the PDH at the brain level by examining the neural correlates of SL on the SRT task in children with DD

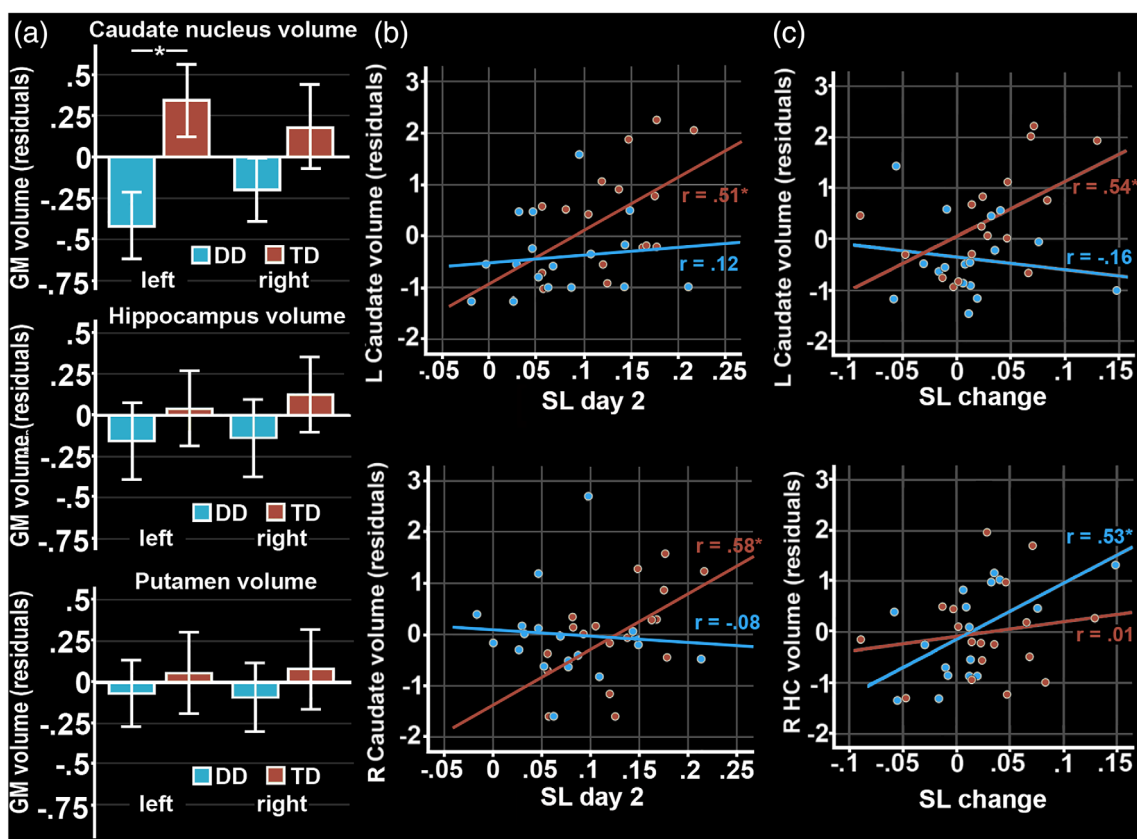


FIGURE 6 (a) GM volume of the HC, CN, and putamen in DD children and TD children. Children in the DD group had on average lower GM volume in the left CN compared with TD children. (b) Significant positive associations between GM volume of the left (top) and right (bottom) CN and sequence-specific learning day 2 (SL day 2) was found within the TD group but not in the DD group. (c) A significant positive association between GM volume in the left CN and change in sequence-specific learning between day 1 and day 2 (SL change) was found in the TD group but not in the DD group (top). A significant positive association between GM volume in the right HC and change in sequence-specific learning between day 1 and day 2 (SL change) was found in the DD group but not in the TD group (bottom)

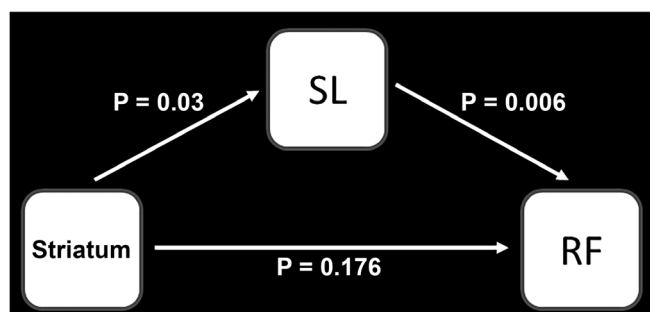


FIGURE 7 The link between striatal sequence-specific brain activity, sequence-specific learning (SL), and reading fluency

compared with TD children. The study was hypothesis-driven and focused primarily on examining specific predictions about group differences at the behavioral, as well as brain functional and structural levels. In addition, whole-brain and ROI-analyses were conducted across all participants in order to establish a general pattern for the neural correlates of SL on the SRT task in children. The study was conducted over 2 days in order to cover learning beyond a single practice session (Hedenius et al., 2021). In the following, we will first

consider the results from the whole-brain and ROI activation patterns across all participants before examining how well each of the specific predictions was borne out.

4.1 | Whole-brain and ROI analyses across all participants

A whole-brain analysis showed significantly stronger activation in response to sequential compared with random stimuli in brain areas previously associated with SL (Batterink et al., 2019; Doyon et al., 2009; Janacsek et al., 2020), including the striatum (bilateral CN and putamen) on both days. This finding is fundamental to the interpretation of the results as it shows that the SRT paradigm employed in the present study provides a suitable means for testing the predictions of the PDH in children.

The degree of activation increase in response to sequence compared with random stimuli in the CN predicted children's SL day 2. This relationship was confirmed by analyses of the CN as a ROI, regardless of whether it was functionally or anatomically defined. This pattern is consistent with previous studies of adults (Doyon et al., 2009;

Janacek et al., 2020) and suggests that the striatum has a crucial role in the processing of sequential stimuli, also in children. The degree of SL change was associated with a decrease in HC activity. In line with previous studies (Albouy, 2008; Pinsard et al., 2019; Rieckmann et al., 2010), this supports the notion that the role of the HC in SL decreases with practice.

4.2 | Prediction 1. Group differences in behavioral SL

At the behavioral level, we predicted that children with DD would show less SL compared with the TD group, either across the task as a whole (Lum et al., 2013) or on day 2 (Hedenius et al., 2021). In line with this prediction, the DD group displayed significantly less learning on both days. This finding is consistent with previous research showing that DD is associated with challenges relating to the implicit extraction of sequential statistical regularities in the input (e.g., Gabay et al., 2015; Hedenius et al., 2013; Hedenius et al., 2021; Howard Jr. et al., 2006; Jimenez-Fernandez et al., 2011; Lum et al., 2013; van Witteloostuijn et al., 2017). The fact that general skill learning was intact in the DD group suggests that the observed SL difficulties are not explained by more general problems with attention, processing speed, or motor abilities (Hari & Renvall, 2001; Willcutt et al., 2010).

Considering that 26 out of the 35 participants in the present study were also part of the study by Hedenius et al. (2021), in which a DD disadvantage emerged only on day 2, it is noteworthy that the DD group in the present study showed poorer SL already on day 1. One possible reason for this discrepancy could be that the DD and TD groups differed with respect to how distracted they were by the MRI environment, which could have led to a group difference in their ability to focus on the task. The difference could also be due to the fact that the ASRT task in the Hedenius et al. (2021) study was self-paced, and allowed participants to proceed at their own pace, whereas the timing of the SRT task used in the present study was fixed. Thus, the results in the present study could have been influenced by a group difference in processing speed (McGrath et al., 2011). However, these explanations are difficult to reconcile with the lack of group differences in overall accuracy and general skill learning, since group differences in attention or processing speed would likely affect these variables as well. Another possibility is that the discrepancy reflects inherent differences in the statistical structure of the sequences in the ASRT task used by Hedenius et al. (2021) and the SRT task used in the present study. In the ASRT task, random trials are interspersed within the sequence in an alternating fashion (i.e., if the sequence is 1-2-4-3-, the statistical structure will be 1-r-2-r-4-r-3). This structure has been shown to primarily (but not solely) induce learning based on “triplets”, that is, participants implicitly learn that certain runs of three subsequent events are more likely to occur than others (Howard & Howard, 1997; Szegedi-Hallgató et al., 2019). By contrast, in the SRT task used in the present study, blocks in which the 12-item probabilistic sequence was repeated three times were interspersed with blocks in which an equal number (36) of random

trials were presented. Such structure-related differences could potentially lead to differences in the neurocognitive underpinnings of the tasks (Conway, 2020), and, in this case, have made initial learning more challenging for the DD group on the SRT task compared with on the ASRT task.

4.3 | Prediction 2. Group differences in the functional neuroanatomy of SL

At the brain activation level, we predicted that the associations between measures of sequence-specific brain activity and measures of SL would differ between the groups with evidence for striatal alterations and HC compensatory activation in the DD group. These predictions were partly borne out.

First, the sequence-specific activation patterns were shown to differ between the groups with decreased recruitment of the (right) CN in the processing of sequential stimuli (i.e., a smaller sequence > random activation difference) in the DD group compared with the TD group. One possible interpretation of this finding is that it reflects a group difference in the extent to which the striatum is involved in the processing of sequential stimuli.

Regarding the prediction of a stronger relationship between striatal sequence-specific activation and SL in the TD group, compared with the DD group, we found no such indications. While counter to the prediction, these findings should be interpreted in the light of overall reduced condition-based activation in the DD group compared with the TD group. Reduced striatal activation in the DD group may underlie the observed SL deficits, but within this group, additional recruitment could still show positive correlations with performance.

The observed group difference in the association between SL change and decrease in HC activation may be partly consistent with the prediction of compensatory HC activation in the DD group. In the TD group, reduced HC activation predicted better SL; a pattern that was not found in the DD group. Although there was no significant positive correlation between SL change and HC activation in the DD group, and thus no direct support for a compensatory role of HC for learning, the lack of a negative correlation suggests an altered HC activation pattern during SL in the DD group compared with the TD group. This finding could indicate that, compared with their TD peers, children with DD rely relatively more on HC for SL also in later stages, a finding that would be consistent with the activation patterns observed in older compared with younger adults (Rieckmann et al., 2010) and in patient groups with striatal pathology (e.g., Moody et al., 2004).

4.4 | Prediction 3. Group differences in the structural neuroanatomy of SL

At the anatomical level, we predicted a group difference in striatal GM volume. We also expected the within-group associations between

SL and HC/striatal GM volumes to differ, with greater learning in the DD and TD groups being associated with greater HC and striatal volume, respectively.

Although the higher-level ANOVA testing the predictions of striatal abnormalities and intact HC in the DD group did not yield any significant effects, analyses targeting the striatum, specifically, pointed to a group difference in CN with smaller GM volume in the DD group compared with the TD group. However, the lack of significance in the higher-level main analyses precludes any strong conclusions, based on the present study, with respect to striatal anatomy in DD.

First, associations between GM volume and SL across all participants showed that the correlation between GM volume in left CN was significantly associated with SL day 2 ($r = .43, p = .009$). Correlations between SL day 2 and GM volume in the right CN, HC and putamen were all nonsignificant ($p > .1$). For associations between GM volume and SL change, the correlation between right HC and SL change was significant ($r = .361; p = .033$). Correlations between SL change and the CN, putamen and left HC were all nonsignificant ($p > .1$).

Second, in line with the prediction of a group difference in the association between striatal GM volume and SL, the within-group analyses showed a correlation between CN volume (left and right) and SL day 2 in the TD group, but not in the DD group. A similar pattern was found for SL change; left CN volume predicted SL in the TD group but not in the DD group. The correlations between SL and CN volume in the TD group is consistent with a crucial role for this region in SL (Janacsek et al., 2020) as well as with the functional findings described above. The lack of associations between CN volume and SL in the DD group appears consistent with the observed group difference in sequence-specific CN activation, and could indicate that this region is less involved in SL in children with DD compared with TD children.

4.5 | The brain—SL—reading link

To the best of our knowledge, the present study is the first to show a possible brain level mechanism for the challenges with SL associated with DD, and how these brain alterations could relate to reading proficiency. The findings suggest that less efficient striatal activation predicts SL difficulties, and that SL difficulties, in turn, predict reading problems. That is, striatal activation appears to be associated with reading fluency, not directly, but via its effect on SL. Crucially, our mediation analysis was strictly hypothesis-driven and set up to specifically test potential direct and indirect effects of striatal alternations on reading as opposed to examining the brain basis of reading fluency (e.g., Langer et al., 2015), and SL (e.g., Janacsek et al., 2020; Orpella et al., 2021), more generally. Further research is needed to determine the relative importance of the striatum in relation to other brain regions implicated in these functions.

The observed correlation between SL day 2 and children's reading fluency replicates the findings of two previous studies in which sequence learning and consolidation was examined over 2 days

(Hedenius et al., 2013, 2021) using the ASRT task (e.g., Howard et al., 2004). Although there was an overlap in participants between the study by Hedenius et al. (2021) and the present study, the results are independently informative as the tasks employed in the two studies differed with respect to their sequential structure, procedure, and were also given several months apart. Taken together with previous research using other statistical learning paradigms (e.g., Gabay et al., 2015; Kahta & Schiff, 2019; van Witteloostuijn et al., 2017) these results suggest that children's capacity for implicitly extracting sequential regularities may be related to their reading proficiency.

It is of great theoretical as well as clinical interest to understand how the SL challenges observed in DD relates to the reading difficulties that define the condition. Learning to read fluently clearly involves learning a vast amount of probabilistic regularities, many of which have a sequential structure (Arciuli, 2018; Frost et al., 2019; Siegelman et al., 2020). The observed associations between experimental tasks tapping such learning, and reading proficiency, may therefore reflect that these activities share some of their underlying cognitive mechanisms. Because the observed associations so far (including the present study) have been correlational in nature, future studies with a longitudinal design are needed before any conclusions can be drawn about cause and effect, that is, do difficulties with learning sequential statistical regularities contribute to reading difficulties? Additionally, because the individual variance in reading proficiency explained by SL is limited, so is its explanatory power for the reading difficulties in DD. Therefore, the potential impact of SL difficulties on the DD phenotype may be best understood in terms of a multi-factorial view in which several underlying cognitive functions (including both risk and protective factors) interact probabilistically (McGrath et al., 2020; Pennington, 2006). On this view, a weakness in the capacity for implicitly extracting sequential statistical regularities could be one of several potential risk factors, possibly shared with other neurodevelopmental conditions, that influence the total risk of developing reading problems (McGrath & Stoodley, 2019). The extent to which the pattern of risk and protective factors associated with DD may be accounted for by alterations of cortico-basal ganglia circuits, and compensatory engagement of the medial temporal lobe, may be further explored in future research.

4.6 | Limitations and future directions

The present study has limitations that may be addressed by future studies. First, the sample size was relatively small and the results need to be validated in a larger group of children in order for more reliable conclusions to be drawn. Second, our study did not include information about children's sleep patterns. It is possible that the inclusion of such data could inform the interpretation of the observed group differences in learning (but see Pan & Rickard, 2015). Third, a majority of the participants had taken part in a previous sequence learning study using the ASRT task (Hedenius et al., 2021) and it remains to be investigated if the results hold when all participants are naïve to the (A) SRT paradigm. Finally, using isolated brain regions as predictors of reading ability may be less informative compared with focusing on

brain networks and their connections (e.g., van den Heuvel & Sporns, 2019). A natural step forward from the present study could be to study the possible influence of connectivity within the cortico-basal ganglia network on SL and reading proficiency.

5 | CONCLUSION

The present study provides the first direct examination of the neural correlates of SL in children with DD, and suggests a possible link between brain function, SL, and individual reading proficiency. The results indicate that striatal alterations contribute to the SL challenges associated with DD, and that SL challenges may in turn explain some of the variance in reading proficiency. Children with DD also differ from their TD peers in the extent to which the HC is recruited during the course of SL, which could indicate compensatory activation. The findings encourage further research into factors that promote learning in children with DD, including through compensatory mechanisms.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data underlying this article is available from the authors upon request.

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