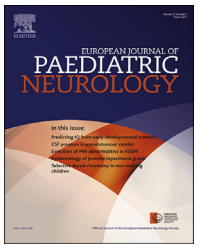
Official Journal of the European Paediatric Neurology Society



Original article

Neural changes associated to procedural learning and automatization process in Developmental Coordination Disorder and/or Developmental Dyslexia

Maëlle Biotteau [a,*], *Patrice Péran* [a], *Nathalie Vayssière* [b], *Jessica Tallet* [a], *Jean-Michel Albaret* [a], *Yves Chaix* [a,c]

[a] *Toulouse NeuroImaging Center, Université de Toulouse, Inserm, UPS, France*
[b] *CerCo, UMR 5549 CNRS UPS, Toulouse, France*
[c] *Hôpital des Enfants, Centre Hospitalier Universitaire de Toulouse, CHU Purpan, Place du Dr Baylac, F-31059 Toulouse Cedex 9, France*

ARTICLE INFO

Article history:
Received 7 January 2016
Received in revised form
8 July 2016
Accepted 29 July 2016

Keywords:
Neurodevelopmental disorders
Comorbidity
fMRI
Learning

ABSTRACT

Objective: Recent theories hypothesize that procedural learning may support the frequent overlap between neurodevelopmental disorders. The neural circuitry supporting procedural learning includes, among others, cortico-cerebellar and cortico-striatal loops. Alteration of these loops may account for the frequent comorbidity between Developmental Coordination Disorder (DCD) and Developmental Dyslexia (DD). The aim of our study was to investigate cerebral changes due to the learning and automatization of a sequence learning task in children with DD, or DCD, or both disorders.

Method: fMRI on 48 children (aged 8-12) with DD, DCD or DD + DCD was used to explore their brain activity during procedural tasks, performed either after two weeks of training or in the early stage of learning.

Results: Firstly, our results indicate that all children were able to perform the task with the same level of automaticity, but recruit different brain processes to achieve the same performance. Secondly, our fMRI results do not appear to confirm Nicolson and Fawcett's model. The neural correlates recruited for procedural learning by the DD and the comorbid groups are very close, while the DCD group presents distinct characteristics. This provide a promising direction on the neural mechanisms associated with procedural learning in neurodevelopmental disorders and for understanding comorbidity.

Published by Elsevier Ltd on behalf of European Paediatric Neurology Society.

* *Corresponding author*. Inserm, Imagerie Cérébrale et Handicaps Neurologiques, UMR 825, CHU Purpan, Place du Dr Baylac, F-31059 Toulouse Cedex 9, France.
E-mail addresses: maelle.biotteau@inserm.fr (M. Biotteau), patrice.peran@inserm.fr (P. Péran), vayssiere@cerco.ups-tlse.fr (N. Vayssière), jessica.tallet@univ-tlse3.fr (J. Tallet), jean-michel.albaret@univ-tlse3.fr (J.-M. Albaret), chaix.y@chu-toulouse.fr (Y. Chaix).
http://dx.doi.org/10.1016/j.ejpn.2016.07.025
1090-3798/Published by Elsevier Ltd on behalf of European Paediatric Neurology Society.

Abbreviations

Groups

DCD	Developmental Coordination Disorder
DD	Developmental Dyslexia
MI	comorbid group (for MIXED)

Tasks

OverTSeq	Overtrained Sequence
NovelSeq	Novel Sequence
DTS	Dual Task Sequence

Brain areas

CC	cortico-cerebellar
CS	cortico-striatal
ACC	anterior cingulate cortex
IPC	inferior parietal cortex
PCC	posterior cingulate cortex

1. Introduction

1.1. *DD and DCD*

Developmental Dyslexia (DD) and Developmental Coordination Disorder (DCD) are both persistent disorder in which children show learning deficits, respectively for reading and for motor skills, despite adequate intelligence, normal sensory abilities, and conventional instruction, sociocultural opportunity and school education.[2,66] In the recent version of the DSM-5, DD and DCD are classified as neurodevelopmental disorders, which include a group of conditions with onset in the early developmental period and are characterized by developmental deficits ranging from very specific limitations of learning or control of cognitive functions to global impairments of social skills or intelligence. An actually important source of interest for many researchers is that neurodevelopmental disorders frequently co-occur (DSM-5). Especially, up to 50% of children with DD also have DCD, and conversely.[8,22] Motor disorders can thus affect about 60% of subjects with dyslexia[8,51] and up to 70% of subjects with DCD have also reading problems.[40] A keen interest is therefore focused on this specific association, certainly participating to heterogeneity and complexity of those disorders.[52,63] If such comorbidity is well-established, very few studies have concerned this specific association. Is these disorders are the same or different in pure occurrence or in association? What impact might comorbidity have on behavioural, neuropsychological or cerebral level? Very little data are available as regard to the association between DD and DCD. Recent research,[3,4] comparing three groups: children with pure DCD, children with pure DD and children with dual-association, show that there are very few differences between groups at behavioural (procedural learning tasks) and neuropsychological level (efficiency, attention, psychosocial). Where differences exist, there were only between DCD and the two other groups, which raises questions about the nature of the DD and DCD comorbidity.

Works of Nicolson and Fawcett[37,38] sustain that procedural learning impairment, commonly encountered in neurodevelopmental disorder[10,35] provide a suitable explanation of the substantial overlap between DD and DCD. This kind of learning refers to motor and cognitive skills acquired progressively and finally automated (performed without effort and conscious control) thanks to repetitive practice. This process of gradual acquisition is known to involve a series of successive stages[12]: the fast learning stage where rapid improvement can be observed within a single session and next, the slow learning stage where further gains gradually appear across several training sessions until the attainment of automatization. For authors, specific developmental disorders should be secondary to an impairment of the procedural learning system (and especially in automatization), contrasting with general learning disabilities (i.e. intellectual developmental disorder) secondary to an impairment of the declarative learning system. A number of skills impaired in DD and DCD are indeed derived in large part from this system and impairment in procedural learning tasks are identified in both DD[34] and DCD.[10,21] However, DD as DCD does not imply a total incapacity to learn motor skills. Children are less efficient and probably need more time and practice to learn and reach a satisfactory level of performance, but they are still able to learn. They especially can achieve short term learning, long-term retention, automatization and transfer (see Refs. 14,41 for DD; and Ref. 5 for DCD).

Procedural learning and automatization are supported by cortico-striatal and cortico-cerebellar loops.[12] In this context, Nicolson and Fawcett[37,38] proposed 'the neural system typography for learning difficulties', in which DD is attributed to the language-related-component of the cortico-cerebellar circuit, as suggested by their difficulties in adaptation and supported by several neuroimaging studies revealing cerebellar abnormalities (for a review see Refs. 56,57), and in which DCD is associated with a deficit in the motor-related component of the cortico-striatal system. Naturally, their model proposes that comorbidity is characterized by impairments in more than one circuit. Even if this model offers explanations of common and distinct deficits presented by DD, DCD and their association, it is important to note that the hypotheses of neural-systems impairments are only deduced from behavioural symptoms, and not from neural studies. Effectively, in both case, neuroimaging studies have focused purely on the cornerstone of these disorders (the motor or reading aspects) and the questions of procedural learning and of comorbidity was not addressed. Briefly, neuroimaging studies conducted in DD report atypical activation of the left perisylvian fronto–temporo-parietal network, especially in the inferior frontal gyrus (Broca's area, BA 44/45), the inferior occipital–temporal area (Visual Word Form Area, BA 37) and the parietal/temporal regions (BA 22, 39, 40) (see Ref. 54 for a recent meta-analysis). But the role of subcortical structures such as the cerebellum or lenticular nuclei have also been highlighted by some authors.[47,56,57] Less neuroimaging studies have been conducted on DCD and dysfunctions of prefrontal, premotor and parietal cortices, basal ganglia and cerebellum are reported (for review see Refs. 6,48). Thus features in cortico-striatal as cortico-cerebellum networks could therefore be envisaged in both disorders.

1.2. *Purpose of the current study*

Procedural learning/automatization deficit seems to provide a robust and consistent explanation for the frequent association between DD and DCD. But the neural system typography for learning difficulties, based on categorization of disorders depending on cerebral loops, has been supported only by behavioural and not by neuroimaging studies. In this context, using a typical practice task of procedural learning (finger tapping task) under functional Magnetic Resonance Imaging (fMRI), the present study aims to combine motor performance (behavioural data) and patterns of cerebral activation (neural correlates of procedural learning) associated to the learning of a procedural task (acquisition up to automatization) in order to compare which parts of the motor learning networks are identical and which are different in three groups: DD, DCD, DD + DCD (MI for mixed group). According to the procedural learning deficit hypothesis,[37] for the same level of behavioural performance, we can expect that the DD group would present a more particular brain recruitment on the cortico-cerebellar loop than the DCD group, whereas the DCD group would present a more particular brain recruitment on the cortico-striatal loop than the DD group. Based on Nicolson and Fawcett's model, we thus hypothesized that the comorbid group would experience additive effects (i.e. a combination of the deficits induced by each primary disorder) at both behavioural and neural levels, with an atypical recruitment in both cortico-striatal and cortico-cerebellar loops.

2. Materials and methods

2.1. *Participants*

A total of 67 children (23 girls, 44 boys, aged from 7 years 8 months–12 years 11 months), participated in the study. The children were recruited from the dedicated Regional Reference Center for Learning Disabilities Diagnosis or by outside therapists and had already been diagnosed with DD or/and DCD before the inclusion visit. All of them were right-handed as assessed by the Edinburgh Inventory,[39] had normal or corrected-to-normal vision and no history of neurological or psychiatric disorders. Children and parents gave their free and informed consent. All experimental procedures received approval from the local ethics committee.

All the participants underwent the same complete neuropsychological evaluation, including an assessment of intellectual abilities,[64] reading skills (l'Alouette test[32] and ODEDYS-2 battery[26]), motor skills (M-ABC[23]), oral skills (EVIP, French version of the "Peabody Picture Vocabulary Test-Revised"[15], ECPA[18] and ECOSSE[31]), attention capacities (CPT-II[9]) and the child's behaviour (CBCL, Achenbach & Rescorla, 2001[1]).

In order to confirm the diagnosis and to evaluate the level of impairment, reading disability was assessed with the ODEDYS-2 test,[26] which evaluated word recognition procedures and consisted in reading series of 20 regular words, 20 irregular words, and 20 pseudo-words (or nonwords) and the French reading test L'Alouette, which yields two indexes of accuracy and speed when reading a text.[32] These two tests give rise to accuracy and speed measures when reading isolated words or a text. They are generally used to subdivide the reading profile of participants (phonological, surface, or mixed dyslexia) and aimed at broadly analyzing reading abilities. In our study, a child was classified as dyslexic only if it meets both of the following criteria: first, his/her reading fluency score in reading isolated words (word or pseudo-word reading on the ODEDYS-2 battery) fell below −1.5 SD and second, his/her reading speed score when reading a text fell below −1.5 SD (Alouette reading test) or a reading speed score below −1 SD associated with a reading accuracy score below −1.5 SD. It should be underlined that the majority of children with DD (29 out of 32) scored at or lower than −1.5 SD on the Alouette reading speed index. A child was classified as reading normally if the score was equal to or above +0.5 SD on reading skills and the Alouette reading test. Children with intermediate results were excluded. Noted that to reduce the heterogeneity and define more homogeneous groups of participants with developmental dyslexia, excluded were children presenting a surface dyslexia defined by a specific disorder in learning to read without difficulty for metaphonological tests and/or an exclusive impairment of the addressing reading route (reading irregular words).

According to the recommendations of the European Academy for Childhood Disability (Blank et al., 2012[69]), motor ability was tested using the French version of the Movement Assessment Battery for Children (M-ABC[55]). A child was classified as DCD if his/her Total Impairment Score on M-ABC (TIS) was below the 5th percentile and was considered to have no motor impairment if the TIS was above the 15th percentile. Children with TIS between the 5th and the 15th percentiles were excluded.

In order to obtain groups as homogeneously as possible, children with Intellectual Disability, Specific Language Impairment or Attention Deficit/Hyperactivity Disorder according to the DSM-IV-TR criteria were excluded. In addition, all children had a medical examination to exclude contraindications to MRI and other neurological and psychiatric diseases.

After the test period, two children were excluded due to low IQ and 17 children because they did not complete the brain scan (failure to arrive, illness, being afraid or moving too much). The remaining 48 participants (17 girls) composed our total sample of children for neuropsychological, behavioural and MRI data analysis, with 16 DCD (4 girls), 16 DD (7 girls), 16 MI (6 girls).

2.2. *Material, tasks and procedure*

2.2.1. *Material*

All auditory and visual stimuli were generated with Presentation software version 12.1 (Neurobehavioral System Inc., Albany, CA) and synchronized with MRI acquisition on a computer connected via optical fibre to MRI-compatible devices. Visual stimuli were displayed on a screen at the rear end of the scanner and were visible via a mirror mounted on the head coil. Button presses were performed with the right hand, and were recorded with an MRI-compatible response pad (FORP, Current Designs).

All the MRI data were acquired in a single session on a Philips 3-T imager (Intera Achieva, Philips, Best, The Netherlands).

2.2.2. Tasks and procedure

In our study, we have chosen to assess procedural learning at the early stage of learning (acquisition) and at the end of learning (automatization) using a motor sequence learning task. Such learning require practice during two weeks with an assessment at the beginning (day 1) and at the end (day 14) of the training. However, to take into account that participants were young children and that the task was effortful in the MRI, in our study we assess the two stages of learning with an original design administrated the same day (as already shown with knitter experiment in[12]). Thus, the day of the MRI session, children were required (i) to produce an overtrained fingers' tapping sequence task (OverTSeq), which corresponds to a Post-test after 15 days of training and (ii) to produce a novel and never practiced fingers' tapping sequence task (NovelSeq), which corresponds to a Pre-test (beginning of training). By comparing the motor performance and patterns of cerebral activation of the NovelSeq and the OverTSeq, we obtained an assessment of learning which corresponds to the difference between the Pre- and the Post–test. Of course, we paid a particular caution that the structure of the two sequences (Novel and Overtrained) was similar: each consisted in five tapping and each finger was used once or twice in each sequence. In the two sequences, movements were self-initiated and self-paced to reduce the risk of differences in the neural underpinnings being linked to internally versus externally triggered movements.[59] Nevertheless, to limit transfer of learning effects and to avoid possible confusion between the two tasks, we ensured that no succession of two fingers was identical between the two sequences and no sequence began with the same finger.

Assessment of end of procedural learning process (slow learning; automatization stage); Overtrained task (OverTSeq): Children were instructed to execute continuously a fingers' tapping sequence task with their right hand, as accurately and rapidly as possible. The task corresponded to the following sequence: 1-2-1-2-3, in which 1, 2 and 3 refer to the index, middle and ring fingers, respectively. The participants were required to perform the task as long as a green cross was displayed. When the cross was red, participants were asked to relax and focus on the screen in front of them without moving in the scanner. No feedback was provided to the participants on whether their finger movements were correct or incorrect. Only two auditory stimuli were given: “go” and “stop” at the beginning and end of the task period respectively. The OverTSeq was tested after a practice of three minutes twice daily during 15 days. The practice was made under direct parental control. A report timetable and hourglass were distributed at the beginning of the practice and controlled before the MRI session. Children have all, without exception, performed the practice seriously three minutes twice daily over the 15 days.

Assessment of beginning of procedural learning process (fast learning); Novel task (NovelSeq): The NovelSeq corresponded to a declination of the Overtrained Sequence but was not practiced before the MRI session. The structure of the NovelSeq was similar to the OverTSeq but the sequence itself was different: 2-3-1-3-1. The NovelSeq has been explained just before the MRI session. Children could familiarize with the task but have never practiced the sequence before the MRI.

Control of automatization process for OverTSeq; Dual Task Sequence (DTS): Even when participants have practised and improved a task after practice, their performance may not achieve automatic status.[29] The evidence that a task has become automatic can be provided only by the ability to perform a secondary task with minimal interference.[43] Therefore, in our study, to assess if OverTSeq performance became automatic, participants were asked to perform a dual-task paradigm before the MRI session. The primary task was the OverTSeq and the secondary task consisted in a visual image-denomination task, in which children were invited to name usual images presented on a screen (e.g. snail, fireplace, kangaroo) and known to be named without errors by this age range. The two tasks were performed simultaneously and the motor performance in single condition (OverTSeq) and in dual-task (DTS) were compared.

2.3. Data acquisition and analysis

2.3.1. Clinical analysis

All statistical analyses were performed using IBM SPSS 21.0.0.0. Chi-square tests were used to compare DCD, DD, MI by gender, sex and CSP status. ANOVAs were conducted to investigate the differences between the three groups with regard to the neuropsychological tests. Tukey post hoc tests were performed to compare the means for the different groups. For all tests, a probability level of $p < .05$ was considered statistically significant.[25]

2.3.2. Behavioural data acquisition

For each participant and each sequence produced inside and outside the scanner, each key tap was recorded with Presentation software version 12.1041008 (Neurobehavioral System Inc., Albany, CA).

First, the number of taps was recorded for each participant and each sequence and the incorrect taps were detected within each sequence produced. Then, the produced sequence was compared to the required sequence for each participant and each sequence. On this basis, we computed an Accuracy Index capturing the performance produced by each participant for each required sequence: OverTSeq performed during six blocks inside the scanner (OverTSeq(inside)), NovelSeq performed during six blocks inside the scanner (NovelSeq(inside)), OverTSeq performed during six blocks outside the scanner (OverTSeq(outside)) and DTS performed during two blocks outside the scanner (DTS(outside)). The Accuracy Index of the sequence produced is given by the formula:

$$AI_x = \frac{SEQ_X}{SEQTh_X}$$

where SEQ_X represents the number of sequences achieved by the participant for the task X and $SEQTh_x$ represents the theoretical number of sequences performed by the participant, given by the formula $SEQTh_X = \sum_{i=1}^{6} \left\lfloor \frac{TAP_X^{B_i}}{5} \right\rfloor$ where $TAP_X^{B_i}$ represents the number of taps achieved during the block $B_i (1 \leq i \leq 6)$ and $\lfloor . \rfloor$ the integer part. For example, if a child performed 96, 100, 95, 96, 99 and 92 taps for the six blocks in

the task X, the theoretical number of sequences $SEQTh_X$ will be calculated by $SEQTh_X = \left\lfloor \frac{96}{5} \right\rfloor + \left\lfloor \frac{100}{5} \right\rfloor + \left\lfloor \frac{95}{5} \right\rfloor + \left\lfloor \frac{96}{5} \right\rfloor + \left\lfloor \frac{99}{5} \right\rfloor + \left\lfloor \frac{92}{5} \right\rfloor$, i.e. $SEQTh_X = \lfloor 19.2 \rfloor + \lfloor 20 \rfloor + \lfloor 19 \rfloor + \lfloor 19.2 \rfloor + \lfloor 19.8 \rfloor + \lfloor 18.4 \rfloor$, i.e. $SEQTh_X = 19 + 20 + 19 + 19 + 19 + 19 + 18$ and finally $SEQTh_X = 114$. As, for this example, the number of sequences achieved by the child was $SEQ_X = 87$, the Accuracy Index is given by $AI_X = \frac{87}{114} \simeq 0.7632$.

2.3.3. *Behavioural statistical analysis*

First, a Group (3) × Learning (OverTSeq(inside), NovelSeq(inside)) ANOVA with repeated measures on Learning was carried out on the Accuracy Index in order to compare the level of learning achieved by the Groups. Second, a Group (3) × Automatization (OverTSeq_B1(outside), DTS_B1(outside)) ANOVA with repeated measures on Automatization was carried out on the Accuracy Index in order to compare the level of automatization achieved by the Groups. This level does not take into account the number of images named correctly during the dual task because no error occurred (all the images were named correctly by all participants). For all analyses, the p value was fixed at $p < .05$ and the η^2 were reported.

2.3.4. *fMRI data acquisition*

The protocol lasted 25 min and included two runs of fMRI acquisition, lasting 360 s each. The OverTSeq and the NovelSeq have been performed 6 blocks of 60 s with alternating Rest (30 s) and Task (30 s).

Particular care was taken to stabilize the children using foam cushions and a Velcro band. To reduce acoustic noise, the children were also provided with earplugs.

Blood-oxygenation-level-dependent sensitive functional images were collected using oblique axial gradient echo-planar imaging (EPI) images (TR = 2500 ms; TE = 35 ms; FA = 90°; FoV = 230 × 230 mm^2; matrix size = 96 × 96; voxel size = 2.4 × 2.4 × 4 mm^3; 33 slices, 144 dynamics). A T1 high resolution anatomical image, using a 3D-sequence (in-plane resolution 1 × 1 mm, slice thickness 1 mm, repetition time/echo time/inversion time = 8.189 ms/3.75 ms/1012.2 ms, flip angle 8°, TFE factor = 150, field of view 240 × 240, and contiguous slices) was achieved.

2.3.5. *fMRI statistical analysis*

Data were analysed by means of SPM8 (Wellcome Department of Cognitive Neuroscience, London) implemented in Matlab (Mathworks, Natick, MA) using the linear model.[20] In order to obtain a dedicated template, the anatomical image of each participant was normalized to the T1 SPM template using segmentation. Then all the normalized images were realigned and the mean was calculated. This mean image was segmented and the grey, white and CSF map of this mean image were used as the template in the segment module. The fMRI data preprocessing was the same than our team members have used in previous fMRI studies[44–46]: slice-scan-time correction (16th slice the reference), movement correction, normalization to dedicated template, and smoothing with an 8-mm FWHM (Full Width at Half Maximum) Gaussian kernel. Statistical analysis was carried out in two steps. The first step consisted of individual analyses performed on each of the 48 participants. For each run, the blood-oxygen-level-dependent (BOLD) response was modelled by convolving a vector that specified stimulus onsets with a canonical haemodynamic response function (HRF).[19] A first level analysis was performed to generate a single contrast image corresponding to each condition (activation minus control task, i.e. fixation cross). Head movements estimated during realignment were considered as regressors in the following statistical analysis. The second step consisted of a group analysis in which previously obtained contrast images were combined in a second-level, random-effect analysis, yielding 'main contrasts' (activation minus control) in each condition. To compare the different conditions, statistics were then input to a repeated measure two-way within-subjects ANOVA and computed as second-level random-effects group analyses. We first examined the main effects of the two factors OvertTSeq and NovelSeq and the interaction. Interactions were further explored by testing post-hoc simple main effects. We report activation that survived a Family Wise Error (FWE) correction for multiple comparisons at voxel-level significance threshold $p < .05$ but, given the conservative nature of random effects, we further explored our data at the uncorrected voxel-level significance threshold of $p < .001$ corrected at cluster level (minimum cluster size = 50).

3. Results

3.1. *Demographic, clinical and neuropsychological results*

Demographic and clinical data are shown in Table 1. Consistent with the literature, boys were over represented in the three groups. The Chi square test revealed no significant between-group differences in age, gender or socio-economic background. The average scores of Total IQ assessed with the WISC-IV[65] were within the normal range for the three groups with no significant difference between groups. Moreover, the three groups performed similarly on the oral language test, attention test (CPT-II) and CBCL and were not

Table 1 – Demographic and clinical characteristics of the three groups.

Child characteristics	DCD only	DD only	MI (DD + DCD)	Test
Children assessed (N)	16	16	16	
Male	12 (75%)	9 (56.3%)	10 (62.5%)	$Khi^2 = 1.3$. df = 2. p = .53
Female	4 (25%)	7 (43.8%)	6 (37.5%)	
Age in years Mean (SD)	9.6 (1.7)	10.3 (1.3)	9.9 (1.1)	F(2.47) = 0.968. p = .388
Total IQ	103.9 (13.1)	110.3 (14.0)	99.6 (18.7)	F(2.47) = 1.915. p = .159

statistically different for vocabulary level, selective or sustained attention or behavioural impact of the disorder.

3.2. Behavioural results

Behavioural data are presented in Table 2.

3.2.1. Assessment of learning

ANOVA revealed a significant effect of Learning on the Accuracy Index $F(1, 45) = 6.135$, $p = .017$, $\eta^2 = 0.120$ (large effect). The ANOVA did not reveal any significant effect of Group $F(2, 45) = 0.466$, $p = .631$ or Group × Learning interaction $F(2, 45) = 0.315$, $p = .732$. Whatever the Group, the mean Accuracy Index was lower for NovelSeq (0.82 ± 0.25) than OverTSeq (0.90 ± 0.85).

3.2.2. Assessment of automatization

In regards to the secondary task (denomination), all the images were named correctly by all participants without exception.

In regards to the primary task (OverTSeq), the ANOVA revealed a significant effect of Automatization on the Accuracy Index $F(1, 45) = 4.323$, $p = .043$, $\eta^2 = 0.088$ (moderate effect) but revealed neither a significant difference between Groups $F(2, 45) = 2.710$, $p = .077$ nor a significant interaction between the Group and the Automatization $F(2, 45) = 0.30$, $p = .971$.

3.3. fMRI results

3.3.1. Main effects of each condition

We first analysed the main contrast for each task (activation during motor task minus activation during rest) to check whether activation patterns were concordant with those reported in the literature for similar tasks. Activations were observed in the cortico-cerebellar and cortico-striatal networks: parietal cortex (BA3), premotor cortex (BA6), thalamus, putamen, anterior and posterior cerebellum, hippocampus and parahippocampus (Table 3).

3.3.2. Within-group analysis

We also analysed the differences between conditions (OverTSeq minus NovelSeq and conversely) to explore the areas specific to one or the other process and to identify learning-related changes (Table 4, Fig. 1). For the DCD group, the NovelSeq versus OverTSeq contrast revealed higher activity in the right caudate and right insula (BA13). The opposite contrast (i.e. OverTSeq-NovelSeq) did not demonstrate any significant difference. For the DD group, the NovelSeq versus OverTSeq contrast revealed higher activity in the left premotor cortex. The opposite contrast (i.e. OverTSeq-NovelSeq) revealed higher activity in the left occipital lobe (BA19) and parahippocampal gyrus (BA36). For the MI group, the NovelSeq versus OverTSeq contrast revealed higher activity in the left premotor cortex (BA6), right inferior and superior parietal lobe (BA40 and BA7), left lingual gyrus, and in the left globus pallidus and caudate. The opposite contrast (i.e. OverTSeq-NovelSeq) did not show any significant difference.

3.3.3. Between-group analysis

For each task, we also analysed the differences between groups in neural activation patterns to see whether the types of pathology or the comorbidity modified the brain networks involved during learning (Table 5, Fig. 2). No differences were found between DD and MI groups. Activity was compared between DCD children and the two other groups. Contrasts [$OverTSeq_{DCD>DD}$] revealed higher activity in the bilateral cingulate gyrus (BA31 and BA24), bilateral sensorimotor cortex (BA4 and BA3), bilateral premotor cortex (BA6), bilateral temporo-parietal cortex (BA40, BA41, BA42, BA43, BA44 and BA22), right insula (BA 13), left thalamus, right anterior cerebellum. The same contrast between DCD and MI groups [$OverTSeq_{DCD>MI}$] revealed higher activity in the right cingulate gyrus (BA24, BA31, BA32), bilateral precentral gyrus (BA4), left premotor cortex (BA6), bilateral temporo-parietal cortex (BA7, BA21, BA22, BA31, BA37, BA41, BA42, BA43), right anterior and posterior cerebellum, left thalamus and left globus pallidus. Identically for the novel task, the contrast [$NovelSeq_{DCD>DD}$] revealed higher activity in the bilateral cingulate gyrus (BA31 and BA24), bilateral thalamus, right caudate and right claustrum. The same contrast for [$NovelSeq_{DCD>MI}$] showed significant difference in the right cingulate gyrus (BA31 and BA23).

4. Discussion

The aim of the present study was to identify the neural characteristics associated to learning and automatization of a motor sequence learning task performed by children with DD, DCD and both disorders. According to the neural systems typography for learning difficulties,[37] we expected that the DCD group would present more atypical recruitment in cortico-striatal loops than the DD group and that the DD group would present more atypical recruitment in cortico-cerebellar

Table 2 – Mean and standard deviation of the accuracy index computed for each Group of children and each Task.

Tasks	DCD Mean (SD)	DD Mean (SD)	MI Mean (SD)	Effects
OS (inside)	0.78 (0.13)	0.87 (0.17)	0.85 (0.19)	$F(2.47) = 1.516$. $p = .231$
NS (inside)	0.70 (0.17)	0.81 (0.17)	0.79 (0.18)	$F(2.47) = 1.823$. $p = .173$
OS (outside)	0.88 (0.09)	0.92 (0.06)	0.9 (0.10)	$F(2.47) = 1.172$. $p = .319$
DTS (outside)	0.81 (0.24)	0.85 (0.22)	0.78 (0.29)	$F(2.47) = 0.319$. $p = .729$

Groups: DCD-Developmental Coordination Disorder; DD-Developmental Dyslexia; MI-comorbid group.
Tasks: OS-Overtrained Sequence; NS-Novel Sequence; DTS-Dual Task Sequence; (inside) or (outside) for tasks performed inside or outside the scanner.

Table 3 – Brain areas activated for each task.

Cerebral regions	Talairach coordinates			Cluster	Z score
	x	y	z	Extend	
Main effect of each tasks (total sample)					
OS task					
Left postcentral gyrus, left medial frontal gyrus (3,6)	−38	−24	56	3481	Inf
Right anterior cerebellum (culmen), right posterior cerebellum (inferior semi-lunar)	10	−54	−20	2399	Inf
Left thalamus	−14	−22	4	211	6.71
Right anterior cerebellum	−22	−56	−28	167	6.15
Left posterior cingulate (29)	−16	−40	12	78	5.81
Left putamen	−24	−2	4	136	5.78
Right precentral gyrus (6)	36	−14	60	31	5.27
Right hippocampus	30	−44	6	83	5.12
Left insula (13)	−44	−4	12	14	4.91
NS task					
Left postcentral gyrus, left medial frontal gyrus, left superior frontal gyrus (3,6)	−38	−24	52	4464	Inf
Right anterior cerebellum, right posterior cerebellum (declive, inferior semi-lunar)	18	−52	−28	2612	Inf
Left thalamus	−16	−22	4	535	7.32
Left anterior cerebellum	−24	−58	−30	278	6.73
Left mammillary body	0	−6	−14	65	5.71
Left putamen, left claustrum	−22	6	10	100	5.48
Left precentral gyrus (6)	−56	0	34	14	5.48
Left substania nigra	−6	−18	−14	24	5.21
Left parahippocampal gyrus (19)	−28	−52	0	36	5.19
Right precentral gyrus (6)	36	−12	58	30	4.96
Main effect of each tasks regardless of groups					
OS task for DD					
Left postcentral gyrus (3)	−38	−26	52	1420	Inf
Right anterior cerebellum (dentate), right posterior cerebellum (declive)	18	−54	−26	802	Inf
Left medial frontal gyrus (6)	−4	−8	56	56	5.44
OS task for MI					
Left postcentral gyrus (3)	−38	−24	52	1578	Inf
Right anterior cerebellum (dentate)	18	−54	−26	999	Inf
Left medial frontal gyrus (6)	−6	−10	56	310	6.97
OS task for DCD					
Left precentral gyrus (4), left postcentral gyrus, left medial frontal gyrus (4,2,6)	−38	−22	56	3695	Inf
Right anterior cerebellum (dentate), right posterior cerebellum (declive)	16	−52	−26	2177	Inf
Left thalamus	−12	−22	2	275	7.34
Left anterior cerebellum	−22	−58	−28	201	6.22
Left lobus pallidus, left putamen, left amygdala	−22	−6	−2	175	5.75
Left insula (41)	−44	−24	16	62	6.14
Right precentral gyrus (4,6)	42	−12	56	86	5.47
Left precentral gyrus (44)	−46	−2	6	64	5.30
NS task for DD					
Left postcentral gyrus (3)	−38	−26	52	1967	Inf
Right anterior cerebellum (dentate), right posterior cerebellum (declive)	14	−52	−24	941	Inf
Left medial frontal gyrus (6)	−4	−8	56	220	6.02
NS task for MI					
Left postcentral gyrus, left medial frontal gyrus (3,6)	−38	−24	54	2483	Inf
Right anterior cerebellum (dentate), right posterior cerebellum (inferior semi-lunar)	16	−54	−24	1757	Inf
Left anterior cerebellum	−22	−58	−28	100	5.76
Left thalamus	−14	−24	6	82	5.76
NS task for DCD					
Left postcentral gyrus, left medial frontal gyrus (2,3,6)	−38	−24	52	3407	Inf
Right anterior cerebellum (dentate), right posterior cerebellum (declive, inferior semi-lunar)	14	−52	−24	1623	Inf
Left thalamus	−14	−22	6	495	7.06
Left anterior cerebellum	−22	−56	−28	51	5.20

Inf: Infinity (Z score > 8).
FWE correction.

Table 4 – Brain areas activated for each group and for direct comparisons between tasks.

Cerebral regions	Talairach coordinates			Cluster	Z score
	x	y	z	Extend	
NS > OS					
NS > OS for DD					
Left middle frontal gyrus (6)	−26	−8	50	228	4.42
Left medial frontal gyrus (6)	−2	16	46	132	3.77
NS > OS for MI					
Left middle frontal gyrus (6)	−24	−10	44	160	4.65
Left globus pallidus, left caudate	−18	−10	6	131	4.38
Left lingual gyrus	−28	−70	−2	214	4.14
Right inferior parietal lobe, right superior parietal lobe, right precuneus (40,7)	34	−44	46	190	3.88
NS > OS for DCD					
Right caudate, right insula (13)	32	−14	26	373	4.07
OS > NS					
OS > NS for DD					
Left parahippocampal gyrus (36)	−32	−32	−18	108	4.24
Left middle temporal gyrus (19)	−40	−58	12	138	4.08

Talairach coordinates and t values for peak activation at the uncorrected voxel-level significance threshold of $p < .001$ corrected at cluster level (minimum cluster size = 50) for the NS and the OS conditions in the DD group versus the DCD group; MI group versus DD; MI versus DCD; and vice et versa.
Note: OS-Overtrained Sequence; NS-Novel Sequence; DCD-Developmental Coordination Disorder; DD-Developmental Dyslexia; MI-comorbid group.

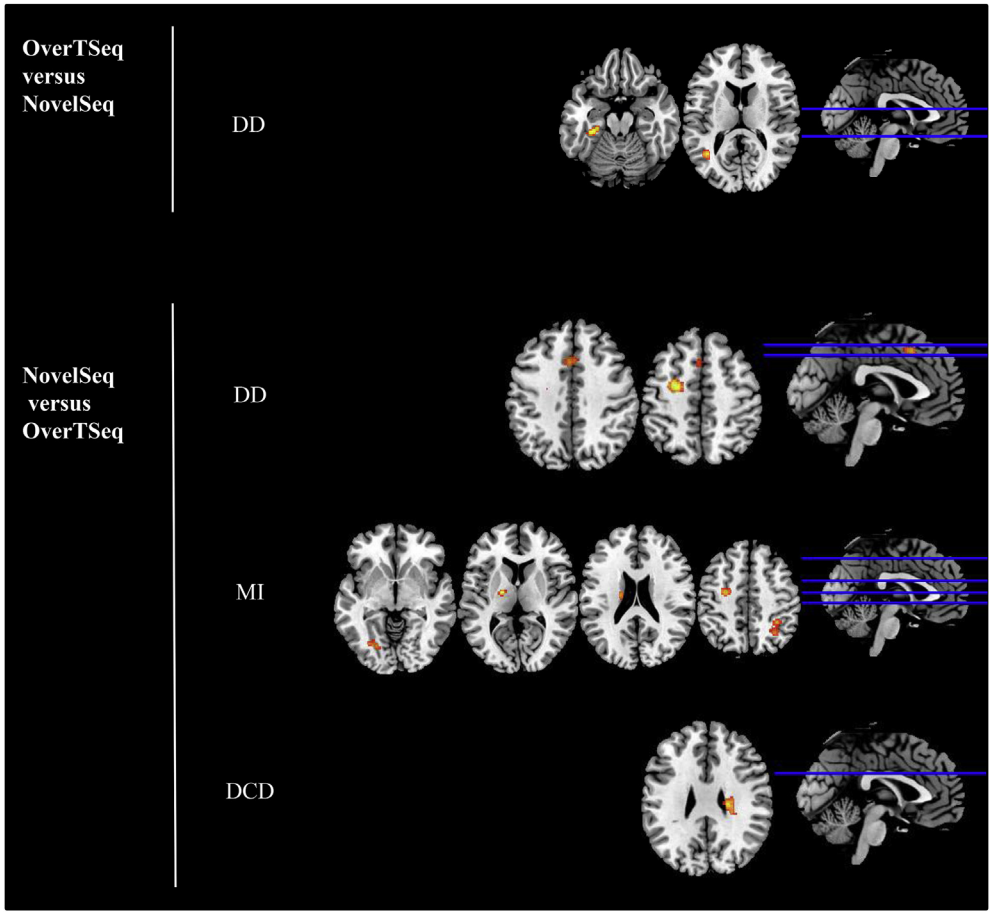


Fig. 1 – Activation maps for DD, DCD and MI groups separately, for [OverTSeq vs. NovelSeq] contrasts, and for [NovelSeq vs. OverTSeq] contrasts. Note: OverTSeq: Overtrained Sequence; NovelSeq: Novel Sequence; DCD: Developmental Coordination Disorder; DD: Developmental Dyslexia, MI: comorbid group.

Table 5 – Differences in neural activation patterns between groups.

	Talairach coordinates			Cluster	Z score
	x	y	z	Extend	
NS task					
DCD > DD					
Right cingulate gyrus (31,24)	22	−36	38	1246	4.90
Right claustrum	34	−2	−2	163	4.03
Left thalamus	−8	−30	8	277	3.95
Right caudate, right thalamus	18	−4	18	328	3.92
DCD > MI					
Right cingulate gyrus (31,23)	26	−36	36	508	4.21
OS task					
DCD > DD					
Left cingulate gyrus, right medial frontal gyrus (31,6)	−16	−38	26	897	5.26
Right postcentral gyrus, right precentral gyrus (3,4)	44	−18	50	1096	4.75
Left cingulate gyrus, right medial frontal gyrus (24,6)	0	4	42	707	4.25
Right transverse temporal gyrus (41,42)	56	−18	14	320	3.65
Left precentral gyrus, left superior temporal gyrus (6,43,22)	−58	−8	12	339	4.02
Right supramarginal gyrus, right superior temporal gyrus (40,22)	60	−46	22	156	3.99
Left precentral gyrus, left sub-gyral (4,40)	−20	−24	56	122	3.92
Right precuneus (31)	14	−58	26	185	3.69
Right precentral gyrus, right insula (44,13)	50	2	8	222	4.06
Left thalamus	−12	−22	0	152	4.05
Right anterior cerebellum, nodule (X)	20	−60	−28	171	3.81
DCD > MI					
Right middle temporal gyrus (31)	22	−48	26	301	4.86
Left precentral gyrus, left middle frontal gyrus (4,6)	−26	−18	48	445	4.37
Right posterior cerebellum, uvula of vermis (IX)	2	−72	−34	141	4.15
Left lateral globus pallidus, left thalamus	−20	−8	0	147	4.14
Right precentral gyrus (4)	42	−12	54	189	4.11
Right anterior cerebellum, culmen (IV,V)	2	−58	−6	118	3.96
Right middle temporal gyrus, right sub-gyral (21,37)	64	−44	0	238	3.92
Left superior temporal gyrus (41,42)	−62	−30	14	139	3.81
Left superior temporal gyrus, left precentral gyrus (22,43,6)	−56	4	4	183	3.80
Right Superior Frontal (6)	2	12	60	126	3.79
Left cingulate gyrus, right parietal (31,7)	−16	−38	26	319	3.78
Right superior temporal gyrus (22)	62	−48	20	120	3.74
Left medial frontal gyrus, right cingulate gyrus (32,24)	0	6	42	125	3.68

Talairach coordinates and t values for peak activation at the uncorrected voxel-level significance threshold of $p < .001$ corrected at cluster level (minimum cluster size = 50) for the NS and the OS conditions in the DD group versus the DCD group; MI group versus DD; MI versus DCD; and vice et versa.
Note: OS-Overtrained Sequence; NS-Novel Sequence; DCD-Developmental Coordination Disorder; DD-Developmental Dyslexia; MI-comorbid group.

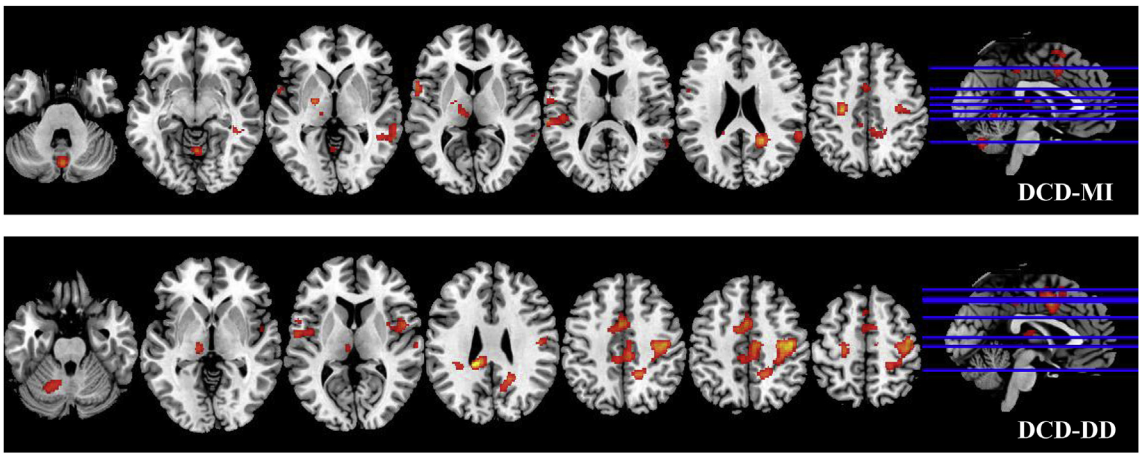


Fig. 2 – Activation maps for the OverTSeq conditions for [DCD vs. DD] contrasts, and for [DCD vs. MI] contrasts. Note: OverTSeq: Overtrained Sequence; NovelSeq: Novel Sequence; DCD: Developmental Coordination Disorder; DD: Developmental Dyslexia, MI: comorbid group.

loops than the DCD group. Compared with the other two groups with primary deficits (DD and DCD pure groups), the comorbid group would experience additive effects, with particularities in both cortico-striatal and cortico-cerebellar loops. As expected, regarding learning, our results suggest that the three groups of children were able to learn because they improve their performances after 15 days of practice. In regards to automaticity, the level of automaticity reached by each group did not differ and all children were able to perform the practiced sequence with the same level of accuracy index without error in the secondary (denomination) task. All in all, children have reached the same level of learning and automatization of the motor sequence but the neural mechanisms associated with this same level of behavioural performance differed between groups. Especially, the neural correlates of the comorbid and the DD groups are very close while the DCD group presents specific and distinct neural characteristics.

4.1. *Automatization*

4.1.1. *Same level of behavioural performance in the three groups*

During the dual-task, for all subjects, the OverTSeq task was performed with minimal interference and without any change in movement parameters when subjects were placed in the dual-task condition. Secondly, no error occurred in the secondary task: all children without exception reached 100% of correct denomination. Participants were not focussing on the OverTSeq task to the detriment of the secondary task. In addition, the accuracy index of the OverTSeq task was the same for all groups which suggests that all children were able to perform the OverTSeq task with the same level of automaticity. Surprisingly, the comorbid group did not present additional behavioural difficulties. They reached the same level of performance than the other two groups with primary deficits. Taken together, our data reveal that all children are able to reach the same performance and have learnt a sequence of movements up to similar level of automaticity whatever the group. It should be noted that we cannot assert that the level of automaticity achieved is normal given the absence of a control group with healthy children. It should also be borne in mind that different results could have been obtained if the tasks had been more complex.

4.1.2. *Distinct brain recruitment in DCD vs DD vs comorbid group*

Despite the fact that automaticity was reached to similar degrees in the three groups, fMRI results suggest that distinct cerebral regions were activated within the three groups to achieve automaticity. More precisely, the DCD group presented a slight difference in cerebral activations during the practiced sequence (corresponding to the post-training session or OverTSeq) compared to the new sequence (corresponding to the pretraining session or NovelSeq) with only an increased activation of the caudate nucleus. Several studies found that the caudate nucleus is activated at the very early stage of learning of sequential movements[27] and its activation decreases rapidly during practice,[49,67] especially during the first hour of the acquisition process.[27,33] This could explain the activation of the caudate during the novel task compared to the overlearned task in DCD children. However, it is surprising that no other decrease in brain activity was found in the overlearned task compared to the novel task, especially in the cerebellum, motor and premotor areas, cingulate cortex, and parietal and prefrontal cortex. This makes the level of brain activity quite similar between the two conditions and suggests that brain activity in DCD participants is not optimally efficient during the process of automaticity. This condition, which normally allows decreased attention and cognitive involvement,[13] does not seem to require a smaller effort from them. This finding is consistent with the results from a growing body of studies on motor skill learning which show that individuals with DCD present difficulties in the procedural learning process.[60,62] For example, Ref. 11 indicated that, while typically developing children exhibited higher activation in many regions when responding to unpredictive (irregular) as opposed to predictive (regular) intervals between stimuli, DCD children presented similar patterns of activation when responding to unpredictive and predictive intervals. The authors concluded that extra processing efforts were needed in DCD children to perceive regularities in visual stimuli. This additional processing could account for the cognitive fatigue and reduced attentional resources for other cognitive tasks during daily motor coordination tasks in DCD children.

For the DD group, within-group analyses revealed that the parahippocampal gyrus and the lingual gyrus were activated specifically for the overlearned sequence compared to the novel sequence. It is well established that these regions are involved in declarative memory processing.[16,36] One interpretation of this result is therefore that DD participants call upon declarative memory at the automatic stage of procedural learning of the sequence, possibly to facilitate the retrieval process. This is supported by previous studies suggesting that the declarative memory remains largely functional in DD and should be able to play compensatory roles for multiple types of impairments across this disorder,[61] and especially for procedural memory deficits.[34] A second hypothesis comes from previous MRI literature which revealed overactivation of the left lingual gyrus in dyslexia (for meta-analysis, see Ref. 53). These results put forth another interpretation which is that the greater activation of the lingual gyrus found in our study is specific to the DD brain but unspecific to activations associated to procedural learning in DD.

For the comorbid group, within-group fMRI analyses revealed that performing the novel sequence compared to the overlearned sequence led to supplementary brain activations in the premotor area, superior and inferior parietal lobes, globus pallidus and caudate nucleus, which suggests the recruitment of motor and attentional activations at the beginning of practice (i.e., for the novel task) which are no longer necessary to perform after practice (i.e., for the overlearned sequence). Surprisingly, this pattern of results is typically found in healthy participants,[12,33,49,67] which suggests that comorbidity does not lead to adverse effect on behavioural performance (especially on the acquisition of automaticity) and its neural correlates. All in all, comorbid group does not seem to combine the deficits induced by each disorder.

4.2. *The DCD group, a separate group?*

4.2.1. *Cortico-cerebellar or cortico-striatal loops recruitment*

According to the theoretical model of Nicolson and Fawcett[37]; we expected an atypical activation in the cortico-cerebellar loop for the DD group, an atypical activation in the cortico-striatal loop for the DCD group, and an atypical activation in both loops for the comorbid group. Our fMRI results are not clearly consistent with the predictions of this theoretical model. Although the between groups differences are well-found in loops corresponding to the model, only the DCD group showed specific recruitment on these areas compared to the other two. More precisely, compared with the two others, the DCD group presented (i) a larger activity in the caudate nucleus when performing a novel motor sequence and (ii) a larger activity in the thalamus, globus pallidus and anterior and posterior cerebellum (lobules IV, V and IX, X) when performing the overlearned sequence. Altogether, these results suggest that the DCD group would present more difficulties to deactivate the cortico-striatal and cortico-cerebellar loops than the DD and comorbid groups with learning. Previous findings in typical participants reveal that the caudate nucleus and globus pallidus are activated early in learning and their activities decrease with practice.[49,67] Regarding the cerebellum, lobules IV and V are involved in the learning process per se.[42] In contrast, posterior regions have been most usually associated with cognitive processing.[58] Consequently, the larger recruitment in the anterior and posterior cerebellum and in the striatum for the DCD group compared to the two other groups may point difficulties in both motor and cognitive functions associated to the procedural learning.

4.2.2. *Other additional neural recruitment of brain regions in the DCD group*

More broadly, compared to the DD and the comorbid groups, NovelSeq as OverTSeq induced greater brain activation in DCD group. Thus, for a similar task and a similar level of performance, it seems that DCD participants need to recruit more extensive brain regions or to engage the usual ones more actively than the two other groups. This increased activation is consistent with those reported in previous studies.[7,68] Zwicker et al.[68] showed that DCD children activated almost twice as many brain regions as those recruited by the normative group to accomplish the same trail-tracing task. Using spectral EEG coherence, Castelnau et al.[7] revealed quite similar results on a synchronization-syncopation task with more brain involvement in DCD children. Altogether, this lends support that DCD children have to invest more effort to achieve similar performance than DD and comorbid groups.

These additional brain activities found in the DCD group compared with the two other occurred mainly on the automatic task in two specific areas. Firstly, additional activity appears in the anterior and posterior cingulate cortex, and inferior parietal cortex (ACC, IPC and PCC), which are brain circuitry related to attention.[17,24] Atypical recruitment of these brain areas has been previously reported in DCD participants through both fMRI and connectivity studies[28,50,68] suggesting atypical activations of attention-related areas (especially the cingulate cortex, ACC and PCC) which may be a good marker of DCD. Secondly, the second area of major additional brain activity found in the DCD group concerns brain areas which are known to be involved in reading and language processes (BA 22, 37,40 in particular). This result is very surprising because a large number of functional neuroimaging studies have demonstrated that these regions are deficient in DD participants, with atypical activation of the left perisylvian fronto-temporo-parietal network,[54] especially in the inferior frontal gyrus (Broca's area, BA 44 and 45), the inferior occipital-temporal area (or Visual Word Form Area, BA 37) and the parietal-temporal regions (BA 21, 22, 39, 40). Hence, the additional activations in DCD might be due to a lower activation of these brain structures in both DD groups. In this context, our results may reflect that dysfunctions in these networks can be present in DD, not only in reading tasks but more broadly in sequential learning tasks.

4.3. *Which status for comorbidity between DD and DCD?*

The results from the comorbid group were particularly relevant. Firstly, and as we noted above, the comorbid group did not present additional behavioural difficulties: they reached the same level of performance as the other two groups with primary deficits. Secondly, in this cerebral correlates, this group did not present additional activations compared to the DD and the DCD groups. Altogether, these results suggest that the comorbid group does not seem to present more deficits than the other two groups with primary deficits. In other words, the comorbid group did not display the expected additive effects that we had hypothesised, even if the lack of a normal control group requires that our results be interpreted cautiously.

Furthermore, the absence of differences between DD and comorbid group and the substantial differences between DCD and comorbid group (especially, typical activations of the DCD group in the attentional circuit did not appear in the comorbid group), questions the nature of the comorbid group which could be viewed as a group closer to DD than to DCD, or, more speculatively, as a sub-group of the DD group. This finding gives a new look into the common and different goals to be developed in the therapy and medical care to help children with DD, DCD and the both disorders to overcome their difficulties. This suggests that it would be useful to take DCD comorbidity into account, both in research and clinical practice. For research, since comorbid DD + DCD children are distinguished from DCD children in behavioural and brain functioning, it seems necessary to paid careful attention to such a comorbidity in inclusion criteria for DCD children. From a clinical perspective, it seems important to paid careful attention to comorbidity when we assess the competencies of these children and propose specific intervention. Especially the differential effects of psychomotor or occupational therapy on DCD and comorbid groups must be investigated further.[30]

Moreover, it would be interesting to establish whether comorbidity with specific language impairments or Attention Deficit/Hyperactivity Disorder induce a similar profile.

4.4. *Confrontation with Nicolson and Fawcett's model, limitations and perspectives*

As a reminder, in view of the theoretical model of Nicolson and Fawcett,[37] we expected an atypical activation in the cortico-cerebellar loop for the DD group, an atypical activation in the cortico-striatal loop for the DCD group, and an atypical activation in both loops for the comorbid group. Our results did not support Nicholson and Fawcett's proposed typography for learning difficulties with no evidence of separable cortico-striatal and cortico-cerebellar loops for DCD and DD respectively.

Instead, our results indicated that behavioural performance was achieved similarly between groups, but with different neural recruitments in DD and DCD groups, highlighting that the strategies to achieve procedural learning was quite different in DD and DCD groups. But these differences were not located clearly on striatal and cerebellar loops.

Compared to the DD group, the DCD group showed specific recruitment on additional areas, especially in the attentional circuit. Since the presence of a disturbance in attention can influence the frequency and intensity of movement disorders, children with ADHD were excluded from our study. Thus the differences between the groups could not be linked to the possible attention deficit. One reason for difference observed between our results and the work of Nicolson and Fawcett, could be at this level.

Results from the comorbid group also failed to provide substantial evidence on Nicolson and Fawcett's model, given that the comorbid group does not present additional activations compared to the DD and the DCD groups.

Our current study contributes to neuropsychological theory regarding learning difficulties by failing to replicate Nicholson and Fawcett's findings and raises questions as to whether motor coordination problems associated with developmental dyslexia are different in nature from the motor coordination problems associated with DCD. Now, it would appear necessary to continue the investigations on the model of Nicolson and Fawcett[37] through the careful and detailed analysis of structural and DTI data to explore structures and connectivity of the striatum and cerebellum in each group. Further studies including a control group with healthy children and a wider range of procedural tasks, with linguistic, cognitive and motor components and different levels of complexity, are also needed to provide normative data at the behavioural and neural levels.

Funding

This work was supported by the Toulouse University Hospital [grant number 1015502 N°IDRCB2010-A00909-30].

Conflict of interest

We certify that the content of this document has not been submitted for publication to another scientific journal, and is not being considered for publication elsewhere. We attest that this work is approved by all the co-authors.

Acknowledgments

We would like to thank all the participating families, all the children, the parents' associations and the referring clinicians. The authors thank Ovid M. Da Silva for his careful checking of the English language and the reviewers for their constructive comments. The authors thank Hélène Gros, Nathalie Vayssière, Lucette Foltier, and Jean-Pierre Désirat of the MRI technical platform (Inserm UMR1214).

REFERENCES

1. Achenbach TM, Rescorla LA. *Manual for the ASEBA school-age forms & profiles*. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families; 2001.
2. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 5th ed. Washington, DC: American Psychiatric Publishing; 2013.
3. Biotteau M, Albaret J-M, Lelong S, Chaix Y. Neuropsychological status of French children with developmental coordination disorder and/or developmental dyslexia: are both necessarily worse than one? *Child Neuropsychol* 2016. http://dx.doi.org/10.1080/09297049.2015.1127339.
4. Biotteau M, Chaix Y, Albaret J-M. Procedural learning and automatization process in children with developmental coordination disorder and/or developmental dyslexia. *Hum Mov Sci* 2015;**43**:78–89. http://dx.doi.org/10.1016/j.humov.2015.07.005.
5. Biotteau M, Chaix Y, Albaret J-M. What do we really know about motor learning in children with Developmental Coordination Disorder? *Curr Dev Disord Rep* 2016;**3**(2):152–60. http://dx.doi.org/10.1007/s40474-016-0084-8.
6. Bo J, Lee C-M. Motor skill learning in children with developmental coordination disorder. *Res Dev Disabil* 2013;**34**(6):2047–55.
7. Castelnau P de, Albaret J-M, Chaix Y, Zanone P-G. Developmental coordination disorder pertains to a deficit in perceptuo-motor synchronization independent of attentional capacities. *Hum Mov Sci* 2007;**26**(3):477–90.
8. Chaix Y, Albaret J-M, Brassard C, Cheuret E, Castelnau P de, Bénesteau J. Motor impairment in dyslexia: the influence of attention disorders. *Eur J Paediatr Neurol* 2007;**11**:368–74.
9. Conners CK, Staff M. *Conners' continuous performance test II: computer program for windows technical guide and software manual*. North Tonawanda, NY: Multi-Health Systems; 2000.
10. Crespo-Eguílaz N, Magallón S, Narbona J. Procedural skills and neurobehavioral freedom. *Front Hum Neurosci* 2014;**8**(449). http://dx.doi.org/10.3389/fnhum.2014.00449.
11. Debrabant J, Gheysen F, Caeyenberghs K, Van Waelvelde H, Vingerhoets G. Neural underpinnings of impaired predictive motor timing in children with Developmental Coordination Disorder. *Res Dev Disabil* 2013;**34**(5):1478–87. http://dx.doi.org/10.1016/j.ridd.2013.02.008.
12. Doyon J, Bellec P, Amsel R, Penhune V, Monchi O, Carrier J. Contributions of the basal ganglia and functionally related brain structures to motor learning. *Behav Brain Res* 2009;**199**(1):61–75.
13. Doyon J, Gaudreau D, Laforce RJ, Castonguay M, Bedard PJ, Bedard F. Role of the striatum, cerebellum, and frontal lobes in the learning of a visuomotor sequence. *Brain Cognit* 1997;**34**:218–45.
14. Du W, Kelly SW. Implicit sequence learning in dyslexia: a within-sequence comparison of first-and higher-order information. *Ann Dyslexia* 2013;**63**:154–70.

15. Dunn LM, Theriault-Whalen CM, Dunn LM. *EVIP, Echelle de vocabulaire en images Peabody*. Toronto: Psycan; 1993.
16. Eichenbaum H. A cortical-hippocampal system for declarative memory. *Nat Rev Neurosci* 2000;**1**:41–50.
17. Fan J, McCandliss BD, Fossella J, Flombaum JI, Posner MI. The activation of attentional networks. *NeuroImage* 2005;**26**:471–9.
18. Flessas J, Lussier F. *Epreuve verbale d'aptitudes cognitives*. Paris: ECPA; 2003.
19. Friston KJ, Fletcher P, Josephs O, Holmes A, Rugg MD, Turner R. Event-related fMRI: characterizing differential responses. *NeuroImage* 1998;**7**:30–40.
20. Friston KJ, Holmes AP, Poline JB, Grasby PJ, Williams SCR, Frackowiak RSJ. Analysis of fMRI time-series revisited. *NeuroImage* 1995;**2**(1):45–53.
21. Gheysen F, Van Waelvelde H, Fias W. Impaired visuo-motor sequence learning in developmental coordination disorder. *Res Dev Disabil* 2011;**32**:749–56.
22. Haslum MN, Miles TR. Motor performance and dyslexia in a national cohort of 10-year-old children. *Dyslexia* 2007;**13**(4):257–75.
23. Henderson S, Sugden DA. *Movement assessment battery for children*. San Antonio, TX: Psychological Corporation; 1992.
24. Hopfinger JB, Buonocore MH, Mangun GR. The neural mechanisms of top-down attentional control. *Nat Neurosci* 2000;**3**:284–91.
25. Huberty CJ, Morris JD. Multivariate analysis versus multiple univariate analyses. *Psychol Bull* 1989;**105**:302–8.
26. Jacquier-Roux M, Valdois S, Zorman M, Lequette C, Pouget G. *ODEDYS: un outil de dépistage des dyslexies version 2*. Grenoble: Laboratoire Cogni-sciences, IUFM Grenoble; 2005.
27. Jueptner M, Frith CD, Brooks DJ, Frackowiak RS, Passingham RE. Anatomy of motor learning. II. Subcortical structures and learning by trial and error. *J Neurophysiol* 1997;**77**:1325–37.
28. Kashiwagi M, Iwaki S, Narumi Y, Tamai H, Suzuki S. Parietal dysfunction in developmental coordination disorder: a functional MRI study. *NeuroReport* 2009;**20**(15):1319–24.
29. Lang CE, Bastian AJ. Cerebellar damage impairs automaticity of a recently practiced movement. *J Neurophysiol* 2002;**87**(3):1336–47.
30. Laurent A, Lareng-Armitage J, Lewandowski C, Abeilhou P, Ballouard A-C, Chaffiotte C, et al. The effects of psychomotor therapy in DCD children with or without comorbidities. 11th International Conference on Children with DCD. Toulouse, 2-4 july. *J Comorbidity* 2015;**5**:88.
31. Lecocq P. *Epreuve de compréhension syntaxico-sémantique*. Villeneuve-d'Ascq: Presses Universitaire du Septentrion; 1996.
32. Lefavrais P. *Test de l'Alouette, version révisée*. Paris: ECPA; 2005.
33. Lehericy S, Benali H, Van de Moortele P-F, Pelegrini-Issac M, Waechter T, Ugurbil K. Distinct basal ganglia territories are engaged in early and advanced motor sequence learning. *Proc Natl Acad Sci U S A* 2005;**102**(35):12566–71.
34. Lum JAG, Ullman MT, Conti-Ramsden G. Procedural learning is impaired in dyslexia: evidence from a meta-analysis of serial reaction time studies. *Res Dev Disabil* 2013;**34**(10):3460–76.
35. Magallón S, Crespo-Eguílaz N, Narbona J. Procedural learning in children with developmental coordination, reading, and attention disorders. *J Child Neurology* 2015;**30**(11):1496–506. http://dx.doi.org/10.1177/0883073815572227.
36. Moscovitch M, Nadel L, Winocur G, Gilboa A, Rosenbaum S. The cognitive neuroscience of remote episodic, semantic and spatial memory. *Curr Opin Neurobiol* 2006;**16**(2):179–90.
37. Nicolson RI, Fawcett AJ. Procedural learning difficulties: reuniting the developmental disorders? *Trends Neurosci* 2007;**30**(4):135–41.
38. Nicolson RI, Fawcett AJ. Dyslexia, dysgraphia, procedural learning and the cerebellum. *Cortex* 2011;**47**:117–27.
39. Oldfield OD. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 1971;**9**:97–113.
40. O'Hare A, Khalid S. The association of abnormal cerbellar function in children with developmental coordination disorder and reading difficulties. *Dyslexia* 2002;**8**:234–48.
41. Orban P, Lungu O, Doyon J. Motor sequence learning and developmental dyslexia. *Ann N Y Acad Sci* 2008;**1145**:151–72.
42. Orban P, Peigneux P, Lungu O, Albouy G, Breton E, Laberenne F. The multifaceted nature of the relationship between performance and brain activity in motor sequence learning. *NeuroImage* 2010;**49**(1):694–702.
43. Passingham RE. Attention to action. *Philos Trans R Soc Lond Ser B Biol Sci* 1996;**351**(1346):1473–9. http://dx.doi.org/10.1098/rstb.1996.0132.
44. Péran P, Catani S, Falletta Caravasso C, Nemmi F, Sabatini U, Formisano R. Supplementary motor area activation is impaired in severe traumatic brain injury parkinsonism. *J Neurotrauma* 2014;**31**(7):642–8.
45. Péran P, Demonet JF, Cherubini A, Carbebat D, Caltagirone C, Sabatini U. Mental representations of action: the neural correlates of the verbal and motor components. *Brain Res* 2010;**1328**:89–103.
46. Péran P, Carbebat D, Cherubini A, Piras F, Luccichenti G, Peppe A, et al. Object naming and action-verb generation in Parkinson's disease: a fMRI study. *Cortex* 2009;**45**:960–71.
47. Pernet C, Poline J, Démonet J, Rousselet G. Brain classification reveals the right cerebellum as the best biomarker of dyslexia. *BMC Neurosci* 2009;**10**(1):67. http://dx.doi.org/10.1186/1471-2202-10-67.
48. Peters LHJ, Maathuis CGB, Hadders-Algra M. Neural correlates of developmental coordination disorder. *Dev Med Child Neurol* 2013;**55**:59–64. http://dx.doi.org/10.1111/dmcn.12309.
49. Poldrack RA, Sabb FW, Foerde K, Tom SM, Asarnow RF, Bookheimer SY. The neural correlates of motor skill automaticity. *J Neurosci* 2005;**25**:5356–64.
50. Querne L, Berquin P, Vernier-Hauvette M-P, Fall S, Deltour L, Meyer M-E. Dysfunction of the attentional brain network in children with Developmental Coordination Disorder: a fMRI study. *Brain Res* 2008;**1244**:89–102.
51. Ramus F, Pidgeon E, Frith U. The relationship between motor control and phonology in dyslexic children. *J Child Psychol Psychiatry* 2003;**44**(5):712–22.
52. Ramus F, Rosen S, Dakin SC, Day BL, Castellote JM, White S, Frith U. Theories of developmental dyslexia: insights from a multiple case study of dyslexic adults. *Brain* 2003;**126**:841–65.
53. Richlan F, Kronbichler M, Wimmer H. Functional abnormalities in the dyslexic brain: a quantitative meta-analysis of neuroimaging studies. *Hum Brain Mapp* 2009;**30**:3299–308.
54. Richlan F, Kronbichler M, Wimmer H. Meta-analyzing brain dysfunctions in dyslexic children and adults. *NeuroImage* 2011;**56**:1735–42.
55. Soppelsa R, Albaret J-M. *Manuel de la Batterie d'Evaluation du Mouvement chez l'Enfant (M-ABC)*. Paris: ECPA; 2004.
56. Stoodley CJ, Stein JF. The cerebellum and dyslexia. *Cortex* 2011;**47**:101–16. http://dx.doi.org/10.1016/j.cortex.2009.10.005.
57. Stoodley CJ, Stein JF. Cerebellar function in developmental dyslexia. *Cerebellum* 2013;**12**:267–76. http://dx.doi.org/10.1007/s12311-012-0407-1.
58. Stoodley CJ, Valera EM, Schmahmann JD. Functional topography of the cerebellum for motor and cognitive tasks: an fMRI study. *NeuroImage* 2012;**59**:1560–70.
59. Taniwaki T, Okayama A, Yoshiura T, Togao O, Nakamura Y, Yamasaki T. Functional network of the basal ganglia and cerebellar motor loops in vivo: different activation patterns

between self-initiated and externally triggered movements. *NeuroImage* 2006;**31**(2):745–53. http://dx.doi.org/10.1016/j.neuroimage.2005.12.032.
60. Utley A, Steenbergen B, Astill SL. Ball catching in children with developmental coordination disorder: control of degrees of freedom. *Dev Med Child Neurol* 2007;**49**(1):34–8.
61. Ullman MT, Pullman MY. A compensatory role of declarative memory in neurodevelopmental disorders. *Neurosci Biobehav Rev* 2015;**51**:205–22.
62. Van Waelvelde H, de Weerdt W, de Cock P, Janssens L, Feys H, Smits Engelsman BCM. Parameterization of movement execution in children with developmental coordination disorder. *Brain Cognit* 2006;**60**(1):20–31.
63. Visser J. Subtypes and comorbidities. In: Geuze RH, editor. *Developmental coordination disorder: a review of current approaches. Marseille: Solal*; 2007. p. 83–110.
64. Wechsler D. *WISC-IV: administration and scoring manual*. San Antonio, TX: Psychological Corporation; 2003.
65. Wechsler D. *Echelle d'intelligence pour enfants et adolescents - 4e édition (WISCIV)*. Paris: Les Éditions du Centre de Psychologie Appliquée; 2005.
66. World Health Organization. *The international classification of diseases, volume 10. Classification of mental and behavioural disorders*. Geneva: World Health Organization Publications; 1993.
67. Wu T, Kansaku K, Hallett M. How self-initiated memorized movements become automatic: a functional MRI study. *J Neurophysiol* 2004;**91**:1690–8.
68. Zwicker JG, Missiuna C, Harris SR, Boyd LA. Brain activation associated with motor skill practice in children with developmental coordination disorder: an fMRI study. *Int J Dev Neurosci* 2011;**29**(2):145–52.
69. Blank R, Smits-Engelsman B, Polatajko H, Wilson P. European Academy for Childhood Disability (EACD): recommendations on the definition, diagnosis and intervention of developmental coordination disorder (long version). *Dev Med & Child Neurol* 2012;**54**(1):54–93.