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Impaired neural processing of transitive relations in children with math learning difficulty

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ABSTRACT

Math learning difficulty (i.e., MLD) is common in children and can have far-reaching consequences in personal and professional life. Converging evidence suggests that MLD is associated with impairments in the intraparietal sulcus (IPS). However, the role that these impairments play in MLD remains unclear. Although it is often assumed that IPS deficits affect core numerical abilities, the IPS is also involved in several non-numerical processes that may contribute to math skills. For instance, the IPS supports transitive reasoning (i.e., the ability to integrate relations such as A > B and B > C to infer that A > C), a skill that is central to many aspects of math learning in children. Here we measured fMRI activity of 8- to 12-year-olds with MLD and typically developing (TD) peers while they listened to stories that included transitive relations. Children also answered questions evaluating whether transitive inferences were made during story comprehension. Compared to non-transitive relations (e.g., A > B and C > D), listening to transitive relations (e.g., A > B and B > C) was associated with enhanced activity in the IPS in TD children. In children with MLD, the difference in activity between transitive and non-transitive relations in the IPS was (i) non-reliable and (ii) smaller than in TD children. Finally, children with MLD were less accurate than TD peers when making transitive inferences based on transitive relations. Thus, a deficit in the online processing of transitive relations in the IPS might contribute to math difficulties in children with MLD.

1. Introduction

The ability to manipulate and understand numerical information is central to academic and professional achievement (Duncan et al., 2007; Parsons and Bynner, 2005). Yet, individuals differ greatly in their math skills and those who struggle the most may have some form of math learning difficulty (MLD) (Geary et al., 1991; Kucian and von Aster, 2015). Even though MLD represents a major societal issue (Butterworth et al., 2011), the condition is much less researched than reading difficulty (Bishop, 2010) and its causes remain unclear.

Over the past ten years or so, studies that investigated neural impairments in children with MLD have consistently pointed to anatomical and functional impairments in the intraparietal sulcus (IPS) (Ansari, 2008; Szűcs and Goswami, 2013). For instance, it has been shown that children with MLD have less grey matter in the IPS than typically developing (TD) peers (Isaacs et al., 2001; Rotzer et al., 2008; Rykhlevskaia et al., 2009). Studies have also found abnormal functional connectivity between the IPS and various fronto-parietal regions in children with MLD (Jolles et al., 2016; Rosenberg-Lee et al., 2015). Finally, activity in the IPS during the processing of numerical and arithmetic stimuli differs between children with and without MLD (Ashkenazi et al., 2012; Iuculano et al., 2015; Rosenberg-Lee et al., 2015; Berteletti et al., 2014; Price et al., 2007; Kucian et al., 2006). The IPS has long been linked to the representation of approximate numerical information in animals and healthy individuals (Ansari, 2008). Therefore, it has been proposed that IPS impairments may affect approximate numerical skills, which in turn may cause MLD (Butterworth et al., 2011; Piazza et al., 2010; Feigenson et al., 2013).

Recently, however, researchers have begun to question this so-called “number sense” hypothesis of MLD for (at least) two reasons (Leibovich et al., 2017; Szűcs and Goswami, 2013). First, it is increasingly believed that the non-symbolic stimuli that are typically used to test approximate numerical abilities may also capture differences in executive functioning (Tokita and Ishiguchi, 2013; Bugden and Ansari, 2016; Gilmore et al., 2013) and continuous magnitude processing (Leibovich et al., 2017). Second, the “number sense” hypothesis is

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difficult to reconcile with the observation that individuals with MLD also exhibit impairments in non-numerical skills such as attention (Ashkenazi et al., 2009; Swanson, 2011), inhibition (Bull and Scerif, 2001; Swanson, 2011; Espy et al., 2004), working memory (Geary, 2011; Bull and Scerif, 2001; Passolunghi and Siegel, 2004; McLean and Hitch, 1999), and serial-order processing (Attout and Majerus, 2015; De Visscher et al., 2015). Because the IPS is central to all of these abilities (Anderson et al., 2010; Pessoa et al., 2002; Attout et al., 2014; Ischebeck et al., 2008), impairments in the IPS may explain difficulties in any of these skills (Szűcs and Goswami, 2013). Thus, it has been proposed that MLD may be a relatively heterogeneous disorder caused by impairments in various numerical and non-numerical skills (Fias et al., 2013; Szűcs and Goswami, 2013). This is consistent with the fact that math relies on a wide range of cognitive skills and that math difficulties in children with MLD may therefore stem from factors that are not necessarily related to basic numerical processing.

Recently, it has been suggested that children with MLD may have impaired transitive reasoning ability (Morsanyi et al., 2013). That is, those children may have difficulty integrating transitive relations such as “The triangle is bigger than the circle” and “The circle is bigger than the square” to infer conclusions such as “The triangle is bigger than the square”. Such a hypothesized impairment in transitive reasoning is likely to significantly affect math learning in children. Indeed, although it is rarely emphasized in curricula, transitive reasoning is an important aspect of scientific thinking in general and of math learning in particular. For instance, it plays a role in understanding concepts such as ordinality (If A comes before B and B comes before C, then A comes before C), set-inclusion (If All As are Bs and All Bs are Cs, then All As are Cs), and measurement in young children (Newstead et al., 1985; Rabinowitz et al., 1994; Wright, 2001). In older children, transitive reasoning is also important for algebra and problem-solving (Morsanyi et al., 2013). Finally, transitive reasoning is central to the notion of deductive proof in geometry (Ayalon and Even, 2008). Therefore, there is little doubt that transitive reasoning significantly contributes to math competence.

Interestingly, several neuroimaging studies have associated transitive reasoning with regions in and around the IPS in healthy adults (Goel, 2007; Prado et al., 2010, 2011, 2013) and TD children (Mathieu et al., 2014). Therefore, it is possible that the processing of transitive relations in the IPS is impaired in children with MLD. The present study aimed to test this hypothesis. Because paradigms that are typically used in the adult neuroimaging literature to study reasoning tend to be repetitive and monotonous (Reverberi et al., 2007; Prado et al., 2011; Monti et al., 2007, 2009), we developed a novel fMRI task (see Fig. 1) in which children from 8 to 12 had to *listen* to scenarios that contained either transitive (e.g., A > B and B > C) or non-transitive relations (e.g., A > B and C > D). Scenarios were embedded within a “choose your own adventure” story to make the task as engaging as possible and lower demands on executive functioning. FMRI activity associated with the processing of transitive relations was measured online during story-listening and systematically compared to activity associated with the processing of non-transitive relations, so as to remove any effect of form of the relation and auditory perception. After listening to scenarios that contained these relations, children also answered questions about the relations between items or characters. This allowed us to evaluate whether transitive inferences were made online during story listening.

2. Material and methods

2.1. Participants

Fifty-one right-handed children from 8 to 12 (grades 4 to 7) were recruited using advertisements in schools, learning disabilities centers, newspapers and social media. Only 46 of these children met our cut-off criteria for either the MLD or TD group based on the standardized tests (see below). Twelve of these participants were further excluded from the analyses because of performance at chance level on the experimental task ($n = 3$), excessive head motion on at least 2 of the 4 fMRI runs ($n = 5$), and technical issues during the scanning session ($n = 4$). Therefore, 34 children were included in the final analyses. All children were native French speakers and had no hearing deficit, no MRI counter-indications and no history of neurological and psychiatric disorder. They also had no diagnosis of mental retardation or high intellectual potential. Parents gave their written informed consent and children gave their assent to participate in the experiment. Families were paid 80 euros for their participation. The experiment was approved by the local ethics committee (CPP Lyon Sud-Est II).

2.2. Standardized tests and criteria for defining MLD

Children were administered various tests assessing cognitive and academic skills. First, the NEMI-2 standardized intelligence test (Cognet, 2006) was used to measure participants' verbal intelligence (estimated using the general knowledge, vocabulary, and comparison

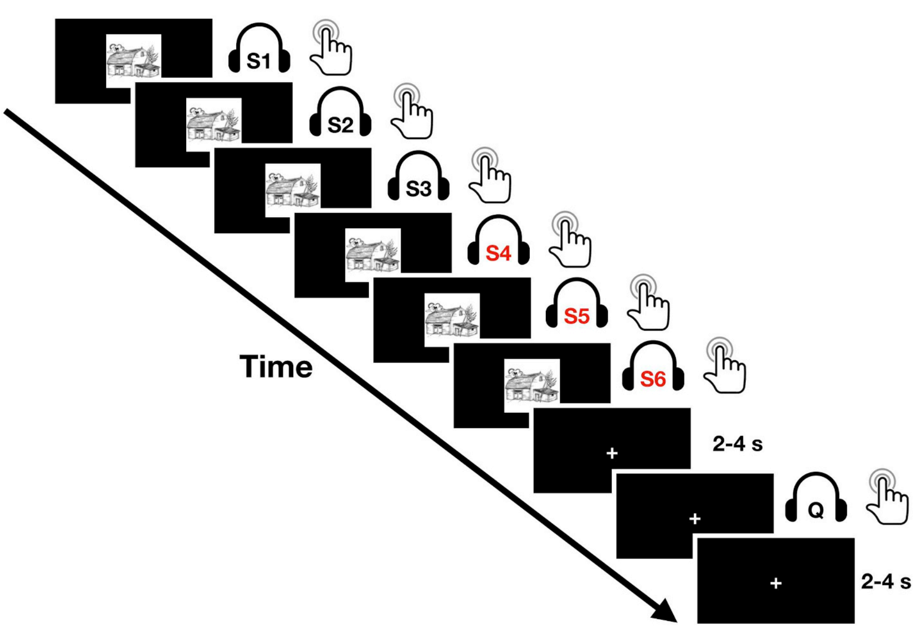

Fig. 1. Timeline for a sample scenario. Each of the 6 sentences (S) was spoken through headphones while a picture was displayed on the screen. The task was entirely self-paced. Participants pressed on a button to indicate that they were ready to listen to the next sentence, which was spoken after a 500 ms delay (not shown). The scenario ended with a question (Q), which was also spoken through headphones. This question was preceded and followed by a jittered interval ranging from 2 to 4 s. The sentences of interest considered in the analyses were sentences 4 to 6 (in red). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 1
Demographic information and psychometric measures.

Measure	TD (n = 18)	MLD (n = 16)	Statistical difference[3]
	Mean (range)	Mean (range)	
Age (in years)	11.10 (9.20–12.59)	11.17 (8.47–12.98)	p = .890
Male/Female	11/7	5/11	p = .082
Verbal IQ (NEMI-2)			
General knowledge[2]	4.61 (2–6)	3.81 (2–6)	p = .092
Vocabulary[2]	4.78 (3–7)	4.19 (1–6)	p = .361
Comparison[2]	5.17 (2–7)	4.56 (2–7)	p = .179
Matrix reasoning (NEMI-2)			
Raven's matrices[2]	4.94 (4–7)	3.06 (1–5)	p < .001*
Working-memory (NEMI-2)			
Digit repetition[2]	4.11 (2–6)	2.25 (1–5)	p < .001*
Reading (Alouette)			
Reading accuracy[1]	98.89 (65–135)	86.25 (65–115)	p = .072
Reading speed[1]	104.44 (85–135)	89.06 (65–115)	p = .034
Math (WJ-III)			
Average math score[1]	114.27 (96–147)	78.83 (63–96)	p < .001*
Math Fluency[1]	107.06 (60–150)	74.44 (50–100)	p < .001*
Calculation[1]	114.00 (88–150)	79.13 (60–112)	p < .001*
Applied Problems[1]	121.78 (97–140)	82.94 (60–117)	p < .001*

Notes. [1] standardized score (Mean = 100, SD = 15), [2] scaled score (min = 1, max = 7), [3] Because data in some of the subtests were not normally distributed (Shapiro-Wilk $p < .05$), non parametric testing (i.e., Mann Whitney U or χ^2 tests) was used to compare groups. * indicates statistical significance after correction for multiple comparisons using the Bonferroni method (critical threshold for 13 tests: $p < .004$).

subtests), matrix reasoning (estimated using the Raven's matrices subtest) and working memory ability (estimated using the digit repetition subtest) (Table 1).

Second, reading fluency was assessed with the Alouette test (Lefavrais, 1967). During 3 min, participants read aloud a text in French. The number of words read and the number of pronunciation errors are used to evaluate reading speed and reading accuracy, respectively.

Finally, math skills were assessed using 3 subtests of the Woodcock-Johnson Test of achievement (WJ III) (Woodcock et al., 2001): Math Fluency, Calculation, and Applied Problems. In the Math Fluency subtest, participants have 3 min to solve as many single-digit addition, subtraction and multiplication problems. The Calculation subtest is an untimed test in which participants solve single-digit and multi-digits operations of increasing difficulty. Some items also require knowledge of algebra and trigonometry. The test is stopped after six consecutive errors or when the last item is reached. Finally, the Applied Problems subtest measures the ability to analyze and solve math problems. While early items call upon basic numerical concepts (e.g., counting, performing simple addition and subtraction, reading clocks and coin values), most items require children to understand and analyze word problems. The test is untimed and testing stops after 6 consecutive errors or when the last item is reached. Because the WJ III is only available in English-speaking countries, we translated all subtests in French and collected norms from 428 children from 4th to 7th grade in the Lyon area before the present experiment (4th grade: n = 76, 41 boys; 5th grade: n = 75, 34 boys; 6th grade: n = 137, 67 boys; 7th grade: n = 140, 77 boys). On average, across all tests and grades, percentile ranks corresponding to raw scores were slightly higher when using the French norms than when using the US norms (e.g., a raw score corresponding to the 25th percentile with the French norms corresponded to the 22nd percentile with the US norms overall, whereas a raw score corresponding to the 40th percentile with the French norms corresponded to the 32nd percentile with the US norms overall).

Using the French norms, we considered that children were in the TD group if their score was at or above the 30th percentile on both the average math score and at least 2 of the math subtests. In contrast, the MLD group was composed of children whose score was below the 25th percentile on either the average math score or at least 2 of the math subtests. Following these criteria, we included 18 children in the TD group and 16 children in the MLD group. All of the children in the TD group were at or above the 40th percentile on the average math score. Most of the children in the MLD group (n = 14) were at or below the 10th percentile on at least one of the math subtests (and 10 out of the 16 children were below the 10th percentile on the average math score). Note that 3 children had a discrepancy in their scores on the math subtests. Specifically, 2 children in the MLD group had a high score on one subtest (> 110) while scoring below the 25th percentile on the two other subtests. Similarly, 1 child in the TD group had a score below the 25th percentile on one subtest, while scoring above the 30th percentile on the two other subtests (and above the 40th percentile on the average score). Because these children fell within our inclusion criteria, they were kept in the analyses. However, we note that the presence of these children, if anything, brings the groups closer in terms of math skills. Arguably, this makes it less (rather than more) likely to find differences between groups in our transitive reasoning task, and therefore cannot explain our main findings. Histograms of average standardized math scores for the samples of TD children and children with MLD are shown in Fig. 2. As is apparent from Fig. 2, 2 children in the TD group had an average math score that was above the 99th percentile. To evaluate the impact that these 2 participants had on the results, we ran another set of analyses without data from these children. The main behavioral and neuroimaging findings remained similar to what was found with the whole sample (see **Results** and **Supplementary Results**).

Demographic information and scores (as well as range) for each measure are shown in Table 1. After correction for multiple

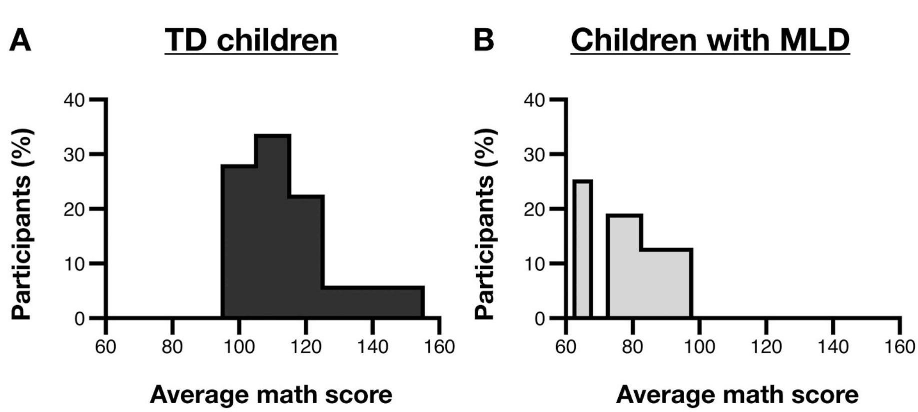

Fig. 2. Histograms of the standardized math scores averaged across all subtests of the Woodcock-Johnson III battery. (A) TD children. (B) Children with MLD.

comparisons, the groups did not statistically differ with respect to age, gender, verbal IQ, and reading. The groups differed, however, on all math subtests. They also significantly differed on measures of matrix reasoning and working-memory.

All children in the MLD group may not technically meet criteria for "specific learning disorder in mathematics" (SLDM) according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Indeed, a diagnosis of SLDM requires a demonstration that children have sustained difficulties with mathematics (e.g., over a period of 6 months). Although arbitrary, the cutoff criteria used to clinically diagnose SLDM are also typically lower than the criteria used here (e.g., 16th or 7th percentile). Finally, several of the children in the MLD group had reading (n = 5) and working-memory (n = 11) scores that were lower than the 25th percentile. Nonetheless, as is clear from their low average math scores (see Fig. 2), there is no doubt that all children in the MLD group struggle with math and therefore present some form of MLD. It is also important to note that deficits in working memory (Geary, 2011; Bull and Scerif, 2001; Passolunghi and Siegel, 2004; McLean and Hitch, 1999) and difficulty with reading (Kaufmann et al., 2013) are frequently observed in MLD. Overall, the criteria that we used to define the MLD group are consistent with (and sometimes even more stringent than) those typically used in the neuroimaging literature (e.g., Ashkenazi et al., 2012; Rosenberg-Lee et al., 2015; Davis et al., 2009).

2.3. Familiarization to the fMRI environment

On the day of standardized testing, children were familiarized with the fMRI environment in a mock scanner. They listened to a recording of the noises associated with all fMRI sequences. A motion tracker system (3D Guidance trak STAR, Ascension Technology Corporation) was used to measure head movements and provide online feedback to participants. Finally, children practiced the task in that mock scanner. The practice session differed in two ways from the brain imaging session. First, the task was shorter (i.e., there was only a single run with 8 trials). Second, the content of the trials differed from the imaging session.

2.4. Reasoning task

In the scanner, participants listened to 4 stories that each included a series of 12 short scenarios (see Table 2). Each scenario ended up with a question that the child had to answer. To maximize children's involvement, the task followed a "choose your own adventure" structure. That is, children were told to pay attention to every scenario because their responses to questions were critical for making progress in the story. To make the task as non-repetitive as possible, we included both linear-order (e.g., X is more than Y) and set-inclusion (e.g., All Xs are Ys) relations in the stories. Specifically, there were 24 scenarios that involved linear-order relations and 24 scenarios that involved set-inclusion relations. In half (i.e., 12) of each type of scenario, the relations were transitive and a conclusion could be inferred. For instance, integrating the linear-order relations "White cows give more milk than black cows" and "Black cows give more milk than brown cows" in the bottom left cell of Table 2 leads to the conclusion that "White cows give more milk than brown cows". Similarly, integrating the set-inclusion relations "All old farms are made of stone" and "All farms that are made of stone are uphill" in the top left cell of Table 2 leads to the conclusion that "All old farms are uphill". The question that followed from these scenarios always tested whether children had inferred the correct conclusion when listening to the scenario. This question was termed *reasoning question*. In the examples above, children were for instance told that they needed to milk the cows that would give the most milk. They were then asked "Are you milking the brown or the white cows?". In the set-inclusion example, children were told that they needed to find an old farm and were asked "Are you going uphill or downhill?". The remaining scenarios also contained two linear-order or set-inclusion relations. However, these relations were not transitive and no particular conclusion could be inferred. For instance, the linear-order relations "The chocolate cake is baking faster than the apple pie" and "The strawberry pie is baking faster than the cheesecake" in the bottom right cell of Table 2 cannot be integrated. Similarly, the set-inclusion relations "All bedrooms with a red door are on the side of the chicken coop" and "All bedrooms with a green door are on the side of the barn" in the top right cell of Table 2 cannot be integrated. In those cases, the question that followed simply tested whether children remembered some information that was explicitly given in the scenario. That question was termed *memory question* (see Table 2).

Each scenario was composed of 6 narrative sentences followed by a question. Sentences 1 to 3 introduced the context (and gave some information that children could be tested on in memory questions). Sentences 4 and 5 were statements that systematically used either linear-order or set-inclusion relations. Sentence 6 was a wrap-up sentence (this sentence gave participants a goal to achieve in scenarios that ended with a reasoning question). In all scenarios, participants had to choose between 2 options in the question. The content of the sentence that followed the question (i.e., the first sentence of the next scenario)

Table 2
Examples of each type of scenario (translated from French).

	Transitive relations	Non-transitive relations
Set-inclusion relations	**1.** "You are going on vacation to the countryside." "You are planning to stay in a farm for a few days." "There are farms uphill and downhill." <u>"All old farms are made of stone."</u> <u>"All farms that are made of stone are uphill."</u> "You have to find an old farm." *Reasoning question: "Are you going uphill (response 1) or downhill (response 2)?"*	**2.** "You are going uphill and you find the old farm. *(response 1)*" / "You are going downhill and the farmers pick you up" *(response 2)* "The farmers invite you in." "You need to bring your bag to your bedroom on the 2nd floor." <u>"All bedrooms with a red door are next to the chicken coop."</u> <u>"All bedrooms with a green door are next to the barn."</u> "The farmers' house is very big." *Memory question: "Are you taking your bag to the 3rd floor (response 1) or to the 2nd floor (response 2)?"*
Linear-order relations	**4.** "You are taking the pastries out of the oven." *(response 1)* / "You let the pastries in the oven and they are overbaked" *(response 2)*. "You would like some milk for your breakfast." "You are going to milk cows with the farmer." <u>"White cows give more milk than black cows."</u> <u>"Black cows give more milk than brown cows."</u> "You need to milk the cows giving the most milk." *Reasoning question: "Are you milking the brown cows (response 1) or the white cows (response 2)?"*	**3.** "You are going to the 2nd floor and bring your bag in." *(response 2)* / "You are going to the 3rd floor and the farmers tell you to go down to the 2nd floor." *(response 1)* "The next morning, the farmer is baking pastries." "The farmer is asking you to take them out of the oven now." <u>"The chocolate cake is baking faster than the apple pie."</u> <u>"The strawberry pie is baking faster than the cheesecake."</u> "It is very hot in the kitchen." *Memory question: "Are you taking the pastries out of the oven now (response 1) or later (response 2)?"*

Notes. Numbers 1 to 4 indicate the order of presentation within the experimental run.

changed as a function of the participant's prior response. Therefore, the story was coherent and children thought they were choosing their own path.

Overall word count was controlled across the 4 types of scenarios. On average, there were 69 words in scenarios with transitive set-inclusion relations, 70 words in scenarios with non-transitive set-inclusion relations, 74 words in scenarios with transitive linear-order relations and 72 words in scenarios with non-transitive linear-order relations. Because word count was not normally distributed (Shapiro-Wilk W test, $p < .001$), non-parametric testing was used to assess differences as a function of type of scenarios. First, a Kruskal-Wallis ANOVA indicated that word count did not differ between types of scenarios ($H_{(3,48)} = 4.14$, $p = .25$). Second, Mann-Whitney tests revealed that word count of sentences 4 to 6 (the critical sentences included in the fMRI analysis, see below) did not differ between scenarios with transitive and non-transitive relations, both for linear-order relations ($Z = 1.56$, $p = .12$) and set-inclusion relations ($Z = -1.18$, $p = .24$).

The task was split into 4 runs that contained one story each. Each story contained 3 scenarios with transitive linear-order relations, 3 scenarios with non-transitive linear-order relations, 3 scenarios with transitive set-inclusion relations and 3 scenarios with non-transitive set-inclusion relations. Two wrap-up sentences concluded each story. Runs were randomized but scenarios were presented in a fixed order within a run. This was because scenarios were embedded in a coherent story. However, two scenarios of the same type were never following one another. Additionally, responses were counterbalanced across different variables. First, the order of the correct response was counterbalanced across type of scenario. Second, within a run, the order of the correct response was counterbalanced between scenarios with transitive and non-transitive relations and between scenarios involving linear-order relations and set-inclusion relations. Third, to prevent participants from developing expectations during the task and using heuristic strategies to respond to reasoning questions, transitive relations were switched around in half of the problems. For example, linear-order relations could be presented in the order “A is faster than B and B is faster than C" in some scenarios and in the order “B is faster than C and A is faster than B" in other scenarios.

2.5. Procedure

Stimuli were generated using Presentation software (Neurobehavioral Systems, Albany, CA). Stories were spoken through headphones sentence by sentence (Fig. 1). During each scenario, a black-and-white picture illustrating the setting was displayed on a computer screen that was viewed by the participants through a mirror attached to the head coil. Behavioral responses were recorded using MR-compatible keypads placed in the left and right hands. The task was entirely self-paced (Fig. 1). Participants were instructed to listen carefully to each sentence and to press on a response button placed below their right index when they were ready to hear the next sentence. Participants were also instructed to press on one of two response buttons to answer the question. If the correct response was the first option heard, they had to press on a button placed below their right thumb. If the correct response was the second option heard, they had to press on a button placed below their left thumb. If no target button was pressed within the 12 s following the onset of a sentence, the next sentence was automatically spoken. The beginning of each story was indicated by a red fixation cross at the center of the screen. The red cross turned orange after 6 s and green after 2 s. The green cross lasted 2 s and was immediately followed by the auditory presentation of the first sentence of the first scenario. There was a 500 ms interval between each sentence in a scenario. A question was spoken after the last sentence of each scenario. This question was preceded and followed by a random interval ranging from 2 s to 4 s (during which a white fixation cross was displayed on the screen). Finally, each story ended with 20 s of visual fixation (during which no sentence was spoken).

2.6. Behavioral data analysis

Shapiro-Wilk W tests indicated that accuracy to questions was normally distributed in TD children ($p = .64$) and children with MLD ($p = .92$). Thus, behavioral differences between groups were assessed by entering accuracy to reasoning and memory questions in a general linear model (GLM) with the within-subject factors Question (reasoning versus memory) and Form of the relation (linear-order versus set-inclusion), as well as the between-subject factor Math ability (TD versus MLD). One-sided one-sample *t*-tests were also used to test whether performance was greater than chance (i.e., 50%) for each question, group, and form of the relation.

2.7. fMRI data acquisition

Functional and anatomical images were acquired with a Siemens 3 T Prisma (Siemens Healthcare, Erlangen, Germany) at the CERMEP Brain Imaging Center in Lyon. A high-resolution anatomical scan was collected for each participant with a standard MPRAGE sequence (TR = 3500 ms, TE = 2.24 ms, flip angle = 8°, slice thickness = 0.90 mm, number of slices = 192, isovoxel resolution = 0.875 mm). Functional sequences were collected with a gradient-echo, echo-planar sequence (TR = 2000 ms, TE = 24 ms, flip angle = 80°). Thirty-two interleaved transverse slices were acquired per volume (slice thickness = 3.48 mm, voxel size = 1.72 × 1.72).

2.8. fMRI data preprocessing

Images were analyzed with SPM12 (Welcome department of Cognitive Neurology, London, UK). The first 4 images of each run were discarded to allow for T1 equilibration effects. Functional images were corrected for slice acquisition delays and spatially realigned to the first image of the first run to correct for head movements. Realigned images were smoothed with a Gaussian filter (4 × 4 × 8 mm full-width at half maximum). ArtRepair (http://cibsr.stanford.edu/tools/ArtRepair/ArtRepair.htm) was used to identify volumes with excessive head motion. Volumes showing rapid scan-to-scan movement > 1.5 mm were substituted by the interpolation of the 2 nearest non-repaired volumes. Runs with > 10% of repaired volumes were excluded from the analysis. Based on these criteria, one run was discarded for eleven participants (i.e., 4 TD children and 7 children with MLD). Finally, functional images were normalized into the standard Montreal Neurological Institute (MNI) space. This was done in two steps. First, after coregistration with the functional data, the structural image was segmented into grey matter, white matter, and cerebrospinal fluid by using a unified segmentation algorithm (Ashburner and Friston, 2005). Second, the functional data were normalized to the MNI space by using the normalization parameters estimated during unified segmentation (normalized voxel size, $2 \times 2 \times 3.5\ mm^3$).

2.9. fMRI data analysis

Statistical analysis of fMRI data was performed according to the GLM. Previous neuroimaging studies indicate that relations are typically integrated on-line during reasoning tasks. Therefore, brain activity should ideally be measured during this integration stage rather than when conclusions are presented and have to be evaluated based on inferences that have already been drawn (Reverberi et al., 2007). In the present experiment, the sentences of interest were those containing transitive and non-transitive relations. These sentences were modeled as epochs with onsets time-locked to the presentation of sentence 4 and with offsets time-locked to the end of sentence 6 (i.e., the wrap-up sentence). Other sentences as well as the question were not explicitly modeled (i.e., they were part of background noise). Because the task was self-paced, different regressors were constructed for each participant based on their own timings. Behavioral results indicated that the form of the relation (linear-order versus set-inclusion) did not interact with group (TD versus MLD) (see below). Therefore, to improve the reliability of the estimate of the neural response, linear-order and set-inclusion relations were merged and modeled within the same regressors. All epochs were convolved with a canonical hemodynamic response function (HRF). The time series data were high-pass filtered (1/128 Hz), and serial correlations were corrected using an autoregressive AR(1) model.

For each subject, the effect of Relation (transitive versus non-transitive) on brain activity was evaluated by contrasting brain activity associated with transitive relations to brain activity associated with non-transitive relations. Individual contrasts were then submitted to second-level one-sample *t*-tests separately for the TD and the MLD groups. Using two-sample t-tests, the interaction between Relation (transitive relation versus non-transitive relation) and Math ability (TD versus MLD) was evaluated by comparing the contrast of transitive versus non-transitive relations in the TD group to the contrast of transitive versus non-transitive relations in the MLD group. The resulting t-maps were thresholded using the non-parametric permutation-based Threshold-Free Cluster Enhancement (TFCE) method (Smith and Nichols, 2009), implemented in the TFCE Toolbox r164 (http://dbm.neuro.uni-jena.de/tfce/). We had a clear a priori hypothesis that transitive relations would be processed in the IPS in TD children (see Introduction). Therefore, clusters were considered significant at a FWE-corrected threshold of $p < .05$, either across the whole-brain or within an anatomical mask of the IPS (i.e., small volume correction) defined using the Anatomy Toolbox v2.2 (Eickhoff et al., 2005). Following Price et al. (2018), the IPS mask consisted in voxels with at least 50% probability of belonging to one of the IPS subdivisions as defined in the Anatomy Toolbox. These subdivisions included hIP1 along the posterior lateral bank, hIP2 along the anterior lateral bank, and hIP3 along the medial bank (Scheperjans et al., 2008,b; Choi et al., 2006). Un-thresholded t-maps are available in NeuroVault, along with the IPS mask: https://neurovault.org/collections/4082/.

3. Results

3.1. TD children were more accurate than children with MLD on reasoning questions, but not on memory questions

Accuracy to reasoning and memory questions is shown in Fig. 3. TD children performed above chance on both reasoning questions (linear-order: $t_{17} = 13.31$, $p < .001$; set-inclusion: $t_{17} = 8.81$, $p < .001$) and memory questions (linear-order: $t_{17} = 11.80$, $p < .001$; set-inclusion: $t_{17} = 13.24$, $p < .001$). Children with MLD also performed above chance on both reasoning questions (linear-order: $t_{15} = 3.58$, $p = .001$; set-inclusion: $t_{15} = 1.98$, $p = .033$) and memory questions (linear-order: $t_{15} = 6.88$, $p < .001$; set-inclusion: $t_{15} = 7.57$, $p < .001$). Differences between groups were assessed by entering accuracy to reasoning and memory questions in a GLM with the within-subject factors Question (reasoning versus memory) and Form of the relation (linear-order versus set-inclusion), as well as the between-subject factor Math ability (TD versus MLD). There was a main effect of Math ability ($F_{1,32} = 22.26$, $p < .001$, $\eta^2 = 0.41$), indicating that MLD participants were overall less accurate than TD participants. Importantly, Math ability interacted with Question ($F_{1,32} = 6.81$, $p = .014$, $\eta^2 = 0.14$). That is, TD children were more accurate than children with MLD on reasoning questions ($p < .001$) but not on memory questions ($p = .163$). This effect did not differ as a function of relation, as indicated by a lack of 3-way interaction between Math ability, Question, and Form of the relation ($F_{1,32} = 0.94$, $p = .341$, $\eta^2 = 0.02$). In other words, TD children were more accurate than children with MLD on reasoning questions. This was the case when questions referred to both linear-order ($p < .001$) and set-inclusion relations ($p < .001$). However, there was no accuracy difference between TD children and children with MLD on memory questions. This was the case when the questions referred to both linear-order relations ($p = .791$) and set-inclusion relations ($p = 1$). Finally, although there was no main effect of Form of the relation ($F_{1,32} = 2.55$, $p = .120$, $\eta^2 = 0.07$), there was a main effect of Question ($F_{1,32} = 9.42$, $p = .004$, $\eta^2 = 0.20$) and an interaction between Question and Form of the relation ($F_{1,32} = 9.73$, $p = .004$, $\eta^2 = 0.23$). This indicated that reasoning questions were responded less accurately than memory questions across all subjects, and that this effect was larger for set-inclusion than linear-order relations.

3.2. Transitive relations were associated with enhanced bilateral IPS activity in TD children, but not in children with MLD

We first identified brain activity associated with the online processing of transitive relations in TD children. Because the behavioral results indicated that Form of the relation (i.e., linear-order versus set-inclusion) did not interact with Math ability (see above), linear-order and set-inclusion relations were merged in the fMRI analyses. Thus, we contrasted all transitive to all non-transitive relations across all TD children. As shown in Table 3 and Fig. 4A, this contrast revealed significant activity in the left IPS (at the level of hIP1 and hIP2) and in the right IPS (at the level of hIP2 and hIP3).

We then aimed to identify brain activity associated with the online processing of transitive relations in children with MLD. No difference in activity between transitive and non-transitive relations could be detected across the whole-brain or in the IPS mask in those children (see Table 3 and Fig. 4B). This result held even when a lenient FWE-corrected threshold of $p < .50$ (using the TFCE procedure, see **Methods**) was applied in the IPS mask. Although this indicates that children with

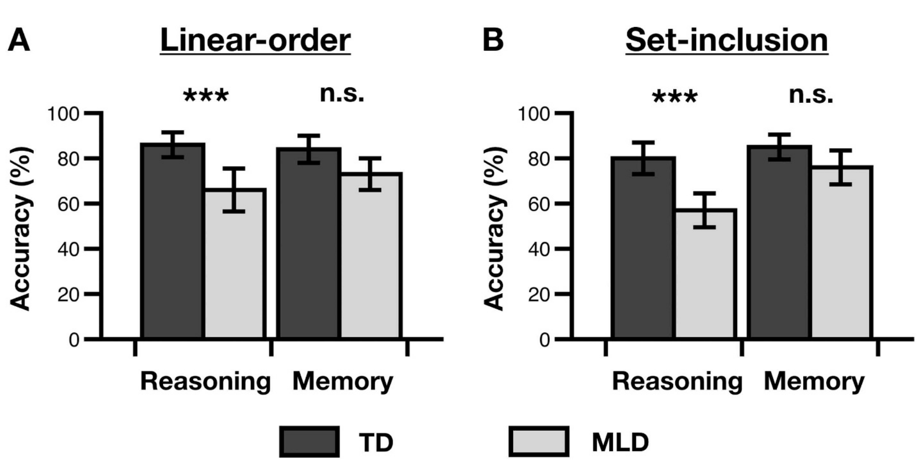

Fig. 3. Accuracy on Reasoning and Memory questions as a function of Math ability (TD and MLD) and type of relation (linear-order and set-inclusion). (A) For linear-order relations, TD children were more accurate than children with MLD on reasoning questions, but not on memory questions. (B) For set-inclusion relations, TD children were more accurate than children with MLD on reasoning questions, but not on memory questions. Error bars denote 95% confidence intervals. n.s., not significant; *** $p < .001$.

Table 3
Clusters activated in the contrast of transitive versus non-transitive relations in TD children and children with MLD.

Anatomical location	Whole-brain $P_{FWE-corr}$	SVC $P_{FWE-corr}$	MNI coordinates X	Y	Z	t-score	Cluster size (mm^3)
TD children							
Left hIP2	0.006	< 0.001	−48	−42	44	7.17	714
Right hIP2/hIP3	0.160	< 0.001	42	−44	44	4.99	1694
Left hIP2/hIP1	0.018	0.001	−42	−50	52	5.47	1148
Children with MLD							
No suprathreshold cluster							
TD children > Children with MLD							
Right hIP2	0.515	0.027	42	−46	44	4.02	154
Children with MLD > TD children							
No suprathreshold cluster							

Notes. BA: Brodmann area; MNI: Montreal Neurological Institute; SVC: Small Volume Correction; FWE-corr: Family-wise error corrected.

MLD showed no evidence for a specific processing of transitive relations in the IPS, these frequentist statistics cannot provide evidence for a null hypothesis. Therefore, we turned to Bayesian statistics (Morey et al., 2016; Lee and Wagenmakers, 2013) to quantify the evidence in favor of no difference in activity between transitive and non-transitive relations (H0) versus a difference in activity between transitive and non-transitive relations (H1) in the IPS. First, brain activity associated with transitive and non-transitive relations in children with MLD was extracted from left and right IPS ROIs, defined based on peak coordinates obtained in the contrast of transitive versus non-transitive relations in TD children (see Table 3 and Fig. 4A). Second, Bayesian paired *t*-tests ran with JASP (https://jasp-stats.org) with default priors revealed substantial evidence for H0 versus H1 in both the left (BF_{01} = 3.82) and right IPS (BF_{01} = 3.80) (Jeffrey, 1939). Therefore, there was evidence for a lack of difference between transitive and non-transitive relations in the IPS in children with MLD.

3.3. IPS activity during the processing of transitive relation was greater in TD children than in children with MLD

We also tested the interaction between Relation (transitive, non-transitive) and Math ability (TD, MLD). Using a two-sample t-test, we directly compared brain activity associated with the processing of transitive relations (versus non-transitive relation) in TD children versus in children with MLD. We found only one region in the right IPS (at the level of hIP2) in which the difference between transitive and non-transitive relations was greater in TD children than in children with MLD (see Table 3 and Fig. 5**)**. No brain region was more strongly associated with the processing of transitive relations (versus non-transitive relation) in children with MLD as compared to TD children.

3.4. Individual differences in working memory and matrix reasoning were related to individual differences in transitive reasoning

Finally, we investigated whether there was a relationship between the (behavioral and neural) correlates of transitive reasoning and the scores on the reading, working memory and matrix reasoning tests across all participants. First, there was no correlation between accuracy to reasoning questions and measures of reading accuracy (r = 0.28, p = .113) and reading speed (r = 0.16, p = .380). There was also no correlation between IPS activity associated with transitive relations (versus non-transitive relations) and measures of reading accuracy (r = 0.02, p = .924) and reading speed (r = 0.10, p = .581).[1] Second, working memory ability was significantly correlated with accuracy to reasoning questions (r = 0.57, p < .001), but not with IPS activity associated with transitive relations (versus non-transitive relations) (r = 0.24, p = .174). Finally, matrix reasoning was significantly correlated with both accuracy to reasoning questions (r = 0.58, p < .001) and IPS activity associated with transitive relations (versus non-transitive relations) (r = 0.46, p = .006). Therefore, whereas individual differences in transitive reasoning ability were not related to individual differences in reading ability, they appeared to be associated with individual differences in working memory and matrix reasoning skills.

4. Discussion

In the present study, we identified the brain mechanisms that contribute to the online processing of transitive relations in TD children. We also tested to what extent these are impaired in children with MLD.

4.1. Transitive reasoning is impaired in children with MLD

Each scenario ended with a question that either tested whether children had drawn the correct conclusion when listening to the relations in the scenario (i.e., reasoning question) or whether children remembered some information that was explicitly given (i.e., memory question). We found that children with MLD made more errors than TD peers when answering reasoning questions. In other words, it was more difficult for them to make correct transitive inferences from relations that were included in the scenarios. Such an impairment was not due to a general difficulty in remembering details from the stories. Indeed, children with MLD and TD children responded equally well to memory questions. Therefore, children with MLD appear to have specific difficulties integrating transitive relations, not remembering information from stories.

These results are consistent with, but also extend findings from a previous behavioral study by Morsanyi et al. (2013). These authors reported that children with MLD perform worse than TD controls when solving transitive reasoning problems that involve linear-order relations. In that study, however, reasoning impairments were restricted to problems leading to conclusions that were logically valid but unbelievable (e.g., “Bicycles are faster than aeroplanes. Cars are faster than bicycles. Are cars faster than aeroplanes?”) or logically invalid but believable (e.g., “Students are older than pensioners. Toddlers are older than students. Are pensioners older than toddlers?”). The ability to solve problems involving such a belief-logic conflict is typically related to executive control (Handley et al., 2004; De Neys and Everaerts, 2008). Because individuals with MLD may be particularly sensitive to interference (De Visscher et al., 2015; De Visscher and Noël, 2014) and have inhibition deficits (Landerl and Kölle, 2009; Bugden and Ansari, 2016; Szucs et al., 2013), it remained unclear whether impaired reasoning performance in belief-laden problems stems from an impaired ability to integrate transitive relations per se or from an impaired ability to suppress the interference caused by the problem content. The present study clarifies these results in two important ways. First, we show that children with MLD exhibit impaired transitive reasoning performance even when they process transitive relations that refer to an imaginary setting and therefore do not conflict with real-world beliefs (all of the relations in the present study were belief-neutral). Second, we show that the transitive reasoning impairments of children with MLD are not limited to linear-order relations, but are also observed with set-inclusion relations involving the quantifier *All*.

[1] In all of these analyses, IPS activity was extracted from the cluster that showed an interaction between Relation (transitive, non-transitive) and Math ability (TD, MLD) (see above).

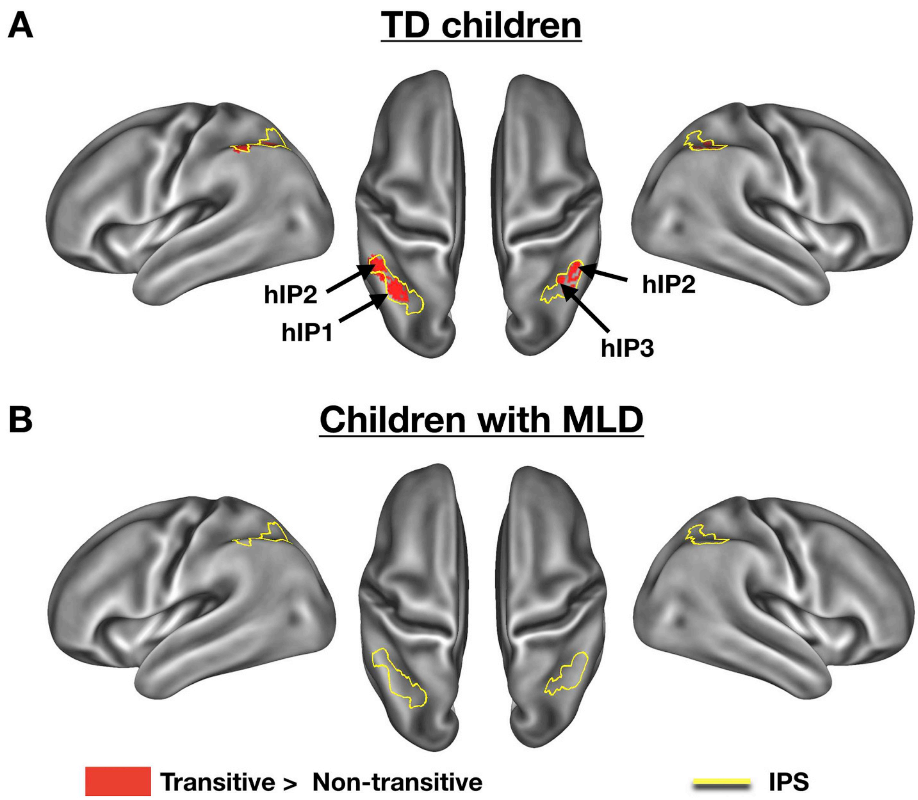

Fig. 4. Brain activity associated with the processing of transitive relations in TD children and children with MLD. (A) More activity was observed for transitive than non-transitive relations in left and right IPS clusters in TD children (in red). (B) No brain region showed more activity for transitive than non-transitive relations in children with MLD. Yellow outlines delineate the IPS mask used for small volume correction (see Methods). Activations are overlaid on an inflated 3D rendering of the MNI-normalized anatomical brain (dorsal and lateral views of the left and right hemispheres). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

4.2. TD children activate the IPS when listening to transitive relations

A novel aspect of the present study is that we used fMRI to identify the brain mechanisms associated with the processing of transitive relations in both TD children and children with MLD. In TD children, the online processing of transitive relations during story listening (i.e., the contrast of transitive versus non-transitive relations) was associated with increased activity in the bilateral IPS. Involvement of the IPS is a frequent finding in neuroimaging studies of transitive reasoning (Fangmeier et al., 2006; Knauff et al., 2003; Prado et al., 2013; Mathieu et al., 2014). For example, a quantitative meta-analysis of the neuroimaging literature on reasoning identified the IPS as a region that is consistently activated across studies in adults (Prado et al., 2011). Lesions of the parietal cortex (encompassing the IPS) have also been associated with transitive reasoning deficits in patients (Waechter et al., 2013). Because of the major role of the IPS in spatial processing (Sack, 2009), IPS activity during transitive reasoning suggests that transitive relations may rely on spatial representations (Prado et al., 2011; Goel, 2007). This is consistent with the Mental Model theory of reasoning, which assumes that relations are represented and integrated into spatial mental models (Goodwin and Johnson-Laird, 2005; Johnson-Laird, 1983). For instance, the linear-order relations “Tom is older than Sam” and “Sam is older than Bill” may lead to the construction of the unified model *Tom - Sam - Bill* (in which the symbol “-” may denote “older than”). The conclusion “Tom is older than Bill” may then be inferred from the scanning of that model. Similarly, the set-inclusion relations “All tulips are flower” and “All flowers are plants” may lead to the construction of the model *tulips - flowers - plants* (in which the symbol “-” may denote “subset of”). Therefore, this hypothesized role of the IPS in integrating transitive relations is consistent with the idea that spatial representations are fundamental to human reasoning (Johnson-Laird, 1983).

4.3. Children with MLD fail to activate the IPS when listening to transitive relations

In contrast to TD children, children with MLD did not activate the

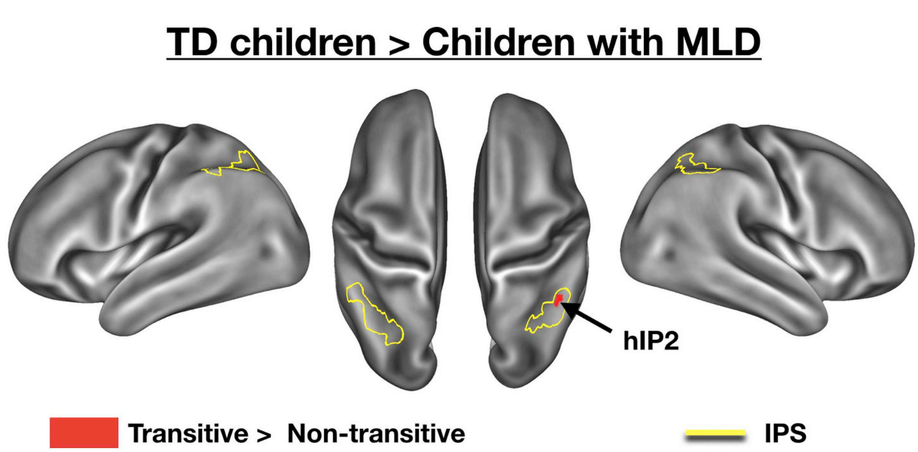

Fig. 5. Interaction between Relation (transitive versus non-transitive) and Math ability (TD versus MLD). The difference of activity between transitive and non-transitive relations was greater in TD children than in children with MLD in the right IPS (in red). Yellow outlines delineate the IPS mask used for small volume correction (see Methods). Activations are overlaid on an inflated 3D rendering of the MNI-normalized anatomical brain (dorsal and lateral views of the left and right hemispheres). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

bilateral IPS (or any other region) when listening to transitive (compared to non-transitive) relations. This was notably confirmed by a Bayesian analysis that showed substantial evidence for a lack of difference between transitive and non-transitive relations in both the left and right IPS in children with MLD. In the right IPS, there was also an interaction between relation (transitive versus non-transitive) and math ability (TD versus MLD), as indicated by a greater difference between transitive and non-transitive relations in TD children than in children with MLD. Anatomical and functional impairments in the IPS are the most consistently reported neural correlates of MLD in the literature. For instance, voxel-based morphometry (VBM) studies have found that MLD individuals have reduced grey matter volume in the IPS when compared to TD peers (Rotzer et al., 2008; Isaacs et al., 2001; Rykhlevskaia et al., 2009). Abnormal IPS activation in children with MLD has also been observed in a range of tasks that involve the processing of numerical information. For example, abnormal activation has been noted in tasks requiring children to perform approximate calculation (Kucian et al., 2006) and exact arithmetic (Ashkenazi et al., 2012; Berteletti et al., 2014). Impairments have also been observed in symbolic (Mussolin et al., 2010) and non-symbolic number comparison tasks (Price et al., 2007). Our results complement these findings by showing that IPS impairments in children with MLD may also affect the processing of non-numerical information (to the extent that such processing normally involves the IPS). That is, the online neural processing of transitive relations – which we found involves the IPS in TD children – appears to be impaired in children with MLD.

4.4. The relationship between math and transitive reasoning skills

Overall, the finding that children with MLD exhibit behavioral and neural impairments with transitive reasoning is in keeping with a growing body of literature that points to a general link between math and transitive reasoning in children, adolescents and adults. For example, Handley et al. (2004) showed that numeracy and arithmetic skills are positively correlated with logical (including transitive) reasoning performance in 10-year-olds. Morsanyi and colleagues further found a specific relationship between transitive reasoning performance and mathematical abilities in adolescents and adults (Morsanyi et al., 2017; Morsanyi et al., 2018). Therefore, the literature suggests that inter-individual differences in math skills may relate to inter-individual differences in transitive reasoning skills.

Why would transitive reasoning skills be impaired in children with MLD? We can think of at least two hypotheses. A first possibility is that IPS deficits in children with MLD may affect mechanisms that are dedicated to processing transitive relations. The existence of such dedicated mechanisms in the human brain is suggested by studies showing that transitive reasoning has a long evolutionary history. For example, using non-verbal tasks, transitive reasoning skills have been shown in infants and young children (Mou et al., 2014; Bryant and Trabasso, 1971; Gazes et al., 2017), as well as in many animal species such as non-human primates, rats, birds, and fish (Vasconcelos, 2008). It is generally believed that this old evolutionary history reflects the fact that transitive reasoning is adaptive because it facilitates the representation of hierarchies in socially organized species (Vasconcelos, 2008). Thus, it is conceivable that verbal transitive reasoning in humans relies on the co-option of those evolutionary old mechanisms in the IPS (and that these mechanisms might be affected in children with MLD).

A second possibility is that transitive reasoning impairments in children with MLD is a by-product of deficits in other mechanisms that (i) are needed when processing transitive relations and (ii) themselves rely on the IPS. For instance, impaired transitive reasoning skills in children with MLD may result from their relatively low working memory or matrix reasoning skills. We found some evidence for this hypothesis.

First, although working memory skill was not related to IPS activity during the processing of transitive relations, it was correlated with accuracy to reasoning questions. Clearly, integrating and keeping track of transitive relations within stories requires reasoners to maintain items (and their order) in working memory. Studies have found activity in the IPS during short-term and working memory tasks, especially when those involve ordinal processing (Attout et al., 2014; Marshuetz et al. 2000). Therefore, working memory impairment in children with MLD might critically contribute to their difficulty with transitive reasoning. It is also possible that a greater influence of working memory on performance and brain activity during transitive reasoning would have been observed had we used a task that explicitly measured order working memory (Attout and Majerus, 2015).

Second, matrix reasoning ability was associated with both accuracy to reasoning questions and IPS activity during the processing of transitive relations. Arguably, both transitive and matrix reasoning tasks measure *reasoning* and therefore the ability to integrate relations. That is, both tasks require participants to consider relationships between different mental representations (Miller Singley and Bunge, 2014). Thus, it is also possible that transitive reasoning deficits in children with MLD stem from a more general impairment in relational integration, a process that has been linked to the posterior parietal cortex (Wendelken, 2015). This would be broadly consistent with studies showing that individuals with MLD often tend to have weaker matrix reasoning skills than TD individuals (De Visscher et al., 2015; Price et al., 2007). Overall, both impaired working memory and relational integration skills might contribute to behavioral and neural deficits in transitive reasoning in children with MLD. Future studies might specifically investigate this possibility.

5. Conclusion

In sum, our results suggest that IPS deficits in children with MLD may impair their ability to process transitive relations. Because transitive reasoning is important in many mathematical domains, our study raises the possibility that a deficit in transitive reasoning contributes to math difficulties of children with MLD. This finding generally supports theories of MLD that emphasize the fact that the disorder may not only be caused by impairments in magnitude processing (Butterworth, 2005; Feigenson et al., 2013; Piazza et al., 2010), but also by impairments in non-numerical functions (Kaufmann et al., 2013; Szűcs and Goswami, 2013). It is also consistent with the idea that impairments in the IPS may contribute to MLD through different mechanisms, thus potentially leading to different MLD profiles (Rubinsten and Henik, 2009).

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Conflict of interest

The authors declare no competing financial interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2018.10.020.

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