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Differential effect of reading training on functional connectivity in children with reading difficulties with and without ADHD comorbidity

Tzipi Horowitz-Kraus[a,b,*], Alexander Hershey[b], Benjamin Kay[b], Mark DiFrancesco[b]

[a] Educational Neuroimaging Center, Faculty of Education in Science and Technology and Faculty of Biomedical Engineering, Technion, Haifa, Israel
[b] Pediatric Neuroimaging Research Consortium, Reading and Literacy Discovery Center, Cincinnati Children's Hospital Medical Center, 3333 Burnett Avenue, Cincinnati, OH, 45229, United States

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ABSTRACT

A comorbidity of attention deficit hyperactivity disorder (ADHD) with reading difficulties (RD) is common in children. However, children with ADHD + RD have a different reading and executive functions (EF) profile than children with RD alone. We compared the effect of an EF-based intervention on neural circuits related to EF in children with RD and those with ADHD + RD. Functional connectivity MRI data from a lexical decision task suggest that the RD-alone group showed greater improvement in EF and reading tests and greater functional connectivity between networks related to both higher- and lower-level visual processing and those related to ventral attention and dorsal attention, as well as semantic processing. Children with ADHD + RD showed greater connectivity between networks related to attention and dorsal attention and those related to visual processing and EF. Results are consistent with the Cognitive Subtype hypothesis and suggest that RD and ADHD + RD, although related behaviourally, are distinct disorders with regard to network response and connectivity during reading and after an EF-based intervention.

1. Introduction

1.1. Reading: past and future

Over a decade ago, Shaywitz and Shaywitz presented one of the first neural processing models for reading (Shaywitz, 2003). The researchers suggested there are three "main players" participating in the reading orchestra: the inferior frontal gyrus for semantic processing, the visual cortex for word recognition, and the supra marginal/angular gyrus for phonological processing. Since then, neuroimaging studies have added a major contribution to this traditional model by suggesting that these regions are part of different networks (visual processing and language networks (Vogel, Petersen, & Schlaggar, 2014; Vogel, Miezin, Petersen, & Schlaggar, 2012)) and that these networks are functionally connected (Horowitz-Kraus, DiFrancesco, Kay, Wang, & Holland, 2015a). Recently, accumulated data have suggested the involvement of neural circuits and networks related to executive functions (EF) in the reading process (anterior cingulate cortex: (Horowitz-Kraus et al., 2014; Horowitz-Kraus & Holland, 2015), superior frontal gyrus: (Horowitz-

* Corresponding author. Educational Neuroimaging Center, Faculty of Education in Science and Technology and Faculty of Biomedical Engineering, Technion, Haifa, Israel.
E-mail address: Tzipi.kraus@technion.ac.il (T. Horowitz-Kraus).

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Kraus et al., 2015a), and the cingulo-opercular network: (Horowitz-Kraus, Toro-Serey, & DiFrancesco, 2015b; Horowitz-Kraus et al., 2015a)). Examination of different populations who commonly demonstrate reading impairment allows a deeper understanding of neural circuits involved in the reading process and compensatory strategies. Our study was designed to examine the reliance of reading ability on neural circuits supporting orthographic, automatic reading ability as well as cognitive control in children with reading deficits, and in children with challenges in reading and in major EF. We also examined the plasticity of the related neural networks, including their ability to change connectivity following training.

1.2. Reading difficulties and executive functions

Dyslexia or reading difficulties (RD) is a disorder affecting approximately 5–15% of children (Shaywitz, 2003) that is characterised by major challenges in fluent and accurate reading, which can be accompanied by a secondary challenge in reading comprehension (IDA, 2011) and with some deficits in EF (Horowitz-Kraus, 2014). Neuroimaging studies indicate specific neuronal characteristics during reading in children with RD, including right-dominant brain activation (Shaywitz, 2003) (Horowitz-Kraus et al., 2014) and greater frontal activation (Horowitz-Kraus et al., 2014) compared to typical readers. Intact and improved reading was associated with greater functional connectivity between regions related to visual processing (occipital) and EF (frontal) (Horowitz-Kraus et al., 2015a; 2015b) and with the attention network during rest, even without diagnosis of an attention-deficit disorder (Vogel et al., 2014). Despite support for the involvement of EF and attention difficulties in children with RD (Shaywitz & Shaywitz, 2008), RD is considered a separate disorder from attention deficit hyperactivity disorder (ADHD), which affects approximately 5–10% of the population (Bishop, 2010; Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007; von Aster & Shalev, 2007).

1.3. Comorbidities between reading difficulties and attention deficit

Approximately 18–45% of all children with ADHD also reach the clinical definition of RD and are considered as “comorbid for ADHD and RD” (Gayan et al., 2005; Langberg, Vaughn, Brinkman, Froehlich, & Epstein, 2010). There is a debate in the literature regarding the differentiation of the comorbid group from RD with some investigators claiming that ADHD + RD is an independent disorder that is different from either RD or ADHD alone (Breznitz & Share, 1992; Hinshaw, 1992; Katz, Brown, Roth, & Beers, 2011; Pennington, Groisser, & Welsh, 1993; Rucklidge & Tannock, 2002). Other studies claim that ADHD + RD is not a separate disorder, but a condition with combined symptoms of RD and ADHD (Bental & Tirosh, 2007; Shanahan et al., 2006; Van De Voorde, Roeyers, Verte, & Wiersema, 2010). Several theories have been offered to explain the profile of the comorbidity group vs. each disorder separately in an attempt to crystalise the characteristics of each condition. Two prominent theories are: 1) *Cognitive Subtype hypothesis* - ADHD + RD has a distinct causal mechanism and could be regarded as an independent disorder (de Jong, Oosterlaan, & Sergeant, 2006; Rucklidge & Tannock, 2002) and 2) *Phenocopy hypothesis* - the deficit in ADHD + RD is ADHD with secondary symptoms of RD and therefore, ADHD + RD is not considered as a separate disorder (Pennington et al., 1993). To date, there is no consensus as to whether ADHD + RD has an etiology distinct from or common to that of RD alone. Mechanistically, it is important to better understand the cognitive/behavioural and neurobiological differences between individuals with RD alone and those with ADHD + RD for potentially more accurate diagnosis and an examination of compensatory pathways following intervention. The current study was designed to examine these points.

1.4. Training both reading and executive functions

As reading challenges are common in children with RD and those with ADHD + RD, improvement in reading fluency is an important goal for both conditions. Fluent reading is crucial for intact reading comprehension, which is a measure used for assessment of knowledge gained in the classroom, and fluency depends on accurate, timely decoding of words (Breznitz, 2006). Word decoding relies not only on intact phonology, orthography, and semantics, but also intact basic cognitive abilities, such as attention, speed of processing, and working memory (which are important for an optimal EF performance) (Christopher et al., 2012). The Reading Acceleration Program (RAP) is an EF-based computerised reading intervention (Breznitz et al., 2013) that focuses on language abilities, while also exercising the domains of attention, working memory, and speed of processing that support EF (Horowitz-Kraus, 2015; Horowitz-Kraus and Holland 2015, Horowitz-Kraus et al., 2015a, 2015b, Horowitz-Kraus and Breznitz, 2014; Horowitz-Kraus et al., 2014). Neuroimaging studies have provided neurobiological support for the effect of the RAP on both EF and reading (Horowitz- Kraus, 2015; Horowitz-Kraus and Holland 2015, Horowitz-Kraus et al., 2015a, 2015b, Horowitz-Kraus and Breznitz, 2014; Horowitz-Kraus et al., 2014). Greater activation occurs in brain regions related to EF [the inferior frontal gyrus, Brodmann area (BA) 44, and anterior cingulate cortex, BA 24] in children with RD after 4 weeks of training performing a functional MRI (fMRI) word-reading task (Horowitz-Kraus et al., 2014). These children also showed greater functional connectivity within the cingulo-opercular network related to error monitoring during rest (Horowitz-Kraus et al., 2015b) and between frontal (BA 24) and visual (fusiform gyrus; BA 37) regions during a functional MRI reading task (Horowitz-Kraus & Holland, 2015) and during rest (Horowitz-Kraus et al., 2015a). These accumulated results suggest that as the RAP forces the reader to read faster and visually attend and track the letters, both EF and attention improve. The RAP forces the reader to visually follow letters (i.e., attention) as they are erased from the screen in the same direction as reading (left to right, in English) (i.e., reliance of working memory) at a progressively faster speed (i.e., speed of processing). Monitoring comprehension ensures that the trainees do not only track the letters with their eyes, but that they also keep this information in their memory and process it linguistically. This procedure forces the reader to process words in a fast, holistic manner to 'release' the bottleneck in working memory, enabling comprehension and in turn, the readers' ability to read words improves as their mental orthographic lexicons become more stable and their error monitoring improves (Horowitz-Kraus & Breznitz, 2014). Since the RAP trains both reading and EF (Horowitz-Kraus & Holland, 2015), two abilities that are diminished in children with RD as well as children with ADHD + RD (Horowitz-Kraus, 2014; Willcutt et al., 2001), we sought to compare the changes in pertinent brain circuits following the RAP training in these two groups.

Despite evidence of the pathways by which the RAP training affects children with RD, there are no previous studies to understand the effects of this unique training technique, which focuses on a combination of abilities impacted by both ADHD + RD and RD. This topic is of particular interest due to the debate regarding the deficit in each group of children (i.e., reading, and mainly phonological deficit for RD vs cognitive control combined with reading deficits for ADHD + RD) (de Jong et al., 2006; Rucklidge & Tannock, 2002) and the gap in knowledge that exists regarding this issue. We sought, for the first time, 1) to study the baseline activation differences between the two RD populations (with and without ADHD) compared to typical readers using a standard General Linear Model (GLM) analysis applied to a reading task and 2) to pinpoint the similarities and differences in the effect of an EF-based reading-intervention training on measures related to reading and EF and neural circuits related to these abilities in RD and ADHD + RD populations compared to typical readers during a reading task. Motivated by previous findings of distinguishing connectivity changes induced by the RAP (Horowitz-Kraus and Holland, 2015; Horowitz-Kraus et al., 2015a; 2015b) and the potential for distinct network involvement in children with and without ADHD manifestation, we chose to include a focus on inter-network functional connectivity using an Independent Component Analysis (ICA) approach. This method allowed demonstration of the change in functional connectivity between networks related to reading (visual, phonology, and semantic abilities) and cognitive control (following (Horowitz-Kraus et al., 2015a)) without limiting our selection of network nodes to standard anatomical regions, but rather letting the data reveal the networks participating in the task (Calhoun, Adali, Pearlson, & Pekar, 2001b, 2001a). This allowed a re-evaluation of the reading model suggested by others (Shaywitz & Shaywitz, 2008). The importance of highlighting the different pathways of effects of the same EF-based reading training program on these two RD populations is crucial for tailoring the most appropriate intervention for each disorder (RD alone vs comorbidity of ADHD + RD), a strategy adapted from the medical field. We therefore hypothesised that children with RD compared to ADHD + RD would demonstrate distinct deviations of activation patterns during reading from those of typical readers due to potential distinctions in cognitive dysfunction. In addition to the behavioural improvement in reading and EF in all three groups, we hypothesised that children with RD alone would primarily demonstrate an increased functional connectivity between networks related to their reading deficit; mainly between networks related to lower-level visual processing (including the fusiform gyrus, a.k.a. the Word Form area) and those associated with EF and language processing (semantic). Moreover, we postulated that children with a comorbidity of ADHD + RD would demonstrate greater functional connectivity of networks related primarily to cognitive control with those related to visual processing and typical readers would separately demonstrate increased functional connectivity between reading-related networks and between networks serving cognitive-control domains. Based on previous findings (Horowitz-Kraus and Holland, 2015; Horowitz-Kraus et al., 2015a; 2015b), we anticipated that the word-reading process in our study populations would invoke a lower- (or ventral-) level visual processing independent component (IC), related directly to reading as it includes the fusiform gyrus (see (Grill-Spector & Malach, 2004; Smith & Nichols, 2009)), and an Attention IC, related directly to improvement in cognitive control following the RAP training and to the cingulo-opercular network (Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008) (Horowitz-Kraus et al., 2015b), that would show the most significant differences between the groups after the RAP intervention. Due to the proposed critical role of orthographic processing and EF in reading, we also anticipated that following training with an EF-based reading program (i.e., the RAP), increased functional connectivity between these neural circuits and other neural circuits related to visual processing and EF would be related to improved reading outcomes (word reading and reading speed) and EF measures.

2. Materials and methods

2.1. Participants

Groups of children with RD, children with ADHD + RD, and typical readers were recruited from posted ads and through commercial advertisement. All groups participating in the study were matched for age and gender (see Table 1). All participants were also matched for nonverbal IQ scores as measured by the TONI-3 (Brown, Sherbenou, & Johnsen, 1997). The RD, ADHD + RD, and typical readers groups underwent baseline behavioural and neuroimaging assessments, 4 weeks of the RAP training, and follow-up

Table 1
Demographic and behavioural data for the three groups.

Measure		Typical readers (n = 18)	RD (n = 18)	ADHD + RD (n = 18)	F test
		Mean(SD)	Mean(SD)	Mean(SD)	
Demographic	Age (years)	9.65(1.46)	9.96(1.46)	9.69(1.18)	$F(2,57) = 0.299$, $P = 0.743$
	Gender	9F, 9M	9F, 9M	9F, 9M	
Behavioural	General IQ (standard score)	103.21(7.1)	103.1(7.42)	103.42(6.11)	$F(2,56) = 0.11$, $P = 0.989$

RD, children with reading difficulties, dyslexia; ADHD + RD, children with comorbidity of RD and attention deficit hyperactive disorder; SD, standard deviation; F, female; M, male.

behavioural and neuroimaging assessments.

All participants were right-handed (determined using the Edinburgh handedness inventory (Oldfield, 1971)), native English speakers with average socioeconomic status, normal or corrected-to-normal vision in both eyes, and normal hearing. None had a history of neurological or psychiatric disorders. All children in the comorbid ADHD + RD group were diagnosed with ADHD prior to the study and shared their diagnoses with the study's team. ADHD in this group had been diagnosed by a neurologist or a psychiatrist based on DSM-4 criteria (having six symptoms or more out of a list of attention and hyperactivity/impulsivity symptoms for a least 6 months). In addition, the existence of current attention deficits was verified during the first study visit using both the Parents and Child report Conners questionnaires (Conners, 1989) version 3 (including five questions related to attention and five questions related to hyperactivity/impulsivity). Attention difficulties were determined by a cutoff score of ≥5, a generally accepted criterion for the Conners questionnaires. No differences were determined between the RD and typical readers groups in attention ability, as measured by the Conners questionnaires [self-report $t(36) = 1.227$, $P > 0.05$ and parents report $t(36) = 0.249$, $P > 0.05$]. The children with ADHD + RD showed higher attention difficulties than either children with RD alone [self-report $t(36) = -5.023$, $P < 0.001$ and parents report $t(36) = -7.522$, $P < 0.001$] or typical readers [self-report $t(36) = -5.108$, $P < 0.001$ and parents report $t(36) = -11.578$, $P < 0.001$]. No differences were found in verbal ability, measured by the vocabulary subtest of the WISC-III (Wechsler, 1999), between the different groups [typical readers and children with RD: $t(36) = 1.278$, $P > 0.05$; children with RD and children with ADHD + RD: $t(36) = 1.514$, $P > 0.05$; typical readers and children with ADHD + RD: $t(36) = 0.352$, $P > 0.05$].

Individuals with RD (from both the RD-alone and the ADHD + RD groups) either had received a formal diagnosis from a psychologist or presented with parentally reported difficulty with reading, which was confirmed by the study's reading battery. Reading ability was evaluated using a battery of normative reading tests in English: 1) word reading accuracy/orthography: Test of word-reading efficiency subtest for word reading (Test of Word Reading Efficiency, or TOWRE; (Torgesen, Wagner, & Rashotte, 1999)); 2) phonological processing: TOWRE subtest for nonwords reading; and 3) contextual oral reading fluency: Gray Oral Reading Test (GORT-III; (Wiederholt & Bryant, 1992)). Children in each RD group had to reach a standard score of −1.5 or below in the three tests (i.e., scores in the orthographic, decoding, and contextual oral reading fluency). Children who did not score −1.5 standard scores or below in all three tests were excluded from the study. Participants in the typical readers group were age-matched students who volunteered for the study and had fluent and accurate reading (according to norms) as verified using the same tests that were used to evaluate the other groups.

To assess the effect of the RAP training on behavioural reading measures, we also collected data in additional reading and reading-related domains (i.e., phonological awareness from the Comprehensive Test of Phonological Processing, or CTOPP (Wagner, Torgesen, & Rashotte, 1999); and reading comprehension and speed as measured by the RAP). To assess the effect of the RAP training on behavioural EF measures, we also collected data for other EF domains (i.e., naming from the CTOPP (Wagner et al., 1999), inhibition and switching as measured by the Stroop test from the Delis-Kaplan Executive Function System, or D-KEFS (Dellis, Kaplan, & Kramer, 2001), and visual attention as measured by the Sky-search subtest from the Test of Everyday Attention for Children, or TEA-Ch (Manly, Robertson, Anderson, & Nimmo-Smith, 1999)). To avoid a priming effect, when available, different forms of all of these same measures were also used after intervention (approximately 5 weeks after the first session), such as the TOWRE, GORT, and CTOPP. The reading tests and Conners questionnaires were administered first, as they were part of the inclusion criteria. The other tests were administered in a randomised order.

The study was carried out in the Imaging Research Center at a Mid-Western Hospital Medical Center in the US. All participants gave their informed written assent and parents provided informed consent prior to inclusion in the study, and all were compensated for their participation. The appropriate Institutional Review Board approved the experiments.

2.2. MRI paradigms

2.2.1. Lexical decision task

Children with RD alone, those with ADHD + RD, and typical readers completed two MRI sessions, one before and one after the reading training, that included alignment and anatomical scans followed by a functional MRI paradigm. Based on previous functional MRI results, the effect of the RAP intervention is related to expanding the mental orthographic lexicon (i.e., specifically to words; (Horowitz-Kraus & Breznitz, 2014; Horowitz-Kraus et al., 2014)) using sentence reading while manipulating subsets of EF (Horowitz-Kraus & Holland, 2015). Therefore, this orthographic route can be examined using the lexical decision task composed of words and pseudowords (Horowitz-Kraus & Holland, 2015; Horowitz-Kraus & Breznitz, 2014; Horowitz-Kraus et al., 2014). The lexical decision task examines the automaticity of entering the mental lexicon when the individual is forced to decide if a presented word is real or not. Based in the Parallel distributed processing model, when the reader encounters a given word, he or she is activating the phonological, orthographical, and semantic processors in the reading process (Seidenberg & McClelland, 1989). When the reader is a good reader and is familiar with the word, greater activation is expected in the fusiform gyrus (Word Form area), and if it's a new unfamiliar word or a pseudoword, which demands decoding, then neural circuits related to phonological processing are activated (Pugh et al., 2000). Since we wanted to know whether the ability of the children participating in this study changed their ability to automatically engage their orthographic route and whether they activated the related neural circuits, we chose to utilise the lexical decision task following previous studies (Horowitz-Kraus & Holland, 2015, accepted for publication; Horowitz-Kraus et al., 2014; Fiebach, Friederici, Müller, & von Cramon, 2002).

The lexical decision task consisted of 12 alternating blocks during which either words or pseudowords were presented exclusively (modeled after (Horowitz-Kraus & Holland, 2015; Horowitz-Kraus et al., 2014)). Word stimuli included 30 high-frequency words (4–6 letters long) matched for imageability and concreteness (adapted from (Van der Mark et al., 2009)). Thirty pseudowords were created by substituting one or two letters in real words. The stimuli were randomised within each block among the participants and presented horizontally in the center of a screen using DirectRT software (version number 2010.2.103.1115). Following the presentation of each stimulus, participants were shown a response screen containing two faces for either "yes" or "no" responses. The participants were instructed to push the button on a response box in their right hand, corresponding with the "yes" sign for real words or the button in their left hand, corresponding with the "no" sign for pseudoword stimuli. Six blocks of words and six blocks of pseudowords were presented alternately, with five stimuli each (a total of 60 stimuli). Each stimulus was presented for 1600 ms, and after each stimulus, the "yes/no" screen was presented for 1000 ms. The functional MRI task lasted 2.6 min (156 s) for each participant. The rationale for choosing relatively short blocks was to minimise variation resulting from motion expected in children with RD and in those with both RD and ADHD who were being asked to read in the scanner while staying still. Practice sessions with 10 stimuli both outside and inside the scanner were performed before the scan session. To avoid priming or anticipation of the stimuli after the first exposure, two different sets of stimuli were used before and after training that were matched for frequency and imageability.

2.2.2. MRI acquisition

Participants were acclimated and desensitised to condition them for comfort inside the MRI scanner (see (Byars et al., 2002; Vannest et al., 2014) for details). Head motions were controlled using elastic straps attached to either side of the head-coil apparatus used for the scan.

MRI scans were obtained using a 3T Philips Achieva MRI scanner. An MRI-compatible audio/visual system (Avotec, SS3150/SS7100) was used for presentation of the stimuli. A gradient echo planar sequence was used for T2*-weighted blood oxygen level dependent (BOLD) functional MRI scans with the following parameters: TR/TE = 2000/38 ms; BW = 125 kHz; FOV = 25.6 × 25.6 cm; matrix = 64 × 64; slice thickness = 5 mm. Thirty-five acquired axial slices covered the entire cerebrum. Seventy-eight image volumes were acquired during the functional MRI experiment for a total acquisition time of 2 min and 36 s. Each block of the task included 15 vol for a duration of 30 s. A 3D T1-weighted inversion recovery gradient echo anatomical whole-brain scan also was acquired from each participant for anatomical co-registration and use in spatial normalisation of the functional MRI data.

2.3. Data analysis

2.3.1. Behavioural data analysis

To assess the effect of the RAP training on behavioural reading and EF measures, we used separate repeated measures Analysis of Variance (ANOVA) using the scores for the different reading and EF domains. Data was corrected for multiple comparisons using a Bonferroni correction.

2.3.2. Neuroimaging data analysis

2.3.2.1. Pre-processing. For data preprocessing using SPM8 (Welcome Department of Cognitive Neurology, London; http://www.fil/ucl.ac.uk.spm), functional images were first slice-time corrected and realigned to the first image of the series. Following co-registration of the 3D anatomical volume to the mean realigned functional image, normalisation to the Montreal Neurological Institute standard template was completed. The resulting normalisation transform was applied to the functional data, which were then resampled to 3 mm^3 voxels and smoothed with an 8 mm Full Width at Half Maximum kernel.

2.3.2.2. Group activation at initial visit. A GLM was applied for voxel-wise analysis of each lexical decision task functional MRI dataset. The design matrix consisted of the time courses for the word and pseudoword blocks, convolved with the canonical haemodynamic response function in SPM8, and six realignment parameters as covariates accounting for residual motion effects. Parameter contrasts for words vs. pseudowords were then applied to group-level one-way ANOVA to assess any main effect of group and differences between pairs of groups.

2.3.2.3. Independent component analysis. After removal of the main task effect on the signal by regression, the pre-processed functional image volumes from the 108 datasets (18 datasets for each of the three groups - RD alone, ADHD + RD, and typical readers - both before and after training) were submitted to subject-wise group ICA, implemented in the Group ICA of the functional MRI Toolbox (GIFT, http://mialab.mrn.org/software/gift). ICA is a multivariate data-driven method that does not assume an *a priori* haemodynamic response function. The subject-wise concatenation technique for group ICA has been shown to produce the best overall performance compared to other proposed methods (Schmithorst & Holland, 2004). Using the Minimum Description Length criteria modified to account for spatial correlation built into GIFT, we estimated 25 group components. The pre-processed functional MRI data were scaled to percent signal change from the mean, and the time series of each voxel was then divided by its average intensity. Principal Component Analysis was used to reduce the data dimension from 156 to 71 time-points per subject (the default value suggested by GIFT) (Yourganov, Schmah, Small, & Strother, 2010) as a pre-processing step to simplify and reduce the complexity of the ICA step, as per the group ICA strategy (Calhoun et al., 2001b, 2001a). Forty-seven principle components from each subject were concatenated temporally for further reduction to 25 components at the group level (across the 108 datasets). Following group ICA, each group IC was back-projected to the individual datasets in GIFT (Calhoun, Adali, Pearlson, & Pekar, 2001a), resulting in a representative spatial distribution and corresponding time course for each dataset. The mean spatial distributions, across all datasets, for the group independent components (ICs) were used to select ICs representing relevant networks for subsequent analyses.

2.3.2.4. Selection of components. Since ICA may produce ICs representing noise (e.g., movement artifact) in addition to biological signals (Hyvarinen & Oja, 2000), a process was implemented to identify ICs of interest. Often, ICs time courses are correlated to the time course of a task to identify task-related ICs (Karunanayaka et al., 2011; Schmithorst, Holland, & Plante, 2006). ICs in the current study were included or excluded based on visual inspection of the mean spatial distribution of the ICs using two previously published criteria: 1) ICs residing primarily in white matter, ventricle(s), or outside of the brain were excluded on the basis that these regions do not generate BOLD signal (Calhoun, Kiehl, & Pearlson, 2008; Damoiseaux et al., 2006) and 2) ICs symmetrically distributed over large portions of the brain were excluded on the basis that they do not describe plausible networks (Kiviniemi, Kantola, Jauhiainen, Hyvarinen, & Tervonen, 2003). After applying the initial exclusion criteria, eight components remained for analysis. We visually searched among these eight components for those representing, in particular, networks hypothesised to be central for visual word processing for our particular subject groups, based on previous findings (Horowitz-Kraus and Holland, 2015; Horowitz-Kraus et al., 2015a; 2015b). We identified a component that represented lower- (or ventral-) level visual processing (IC1), related directly to reading (see (Grill-Spector & Malach, 2004; Smith & Nichols, 2009)), and a component for attention (IC2), related directly to improvement in cognitive control and to the cingulo-opercular network (Dosenbach et al., 2008) (Horowitz-Kraus et al., 2015b). Mean spatial patterns for each of the eight group ICs chosen for analysis are shown in Supplementary material (see S1, IC1 and IC2).

2.3.2.5. Statistical analysis of inter-component connectivity. While regions within each IC are viewed as forming a functionally connected network, our approach assessed the degree of interplay between the identified networks. Functional connectivity between pairs of brain networks was defined as the Pearson correlation between the mean time courses of the corresponding ICs. Since the RAP intervention primarily impacts orthographic processing (Horowitz-Kraus et al., 2014; Horowitz-Kraus & Breznitz, 2014), we focused on the functional connections between networks specifically during the presentation of word stimuli in the lexical decision task (following (Horowitz-Kraus et al., 2014; Horowitz-Kraus & Holland, 2015)). Thus, the portions of each IC time course corresponding to word blocks were concatenated before calculating between-network correlations. We compared the functional connectivity between ICs during word reading among the three groups (children with RD, children with ADHD + RD, and typical readers) and between the different time points: a) during baseline, Test 1 (T1) prior to training, across the three groups using a one-way ANOVA and b) T1 vs. Test 2 (T2) after training for each group separately using a paired *t*-test; 108 datasets overall. The number of comparisons was limited by designating IC1 (lower-level visual component) and IC2 (attention) as our central ICs of interest and considering only the seven correlations between each central component and the other ICs. All results were corrected for multiple comparisons using the False Discovery Rate method for all inter-component comparisons of each condition and thresholded for statistical significance at $P < 0.05$.

2.3.2.6. Correlation of behavioural results and correlation value of the ICs. We also aimed to verify the relationship between the behavioural gains in reading and EF after training to the change in correlation coefficient of the central components of interest with the other ICs. We therefore exported the R-values for each pair of components before and after intervention. We calculated the difference between the R-values before and after training for each pair of components for each participant. This difference in connectivity was correlated with the difference in reading and EF measures for each participant.

2.4. Reading acceleration program

2.4.1. Stimuli

The RAP bank of 1500 sentences is composed of moderate-to-high frequency of words in the English language (http://www.wordfrequency.info/). Each stimulus is a sentence with a multiple-choice question followed by four possible answers. Each sentence length is 9–12 words, comprised of 45–70 letters with letter width of 5 mm, extending over 1 to 2 lines, and with 18 mm between lines. Each sentence is presented once during the entire training intervention. The RAP sentences have been tested and verified for their level of difficulty in previous studies (Breznitz, 2006; Breznitz et al., 2013; Horowitz-Kraus & Breznitz, 2014).

2.4.2. Training procedure

Reading training was administered via the internet using a computer in the participants' homes. The participants were trained for 4 weeks, five times each week at 15–20 min per session for a total of 20 sessions and reading a different set of 50 randomly presented sentences in each session. The participants' compliance was monitored by remote access to the training records. Only data from participants who completed at least 18 total training sessions (out of an overall of 20 sessions) were included in the study. The initial and final reading pace and comprehension were measured by the evaluation mode of the RAP, which measures these variables in a self-paced reading condition (Breznitz et al., 2013).

The duration of a sentence display on the screen was calculated individually for each participant based on the evaluation mode and controlled by text erasure, starting from the beginning of the sentence and advancing at a given per-character rate. All participants were presented with the same sets of sentences, in the same order. They were instructed to read the sentence silently and while doing so, the sentence disappeared from the computer screen and a multiple-choice comprehension question appeared and remained on the screen until the participant responded. They were instructed to choose the correct answer by pushing the corresponding number on the numeric keypad of the computer. The disappearance of the question from the computer screen prompted appearance of the next sentence.

2.4.3. Presentation rate and evaluation mode

The initial text erasure rate was determined specifically for each participant based on a pre-test evaluation mode administered prior to training. The evaluation mode consists of 12 sentences and 12 multiple-choice questions (Breznitz & Leikin, 2001). The sentences in the evaluation mode remained on the screen until the participants finished reading them. The participants were instructed to read the sentences silently and to push the space button on the keyboard when finished reading, which prompted a comprehension question. The mean reading rate (ms per letter) for the sentence correctly answered determined the initial presentation rate of the RAP for that participant.

2.4.4. Accelerated training condition

The initial reading rate in the RAP training mode is determined based on the reading rate calculated in the evaluation mode (based on the reading rate for 12 sentences). In the first training session, 50 sentences were presented consecutively on the screen. The letters in each sentence disappeared one after the other, according to the mean reading time (ms per letter) recorded on the pre-test. Following the disappearance of the sentence from the computer screen, participants were instructed to answer a comprehension question. The per-letter "presentation rate" decreased from one sentence to the next by 2% for each subsequent sentence (Breznitz, 1997a, 1997b), and the "disappearance rate" increased only when the participant's answers to the probe questions were correct on 10 consecutive sentences. In other words, the computer pacing is adjusted periodically based on participant performance, with the letter disappearance rate increasing by 2% after each group of 10 sentences comprehended by the participant. The goal of this acceleration is to increase the reading pace over what would otherwise be chosen by the participant.

3. Results

3.1. Behavioural data

The two-way (3 × 2) repeated measures ANOVA {[Group (children with RD, children with ADHD + RD, typical readers)] x [Test (T1, T2)]} revealed greater improvement in T2 after training compared to T1 before training in both reading and cognitive measures involving speed in individuals with RD [reading: single word/nonword reading (from TOWRE-2), contextual sentence reading speed (RAP pace), contextual reading fluency and rate (from GORT-III); cognitive measures: speed of processing based on naming objects (from CTOPP), visual attention (from TEA-Ch), inhibition and switching (from D-KEFS)]. Individuals with ADHD + RD showed greater improvement in T2 compared to T1 and, compared to the other reading groups, in reading measures related to accuracy [reading words/nonwords (from TOWRE-2), rate (from GORT-III), phonemic awareness (from CTOPP), contextual reading accuracy and comprehension (from GORT-III) and cognitive measures [visual attention (from TEA-Ch) and inhibition (from DKEF)]. See Table 2 for averages, standard deviations, and gain measures for each group and test, as well as the statistical analyses results.

3.2. Neuroimaging data

3.2.1. Neuronal response to the lexical decision task

The one-way ANOVA among the three groups resulted in a significant or trending main effect of group in voxel clusters in the precentral, postcentral, parietal, occipital, and cerebellar regions for the words vs pseudowords contrast (see Supplementary Figure S2 and Table S1).

Comparisons between pairs of groups resulted in no significant voxel clusters after correction for multiple comparisons. There was a tendency for children with RD to have a stronger activation for words vs pseudowords than typical readers in temporal, parahippocampal, frontal, and occipital areas (Supplementary Figure S3). Activation for the RD group for words vs pseudowords also tended to be greater than activation in the ADHD + RD group in the basal ganglia and visual regions (Supplementary Figure S4).

3.2.2. Defining the independent components

The eight ICs that survived our exclusion criteria (designated IC1 − IC8) are listed in Table 3 and include IC1, representing lower-level visual processing (fusiform gyrus) related to orthographic reading (Cohen & Dehaene, 2004), and IC2, related to attention and error monitoring, which were selected as the central ICs of interest. A functional attribute is assigned to each component based on prior experience and previously identified canonical resting-state networks (Horowitz-Kraus et al., 2015b). Corresponding mean spatial maps of the eight ICs are presented in Supplementary material (Figure S1).

3.2.3. Correlation coefficient of the components of interest with the other ICs

Since all correlation coefficients subjected to comparison were less than 0.5 in absolute value, Fisher z-transformation was not necessary.

3.2.4. Baseline differences between the groups

Results from the ANOVA suggest that at baseline (T1) the three groups differed in functional connectivity between IC1 for visual processing and IC6, representing a network supporting EF [$F(2,52) = 3.19$, $P < 0.05$]. Post-hoc tests pairwise comparison between the groups for this connection revealed that typical readers showed significantly stronger functional connections between IC1 and IC6, followed by the RD group, with the smallest functional connection between these ICs for the comorbid ADHA + RD group. No baseline differences between the groups were found for IC2 related to attention or any of the other ICs.

Table 2
The effect of the Reading Acceleration Program training in children with reading difficulties, those with both attention deficit hyperactivity disorder and reading difficulties, and in typical readers on reading and executive functions measures.

Test	RD		ADHD + RD		TR		F-test	Gain: T2-T1	Paired *t*-test
	T1 (A)	T2 (B)	T1 (C)	T2 (D)	T1 (E)	T2 (F)			
Automatic single words reading (TOWRE SWE), number of words in 45 s	49.71 (10.47)	54.19 (11.47)	48.00 (10.70)	50.79 (11.48)	70.35 (9.36)	77.25 (9.18)	Test [F(1,57) = 55.721, $P < 0.001$, $\eta^2 = 0.494$]	4.47 (5.2) (B > A)	t(18) = −3.943, $P < 0.01$
							Test*Group [F(2,57) = 3.485, $P < 0.05$, $\eta^2 = 0.109$]	2.78 (4.68) (D > C)	t(18) = −2.502, $P < 0.05$
							Group [F(2,57) = 34.420, $P < 0.001$, $\eta^2 = 0.547$]	6.69 (4.58) (F > E)	t(18) = −6.727, $P < 0.001$
Automatic nonwords reading (TOWRE PDE), number of nonwords in 45 s	17.62 (7.41)	21.19 (7.90)	16.58 (6.53)	18.95 (6.97)	39.10 (9.76)	45.20 (9.47)	Test [F(1,57) = 45.099, $P < 0.001$, $\eta^2 = 0.442$]	3.57 (5.08) (B > A)	t(18) = −3.219, $P < 0.01$
							Test*Group [F(2,57) = 3.332, $P < 0.05$, $\eta^2 = 0.105$]	2.36 (3.93) D > C	t(18) = −2.625, $P < 0.05$
							Group [F(2,57) = 41.261, $P < 0.001$, $\eta^2 = 0.547$]	6.1 (4.72) (F > E)	t(18) = −5.776, $P < 0.001$
Contextual reading rate (GORT-IV), percentile	10.43 (7.97)	16.95 (15.66)	12.74 (9.52)	14.84 (9.32)	56.60 (19.71)	67.60 (15.03)	Test [F(1,57) = 33.152, $P < 0.001$, $\eta^2 = 0.368$]	6.52 (10.06) (B > A)	t(18) = −2.969, $P < 0.05$
							Test*Group [F(2,57) = 4.985, $P < 0.05$, $\eta^2 = 0.149$]	2.1 (3.19) (D > C)	t(18) = −2.872, $P < 0.05$
							Group [F(2,57) = 94.275, $P < 0.001$, $\eta^2 = 0.768$]	11.0 (10.75) (F > E)	t(18) = −4.574, $P < 0.001$
Contextual comprehension (GORT-IV), percentile	22.67 (15.20)	32.90 (16.11)	26.95 (17.70)	44.26 (21.00)	69.68 (15.38)	76.47 (17.02)	Test [F(1,56) = 27.408, $P < 0.001$, $\eta^2 = 0.329$]	10.23 (2.45) (B > A)	t(18) = −2.777, $P < 0.05$
							Group [F(2,56) = 51.261, $P < 0.001$, $\eta^2 = 0.647$]	17.31 (7.64) (D > C)	t(18) = −4.064, $P < 0.01$
								6.79 (1.55) (F > E)	t(18) = −2.025, $P = 0.058$
Fluency, sentences level (from the RAP), milliseconds per letter in a sentence	179.81 (73.40)	131.18 (38.41)	165.73 (67.64)	140.61 (40.15)	101.10 (36.92)	70.72 (19.01)	Test [F(1,57) = 19.851, $P < 0.001$, $\eta^2 = 0.258$]	40.96 (78.95) (A > B)	t(18) = 3.056, $P < 0.01$
							Group [F(2,57) = 20.059, $P < 0.001$, $\eta^2 = 0.413$]	3.73 (7.04) (C > D)	t(18) = 1.597, $P = 0.128$
								31.97 (29.76) (E > F)	t(18) = 4.649, $P < 0.001$
Visual attention (time per Target, Sky Search, TEA-Ch), standard score	7.00 (3.48)	9.61 (2.59)	7.42 (1.74)	9.84 (1.70)	8.68 (2.02)	10.05 (2.69)	Test [F(1,53) = 23.882, $P < 0.001$, $\eta^2 = 0.311$]	2.61 (3.85) (B > A)	t(18) = −2.876, $P < 0.01$
								2.42 (2.34) (D > C)	t(18) = −4.508, $P < 0.001$
								1.36 (3.45) (F > E)	t(18) = −1.728, $P = 0.101$
Speed of processing (Rapid objects naming, CTOPP-2), standard score	5.52 (2.69)	6.24 (2.80)	5.26 (2.02)	5.53 (2.11)	8.00 (2.75)	8.25 (3.12)	Test [F(1,57) = 4.939, $P < 0.05$, $\eta^2 = .0080$]	0.71 (1.18) (B > A)	t(18) = −2.752, $P < 0.05$
							Group [F(2,57) = 6.567, $P < 0.01$, $\eta^2 = 0.187$]	0.26 (1.52) (D > C)	t(18) = −0.754, $P = 0.461$
								0.25 (1.55) (F > E)	t(18) = −0.721, $P = 0.480$

(*continued on next page*)

Table 2 (*continued*)

Test	RD		ADHD + RD		TR		F-test	Gain: T2-T1	Paired *t*-test
	T1 (A)	T2 (B)	T1 (C)	T2 (D)	T1 (E)	T2 (F)			
Inhibition (time for Stroop, color/word interference, D-KEFS), seconds	112.26 (19.68)	83.74 (20.02)	109.74 (31.17)	91.00 (22.45)	88.84 (28.51)	85.37 (32.42)	Test [F(1,54) = 13.688, $P < 0.01$, $\eta^2 = 0.202$]	28.52 (5.25) (A > B)	t(18) = 3.828, $P < 0.01$
							Test*Group [F(2,54) = 2.543, $P = 0.088$, $\eta^2 = 0.086$]	18.74 (4.55) (C > D)	t(18) = 3.957, $P < 0.01$
								3.47 (1.22) (E > F)	t(18) = 0.331, $P = 0.744$
Switching (time for Stroop, color/word interference, D-KEFS), seconds	111.47 (26.23)	84.79 (16.40)	93.26 (17.60)	89.00 (14.54)	88.32 (26.76)	85.26 (36.83)	Test [F(1,54) = 6.275, $P < 0.05$, $\eta^2 = 0.104$]	26.68 (6.64) (A > B)	t(18) = 3.797, $P < 0.01$
							Test*Group [F(2,54) = 2.884, $P = 0.065$, $\eta^2 = 0.097$]	4.26 (4.0) (C > D)	t(18) = 1.321, $P = 0.203$
								3.06 (2.24) (E > F)	t(18) = 0.274, $P < 0.787$

RD, reading difficulties; ADHD, attention deficit hyperactivity disorder; TR, typical readers; T1, Test 1; T2, Test 2.
Mean (SD) for the reading measures for children with RD or with ADHD + RD and in typical readers are noted in columns A-F. Changes from T1 to T2, mean (SD), are noted in the “Gain” column.

Table 3
The independent components of interest in this study, the network each represents, and the anatomical regions of which each is composed.

IC	Network	Anatomical regions	X	Y	Z	BA
IC1	Lower-level Visual processing	Right fusiform gyrus	15	−72	−15	37
		Left fusiform gyrus	−24	−79	−15	37
IC2	Attention	Right anterior cingulate cortex	3	39	6	32
		Left anterior cingulate cortex	−6	36	6	32
IC3	Explicit Memory	Right parahippocampal gyrus	24	−27	−18	35
		Left parahippocampal gyrus	−18	−27	−18	35
IC4	Semantics, Articulation	Right insula	45	0	0	13
		Left Insula	−48	6	−6	13
IC5	Higher-level Visual processing	Right lingual gyrus	3	−75	0	19
		Left lingual gyrus	−9	−81	0	19
IC6	Executive functions	Right superior frontal gyrus	3	51	27	9
		Left superior frontal gyrus	−9	51	24	9
IC7	Phonology	Right supramarginal gyrus	48	−42	51	40
		Right angular gyrus	33	57	51	7
		Left supramarginal gyrus	−51	−42	51	40
		Left angular gyrus	−30	−63	51	7
IC8	Dorsal attention	Right precuneus	6	−72	33	7
		Right posterior cingulate cortex	6	−30	33	23
		Left precuneus	−12	−72	33	7
		Left posterior cingulate cortex	−3	−30	33	23

IC, independent component; BA, Brodmann area.
Coordinates listed (X, Y, Z) are in Montreal Neurological International space.

3.3. *Effect of the RAP training*

An examination of the effect of the RAP training on inter-component correlation (i.e., the difference between T1 and T2) in each group separately yielded the result that, among all groups, three ICs changed correlation strength with the IC1 Visual processing component (Table 4: IC6, EF; IC7, Phonology; IC8, Dorsal attention), and four changed correlation with the IC2 attention component (Table 5: IC3, Explicit memory; IC4, Semantics, Articulation; IC5, Higher-level Visual processing; IC8, Dorsal attention). Significance levels were corrected for multiple comparisons using the False Discovery Rate correction.

3.3.1. *Effect of training on functional connectivity of each IC with the visual (IC1) and attention (IC2) central components of interest*

3.3.1.1. IC1: lower-level visual processing (ventral pathway). The pairwise change in functional connectivity (T1 vs. T2) between IC1 and each of the other seven ICs are depicted in Fig. 1. After intervention, children with RD alone showed greater functional connectivity between IC1 and IC8 (Dorsal attention component), children with ADHD + RD showed greater functional connectivity between IC1 and IC6 (EF component), and typical readers (controls) showed greater functional connectivity between IC1 and IC7 (Phonological component) than before intervention. See Table 4 for the results.

3.3.1.2. IC2: attention. The functional connectivity between IC2 and each of the other seven ICs is depicted in Fig. 1. After intervention, children with RD alone showed greater functional connectivity between IC2 and IC4 (Semantic component) and between IC2 and IC5 [higher- (dorsal-) level Visual component], children with ADHD + RD showed greater functional connectivity between IC2 and IC8 (Dorsal attention component), and typical readers (controls) showed greater functional connectivity between IC2 and IC3 (Memory component) than before intervention. See Fig. 1 and Table 5 for the results.

Table 4
Change in correlation coefficient of the lower level (ventral) Visual processing component (IC1) with other components after the Reading Acceleration Program training in children with reading difficulties, those with both attention deficit hyperactivity disorder and reading difficulties, and in typical readers.

Comparison	Network	r1	r2	r2-r1
Test 1 compared to Test 2	IC6: Executive functions	−0.073	0.150	0.223***
	IC8: Dorsal attention	0.107	0.268	0.161**
RD Test 2 compared to RD Test 1	IC8: Dorsal attention	0.068	0.378	0.310***
ADHD + RD Test 2 compared to ADHD + RD Test 1	IC6: Executive functions	−0.112	0.116	0.228*
TR Test 1 compared to TR Test 2	IC7: Phonology	0.239	0.393	0.154*

r1, correlation coefficient value for Test 1; r2, correlation coefficient value for Test 2; Test 1, testing prior to training; Test 2, testing after training; IC, independent component; RD, reading difficulties; ADHD, attention deficit hyperactivity disorder; TR, typical readers.
*, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$.

Table 5

Change in correlation coefficient of the Attention component (IC2) with other components after the Reading Acceleration Program training in children with reading difficulties, those with both attention deficit hyperactivity disorder and reading difficulties, and in typical readers.

Comparison	Network	r1	r2	r2-r1
Test 1 compared to Test 2	IC8: Dorsal attention	−0.006	0.155	0.161**
RD Test 2 compared to RD Test 1	IC4: Semantics, Articulation	0.350	0.072	0.278**
	IC5: Higher-level Visual processing	0.013	0.204	0.191*
ADHD + RD Test 2 compared to ADHD + RD Test 1	IC8: Dorsal attention	−0.065	0.268	0.333***
TR Test 1 compared to TR Test 2	IC3: Memory	−0.039	0.169	0.208*

r1, correlation coefficient value for Test 1; r2, correlation coefficient value for Test 2; Test 1, testing prior to training; Test 2, testing after training; IC, independent component; RD, reading difficulties; ADHD, attention deficit hyperactivity disorder; TR, typical readers.
*, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$.

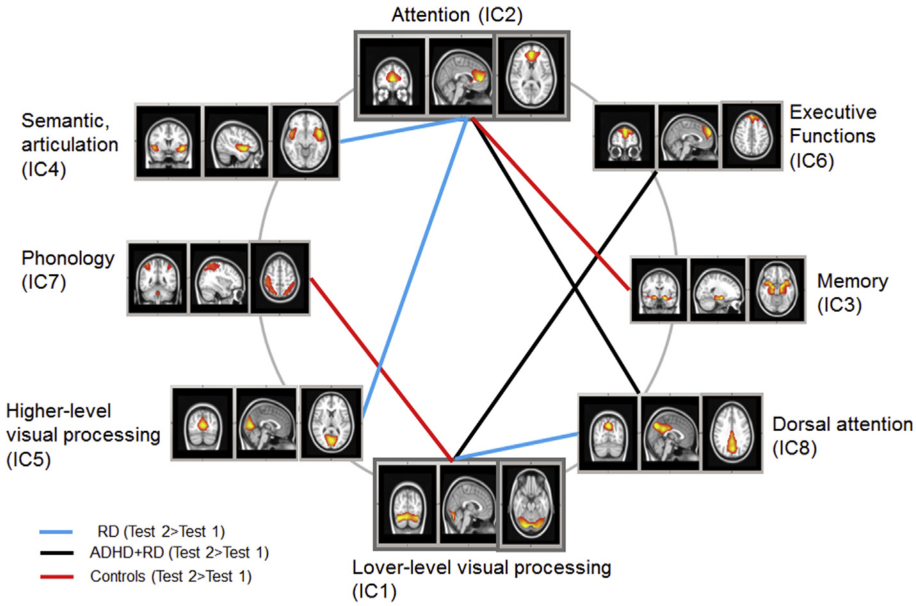

Fig. 1. Correlation coefficient for independent components (ICs) of interest. IC1: lower-level Visual processing and IC2: Attention with other ICs. Figures are in radiological orientation (Right = Left, Left = Right) and displayed as coronal (left), sagittal (middle), and axial (right) slices for ICs 1–8. Coloured lines represent an increase in functional connections between IC1 or IC2 and ICs 3–8 after training (Test 2 > Test 1) for children with reading difficulties (RD) (blue), those with ADHD + RD (black), and typical readers (red). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

3.3.2. Correlation of behavioural and imaging data between functional connectivity changes and behavioural changes resulting from the RAP training

3.3.2.1. IC1: lower-level visual processing. Pearson correlation between the change in correlation coefficient (T2 vs. T1) of the visual processing component and the other seven ICs and the gain in reading and cognitive abilities across the three groups was performed. Analysis revealed a positive association between the gain in reading speed from the RAP training and increased correlation coefficient values between the Lower-level Visual component (IC1) and the EF component (IC6) ($r = 0.375$, $P < 0.05$) and between IC1 and the Dorsal attention component (IC8). There was also a trend for a positive association between these connectivity increases and the gain in percentiles for word reading from the TOWRE ($r = 0.234$, $P = 0.08$). These results indicate that greater gain in reading speed and automatic word reading is positively correlated with an increase in functional connectivity between the Visual and EF components and the Visual and Visual attention components, respectively.

3.3.2.2. IC2: attention. Pearson correlation between the change in correlation coefficient of the Attention component (IC2) and the other seven ICs and the gain in reading and cognitive abilities revealed a positive association between the gain in Stroop time and greater functional connectivity between IC2 (Attention component) and IC5 (Higher-level Visual component). See Fig. 2. These results indicate that faster performance during the Stroop test is positively correlated with an increase in functional connectivity between the Attention and Visual components. See Supplementary Figure S5 for the scatter plots.

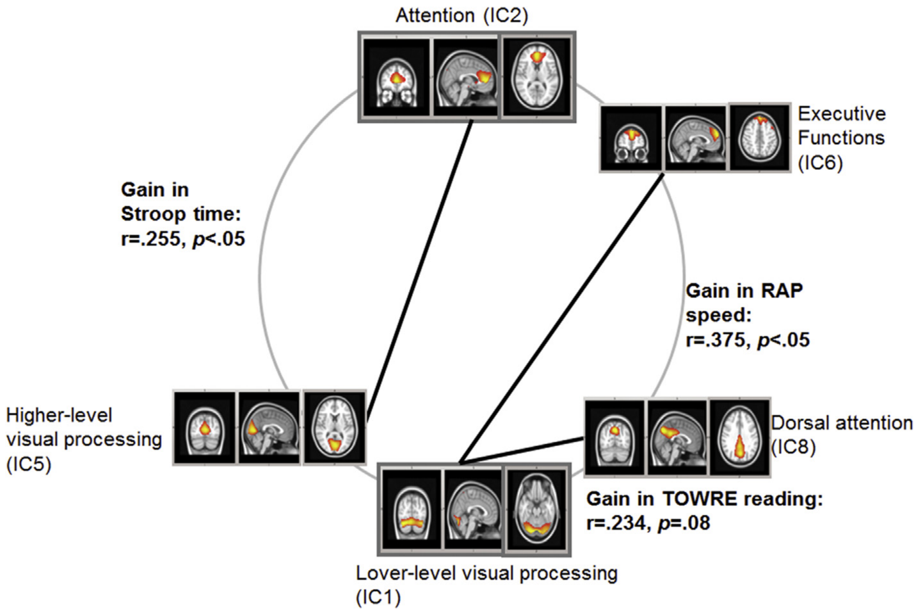

Fig. 2. Pearson correlation for the correlation coefficient values between the independent components (ICs) of interest. IC1: lower-level Visual processing and IC2: Attention after reading training and the other ICs, with gain in behavioural measures after training. Figures are in radiological orientation (Right = Left, Left = Right) and displayed as coronal (left), sagittal (middle), and axial (right) slices for ICs 1–8. Black lines represent a significant correlation found between IC1 or IC2 and ICs 3–8 after training (Test 2 > Test 1), with gain in behavioural measures in the entire cohort [children with reading difficulties (RD), those with ADHD + RD, and typical readers]. Data was corrected for multiple comparisons.

4. Discussion

The current study was designed to extend the neurobiological model for reading by examining two clinical populations. Our results provide a basis for more deeply addressing the debate that exists in the literature about whether ADHD + RD is distinct from RD alone by assessing the neural circuits suggested by the Cognitive Subtype hypothesis. We investigated differences in response between the clinical and typical readers groups to the same EF-based reading intervention, focusing on functional connectivity changes between networks pertinent to reading and EF. A significant main effect of group was observed for our reading task at baseline. Although comparison of group pairs was not powered adequately for statistical significance, activation to the reading task at baseline tended to be weaker in the left hemisphere and stronger in the right hemisphere for children with RD compared to typical readers, as previously reported (Horowitz-Kraus et al., 2014). Also, children with RD had a tendency for widespread increased activation compared to those with ADHD + RD.

In support of our hypotheses, both children with RD and those with ADHD + RD showed improved reading and EF abilities after training. However, changes observed in the connectivity between neural circuits involved in this improvement were different for each group. Children with RD alone demonstrated greater functional connectivity between ICs related to both higher- and lower-level visual processing and those related to language (semantic) and attention abilities as a result of the RAP. The change in children with ADHD + RD was mainly in neural circuits related to attention and dorsal attention and in visual processing and EF, which were more functionally connected with the component after training. The training for typical readers had a positive effect directly on functional connectivity between language networks (lower-level Visual processing and Phonology ICs) and between cognitive-control-related networks (Memory and Attention ICs). Interestingly, improved reading for all three groups was associated with greater functional connectivity between components related to lower-level visual processing and EF. Our results are in line with the Cognitive Subtype hypothesis since they demonstrate that each group utilises distinct neural circuits during reading and different compensatory pathways.

4.1. Differences and similarities between RD and ADHD + RD

In the current study, we found that activation induced by reading words vs. pseudowords differed among the RD, ADHD + RD, and typical readers groups in frontal, parietal, occipital, and cerebellar regions, which confirms that children with RD and those with ADHD + RD have distinct alteration in neural circuits related to reading deficits, as suggested by the Cognitive Subtype hypothesis. Specifically, children with a comorbidity of ADHD + RD had greater bilateral activation in frontal, parietal, and occipital lobes, but not at a significant level after correcting for multiple comparisons. The lack of power may be due to the short duration of the paradigm used in the current study. Nevertheless, this outcome motivates larger studies using a longer reading task to confirm distinct neuronal strategies for reading between these groups.

Many of the brain regions identified in the baseline GLM analysis (e.g., results from the ANOVA, Figure S1 and Table S1) were represented in our ICA components. The ADHD + RD group had weaker functional connectivity between visual processing and EF neural networks, as expected.

We also found that the EF-based reading intervention had a different effect on functional connectivity related to reading and EF in children with RD alone and those with ADHD + RD, supporting the Cognitive Subtype hypothesis. Children with ADHD + RD showed greater effects on neural circuits related specifically to attention and dorsal attention and lower-level visual processing and EF related to reading, which supports literature describing this group of readers with RD mainly due to their attention deficit (de Jong et al., 2006).

It has been suggested that the combination of ADHD with RD causes an overall "slowness" that results in an overload on working memory during reading, which in turn affects fluency and comprehension (Jacobson et al., 2011). The causal effect of poor EF on reading ability in this population as a primary cause is well documented, especially in aspects related to speed of processing (Tamm et al., 2014). Tamm and colleagues have demonstrated that changes in reaction times were related to difficulties in maintaining cognitive control, and both were related to reading challenges in this group of readers (Bellgrove, Hester, & Garavan, 2004; Tamm et al. 2012, 2014). Indeed, in the current study, children in the ADHD + RD group benefited from intervention in their impaired domains; time-related measures as described by Tamm and colleagues (e.g., inhibition and switching time), as well as visual attention and reading measures. The neural-correlates for this improvement were manifested by increased functional connectivity between ICs related to attention and dorsal attention combined with increased functional connectivity between lower-level visual processing and EF.

Mechanistically, we suggest that the EF component of the RAP (i.e., training of speed of processing, working memory, and visual attention abilities, which are impaired in children with ADHD (Tamm et al., 2014)) may drive the positive effect that this training had on neural circuits related to these abilities. We also suggest that the EF components that are an integral part of the RAP manipulation (Horowitz-Kraus & Holland, 2015; Horowitz-Kraus et al., 2015a) may drive the improvement in EF and reading abilities in children with ADHD + RD. This is supported by the significant positive correlations of the change in connectivity between lower-level Visual processing and EF ICs with the improvement in reading fluency found in the entire sample. Causal modeling analysis to measure the causality and directionality of activation could be used to verify this point in the future.

After the RAP training, improvement in all domains of reading as well as in EF was previously observed in children with RD (Breznitz et al., 2013; Christopher et al., 2012). There, it was suggested that training with the RAP helped the participants to overcome their working-memory limitations (Breznitz et al., 2013; Christopher et al., 2012). As suggested in previous studies (Breznitz & Share, 1992; Leikin & Breznitz, 2001), accelerating the presentation rate of the stimuli during the RAP training might train individuals with RD to bypass their phonological (decoding) deficits and read the presented words automatically in a holistic-orthographical manner, as is more often employed by typical readers (see (Seidenberg & McClelland, 1989)). This assumed change in strategy may help individuals with RD to store "patterns" of words and meanings in their mental lexicon, and therefore create a greater awareness of any reading errors committed. It is possible that letters/syllables are processed in the working-memory system at a rapid rate into meaningful units (words), which are then stored in the mental lexicon, minimising any mismatch between the desired word in its written form and the correct representations in the spoken lexicon. That process might be reflected in an increase in event-related potential amplitudes related to cognitive control (i.e., Error Related Negativity; see (Horowitz-Kraus & Breznitz, 2014)) that increase functional connectivity between regions related to reading (the Word Form area) and cognitive-control regions (e.g., the anterior cingulate cortex) during both reading (Horowitz-Kraus & Holland, 2015) and rest (Horowitz-Kraus et al., 2015a), as well as within the cingulo-opercular network itself during rest (Horowitz-Kraus et al., 2015b).

Previous studies were focused on the lower-level visual processing regions primarily related to word reading (Cohen et al., 2000) and their functional connectivity with regions related to cognitive control (components related to attention) (Horowitz-Kraus & Holland, 2015), which contributes to reading improvement in children with RD. The current study adds to these findings by extending the effect of the RAP on the association between lower-level visual processing and dorsal attention regions, which were previously reported to be related to the reading process (Vogel et al., 2012; 2014) and were related to better word reading in the current study (i.e., significant positive correlation in the entire sample). In addition, our results indicate that the RAP training also affects higher-level visual processing regions that have been previously related to kinetic, somatosensory processing and illusory contours (see (Grill-Spector & Malach, 2004)).

The RAP training resulted in greater functional connectivity between ICs related to higher-level visual processing and those related to attention. This finding may provide an interesting explanation as to the underlying mechanism for the reading improvement and the functional connection between ICs related to lower-level visual processing and dorsal attention. We postulate that due to the special characteristics of the RAP manipulation, when the letters are being deleted from the screen (i.e., involving a "motion-like" reading pattern), the reader's attention is directed to the visual characteristics of the words as a whole (i.e., triggers holistic reading). As a consequence, the word becomes meaningful and therefore also involves the higher-level visual processing regions, just as in the case of illusory contours that are perceived as one meaningful unit (see (Grill-Spector & Malach, 2004)). The meaning of the word then becomes available for the reader, as is evident by the greater functional connectivity between ICs related to attention and semantic processing. This point is strengthened by the positive correlation between a change in functional connectivity in the higher-level visual processing and attention ICs and faster Stroop time, which relies on faster recognition of the color of the word while engaging inhibitory control and ignoring the word. To validate this theory, a future study using a dynamic casual modeling analysis involving both the lower- and higher-level visual processing regions as well as cognitive-control and language-related regions should be performed.

The typical readers in the current study did show improvement in reading and EF. However, neurologically, they did not demonstrate the same "between modalities" change that children with RD alone and those with ADHD + RD showed. Echoing past assumptions of neuroplasticity, that beginning at a higher starting point may result in a lower gain, typical readers showed only a within-modalities increase in functional connectivity, meaning within the EF system (ICs related to dorsal attention and memory) and within the language-reading modalities (lower-level visual processing and phonological processing). This supports our previous results (Horowitz-Kraus et al., 2015a) showing increased functional connectivity between regions related to reading (i.e., the Word Form area, part of the lower-level visual processing component) and regions related to language processing (inferior frontal gyrus) during rest. In order to achieve a "between modalities" change in functional connectivity (i.e., between reading and EF ICs), more intensive or longer intervention may be required. A future study should verify this point.

4.2. New model for processing reading - convergence of EF, language, and visual networks: an extension of the original model related to reading

The results of the current study, indicating the participation of neural circuits related to attention and cognitive control, extend the traditional model for reading (Pugh et al., 2000; Shaywitz, 2003). They also highlight the importance of neural circuits related to EF, attention, and dorsal attention in intact reading and reveal not only a role for the traditional Word Form area (lower-level visual processing), but also the involvement of higher-level visual processing regions that may be important for the holistic intact way to read words. Our results also demonstrate that there is no one single way of reading improvement, but rather that the engagement of additional neural circuits related to reading changes depends on the main cause for the reading impairment, whether that is reading (in the case of RD alone) or also EF (in the case of RD with ADHD).

4.3. Study limitations

In this study, we found that the functional connections between networks associated with language, visual processing, and EF were related to better reading after the RAP intervention in different ways among the populations studied, which strengthens our original hypothesis that individuals with RD and those with ADHD + RD should be considered as distinct populations. However, the results of the study should be evaluated taking into account some limitations. First, although we suggest that the activation of higher-level visual processing occurred prior to the involvement of lower-level visual processing, we did not measure the exact sequence of events during reading following intervention or determine the direct temporal relationship between higher- and lower-level visual processing. Dynamic causal modeling including these neural circuits should be performed to verify this point. Second, although the ICs chosen for the current analysis were composed, in part, of regions related to already-identified networks (e.g., the anterior cingulate cortex, as part of the cingulo-opercular network), a preferred and more holistic approach to examine the relationship between the networks in each disorder would be to use parcellation and identify all of the neural circuits related to language, visual processing, and EF mentioned to examine the functional connectivity between these networks (see (Gordon et al., 2014) for this analysis). A future study should examine this approach. Third, although we used a task with short blocks (5 stimuli per block) to avoid prediction and motion, an additional study using an event-related lexical decision task should be employed. Fourth, since we performed group ICA on datasets comprised of a relatively small number of timepoints (156), this may have limited the robustness of our resulting ICs. Nevertheless, the mean spatial distributions back-projected among the datasets are well delineated and clearly identifiable compared to known canonical functional networks. Relatedly, once determining the ICAs for the entire task, we used 78 timepoints from the mean IC timecourses (corresponding only to the word stimuli of the task) to calculate our inter-network functional connectivity by Pearson correlation. This likely limits the power available for statistical comparisons and should be treated with caution. Future studies should seek longer tasks and/or the use of multi-band techniques to obtain more time points. Lastly, although our results indicate the positive effect of the RAP training in both individuals with RD alone and those with ADHD + RD, we have not yet determined the relationship and causality between executive deficits and slower processing, which is a topic of debate within the ADHD field that should be further investigated.

5. Conclusions

The results of this study indicate that the difficulty with reading associated with having RD and ADHD + RD might alter different neural circuits. It also suggests that the RAP, an intervention designed to improve reading performance in children with RD, shows a positive effect on reading and EF not only in children with RD alone, but also in those with a comorbidity of RD and attention difficulties (ADHD + RD), as well as in typical readers. However, this positive effect is associated with differential effects on neural circuits related to subcomponents of EF, visual processing, and language in each disorder. These results suggest that there are differences between RD and ADHD + RD that support previous studies that argue these should be considered as different disorders, as described by the Cognitive Subtype hypothesis. We feel that our results can support more accurate diagnoses of RD vs. ADHD + RD and guide more appropriate intervention. The results also have the potential to allow the definition of distinct compensatory pathways in each of the disorders allowing additional complementary interventions as needed, based on the regions involved in the neuronal response. In light of the involvement of neural circuits related to EF in reading improvement, we suggest that reading intervention programs should include an attention/EF/memory component in order to specifically train these abilities as part of reading remediation.

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Appendix A. Supplementary data

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