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Altered activation and functional asymmetry of exner's area but not the visual word form area in a child with sudden-onset, persistent mirror writing

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ABSTRACT

Mirror writing is often produced by healthy children during early acquisition of literacy, and has been observed in adults following neurological disorders or insults. The neural mechanisms responsible for involuntary mirror writing remain debated, but in healthy children, it is typically attributed to the delayed development of a process of overcoming mirror invariance while learning to read and write. We present an unusual case of sudden-onset, persistent mirror writing in a previously typical seven-year-old girl. Using her dominant right hand only, she copied and spontaneously produced all letters, words and sentences, as well as some numbers and objects, in mirror image. Additionally, she frequently misidentified letter orientations in perceptual assessments. Clinical, neuropsychological, and functional neuroimaging studies were carried out over sixteen months. Neurologic and ophthalmologic examinations and a standard clinical MRI scan of the head were normal. Neuropsychological testing revealed average scores on most tests of intellectual function, language function, verbal learning and memory. Visual perception and visual reasoning were average, with the exception of below average form constancy, and mild difficulties on some visual memory tests. Activation and functional connectivity of the reading and writing network was assessed with fMRI. During a reading task, the VWFA showed a strong response to words in mirror but not in normal letter orientation – similar to what has been observed in typically developing children previously – but activation was atypically reduced in right primary visual cortex and Exner's Area. Resting-state connectivity within the reading and writing network was similar to that of age-matched controls, but hemispheric asymmetry between the balance of motor-to-visual input was found for Exner's Area. In summary, this unusual case suggests that a disruption to visual-motor integration rather than to the VWFA can contribute to sudden-onset, persistent mirror writing in the absence of clinically detectable neurological insult.

1. Introduction

Literacy is important in modern society, but until a few hundred years ago, only a small proportion of the world's population was literate. An important prerequisite to reading is the ability to distinguish mirror reflected letters, such as *b* and *d,* and *p* and *q* (Borst et al., 2014; Cornell, 1985; Danziger and Pederson, 1998;; Duñabeitia et al., 2011; Kolinsky et al., 2011; Lachmann and Geyer, 2003). The production of correctly oriented letters is similarly critical to writing. It is thought that infants see mirror images as equivalent stimuli (Bornstein et al., 1978), and that young children are initially blind to letter orientation. This phenomenon, called mirror invariance fades with reading experience (Blackburne et al., 2014). Interestingly, the ability to discriminate mirror images seems to involve active suppression of mirror invariance, rather than a rewriting of the visual pathways involved (Borst et al., 2014; Duñabeitia et al., 2011). Once learned, mirror discrimination applies to all directional script, regardless of a reader's familiarity with the language to which the symbol belongs (Dehaene et al, 2010; Pegado, Nakamura et al., 2011).

Mirror writing is the practice of creating script that looks normal

Abbreviations: WRAVMA, Wide Range Assessment of Visual Motor Abilities; NEPSY-II, A Developmental Neuropsychological Assessment, Second Edition; WISC-IV, Wechsler Intelligence Scale for Children, Fourth Edition; WRAML-2, Wide Range Assessment of Memory and Learning – Second Edition; TVPS-3, Test of Visual Perceptual Skills, Third Edition

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when reflected in a mirror. Notable artists and literary figures like Leonardo da Vinci and Lewis Carroll have brought the phenomenon to public attention by writing in mirrored form (Nakano, 2003; Schott, 1979, 2007; Cornell, 1985). Voluntary and involuntary mirror writing have elicited considerable scientific interest over the past century, and a variety of causal theories have been proposed (Schott, 2007; Angelillo et al., 2010; Brennan, 2012; Fischer, 2012). Despite their heterogeneity, these ideas contribute to the broader quest to understand the neural networks underlying literacy in general.

Childhood mirror writing is well-established as a transient and partial phenomenon in emerging readers, who occasionally make letter reversals as they master reading and writing (Cornell, 1985). This phenomenon diminishes with experience in reading, and typically disappears by the age of eight (Cornell, 1985; Bornstein et al., 1978). Thereafter, involuntary mirror writing is atypical. It has been observed in left-handers under stress, in amputees, and in right-handers with extrapyramidal disorders who are asked to write with the non-dominant, left hand (Beale et al., 1972; Critchley, 1926). It has also been described in right-handed patients with left-sided stroke who are writing with the left hand (Angelillo et al., 2010), in patients with conversion disorder (Jokel and Conn, 1999), in patients with dissociative identity disorder writing with the right, dominant hand (Le et al., 2009), and in those with traumatic brain injury (Gottfried et al., 2003), cerebral hypoxia (Pflugshaupt et al., 2007), concussion, and altered states of consciousness (Critchley, 1926). These heterogeneous presentations have led to a variety of causal theories.

There has not been sufficient time for specialized neural systems to have evolved; instead, reading and writing must use existing brain systems. Like many other tasks, reading and writing engage primary visual and motor cortices. Early theories, therefore, framed mirror writing as a perceptual deficit, whereas others pointed to a motor deficit (Brennan, 2012; Fischer and Tazouti, 2012). Neuropsychological case studies as well as neuroscience research across development have, however, also revealed a number of more specialized regions involved in reading and writing. The visual word form area (VWFA) in the inferotemporal cortex is repurposed from general object recognition to reading-specific functions during literacy acquisition (Dehaene and Cohen, 2011; Vogel et al., 2014). Exner's area in the superior premotor cortex is specifically recruited in writing, and is thought to store graphemes (Planton et al., 2017; Potgieser et al., 2015; Roux et al., 2009). The left-lateralized Broca's area is engaged by reading and writing, and by spoken language tasks. During literacy acquisition, these regions interact to break down mirror invariance to letter representations (Blackburne et al., 2014; Pegado et al., 2014).

Here, we present an unusual case of sudden-onset mirror writing in a seven-year-old girl named LM. Despite otherwise normal functioning and previously typical literacy development, she spontaneously but persistently began to mirror write with her dominant, right hand. We characterised her perceptual and motor functioning for written and pictorial content, and used functional magnetic resonance imaging (fMRI) to detect disruption to the brain systems underlying reading and writing. Given the specificity of her impairment, we focused our analysis on those brain systems associated with literacy acquisition and the typically associated break down of mirror invariance (Pegado et al., 2014). We examined fMRI activation of those regions discussed by Pegado et al. (2014) in LM during reading and writing. Her results were compared to those reported for children of similar age in the previous literature (Blackburne et al., 2014). Blackburne et al. showed greater activation of visual, parietal and temporal regions (including the VWFA) for mirrored compared to reversed letters in young adults but not in 5–12 year-old children. In combination with EEG results also included in their study, they conclude that while adults can distinguish mirrored and normal letter orientations in early stages of visual processing, children who are still learning to read and write can not. We were interested whether those regions would show the same lack of discrimination in LM, or whether she might recruit other areas or show distinct or stronger activation for normal compared to mirrored letters. Furthermore, given the importance of the brain's connectome in shaping its function (Sporns, 2011), we also used resting-state fMRI to examine the functional connectivity of three regions most strongly associated with literacy (the VWFA, Exner's area and Broca's area) to the perceptual and motor systems that provide their input and output (Pegado et al., 2014).

1.1. Case description

A seven-year, four-month-old, previously healthy girl (LM) presented with sudden-onset, persistent mirror writing beginning on October 5, 2013. One week prior to its onset, she had complained of difficulty seeing words, and had been prescribed corrective lenses for hyperopia and astigmatism. She visited her family physician and a general paediatrician prior to being referred to paediatric neurology. Assessment revealed a right-hand dominant girl of British-Canadian ancestry. She was in the second grade, and had been reading and writing at grade level prior to her presentation. Samples of her printing indicate that she had previously reversed letters only occasionally; she had never reversed words or sentences. Birth and other developmental history were unremarkable. Review of systems revealed a new sensitivity to noise, and some difficulty remembering coordinated movements such as a forward roll in gymnastics. There was no history of headache, head injury, seizure, major illness, traumatic life event, or alteration in gait, speech, or swallowing. Family history was significant for dyslexia in a cousin and early stroke in the maternal great-grandmother.

Physical examination revealed a well-appearing, cooperative child with normal growth parameters, normal vital signs, and no dysmorphic features. Cranial nerves examination was unremarkable. The right fundus had a deep cup, but there was no papilledema or visual field deficit. Muscle bulk, power, tone and deep tendon reflexes were normal. Fine motor and rapid alternating movements were normal for age. Cerebellar testing and gait were normal. The cardiac, respiratory and abdominal examinations were unremarkable. On dermatologic assessment, a small birth mark was noted on the left flank, which had the appearance of an involuted hemangioma. She was evaluated by a paediatric ophthalmologist, who concluded that the eye examination was normal. Multiplanar, multisequence magnetic resonance imaging of her brain revealed normal sulci, ventricles and basal cisterns, with no atrophy, mass effect, stroke, hemorrhage, or abnormal parenchymal signal. Vascular flow voids were within normal limits. In summary, allowing for mild-to-moderate motion artifact, clinical imaging of the brain was normal.

1.2. Neuropsychological testing

Three weeks following the onset of mirror writing, LM participated in a detailed assessment with a paediatric neuropsychologist over a period of two days (Table 1). Her intellectual function was typical, as was her language function, verbal learning, and memory. Finger dexterity and motor speed were also normal. She had no difficulty imitating a series of rhythmic movement sequences with her hands, but had some difficulty in imitating finger and hand positions with both hands. On a standardized drawing test (WRAVMA Drawing), her ability to copy shapes and configurations was average; of note, most shapes on this test are symmetric, and LM copied only an L-shaped line drawing in mirror image. Additional tests were administered to assess visual perception, visual reasoning and visual memory. LM achieved scores in the average range on most visual perceptual tests, but had difficulty identifying shapes that differed in size, shading, or rotation (form constancy). Her scores were average on all visual reasoning tests and on all tests of visual processing speed.

On visual memory tests, she had mild difficulty identifying previously-seen drawings from within a group of drawings, identifying

Table 1
Neuropsychology testing.

Intellectual Function (WISC-IV)			**Visual Perceptual and Visual Reasoning**		
Full Scale IQ (FSIQ)	93^{x}	Average	WISC-IV		
Verbal Comprehension Index (VCI)	100^{x}	Average	Block Design	10^{y}	Average
Perceptual Reasoning Index (PRI)	93^{x}	Average	Picture Concepts	9^{y}	Average
Processing Speed Index (PSI)	100^{x}	Average	Matrix Reasoning	8^{y}	Average
Working Memory Index (WMI)	88^{x}	Low average	Picture Completion	11^{y}	Average
			Coding	11^{y}	Average
Language Function			Symbol Search	9^{y}	Average
EOWPVT – 4	93^{x}	Average	Cancelation	9^{y}	Average
NEPSY-II Word Generation - Semantic	9^{y}	Average	WRAVMA Matching	105^{x}	Average
NEPSY-II Comprehension of Instructions	12^{y}	Average	NEPSY-II Arrows		Average
			TVPS – 3		
			Visual Discrimination	9^{y}	Average
			Spatial Relation	13^{y}	High average
			Figure Ground	9^{y}	Average
			Visual Closure	8^{y}	Average
			Form Constancy	3^{y}	Below average
Verbal Learning and Memory (WRAML – 2)					
Story Memory; Immediate /Delayed Recall	11/11^{y}	Average	**Visual Memory**		
Verbal Learning / Delayed Recall	10/10^{y}	Average	TVPS – 3		
			Visual Memory	7^{y}	Low Average
			Sequential Memory	6^{y}	Low Average
			WRAML – 2		
			Design Memory	12^{y}	Average
			Picture Memory		
			– correct items	7^{y}	Low average
			– commission errors	$z < 2.0$	Below Average
Motor and Visual Motor Function					
NEPSY-II Manual Motor Sequences	26–75th %ile	Average	**Academic Achievement**		
NEPSY-II Imitating Hand Positions			WIAT-III[a]		
Right	11-25th %ile	Average	Numerical Operations	89^{x}	Low average
Left	3-10th %ile	Low Average	Word Reading	82^{x}	Low average
WRAVMA Pegs			Oral Reading Fluency		
Right	91x	Average	Accuracy	85^{x}	Low average
Left	103x	Average	Rate	81^{x}	Low average
WRAVMA Drawing	97	Average	Spelling	93^{x}	Average
NEPSY-II Fingertip Tapping			WJ-III		
Right	12y	Average	Writing samples	113^{x}	High average
Left	12y	Average			
NEPSY-II Visuomotor Precision					
Time 7					
Errors > 75th %ile					

WRAVMA = Wide Range Assessment of Visual Motor Abilities (Adams and Sheslow, 1995); NEPSY-II (Korkman et al., 2007). WISC-IV = Wechsler Intelligence Scale for Children, Fourth Edition (Wechsler, 2003); WRAML-2 = Wide Range Assessment of Memory and Learning – Second Edition (Sheslow and Adams, 2003). TVPS-3 = Test of Visual Perceptual Skills, 3rd Edition (Martin, 2006);WIAT-III = Wechsler Individual Achievement Test, Third Edition (Wechsler, 2009); WJ-III = Woodcock Johnson III Tests of Achievement (Woodcock et al., 2007); EOWPVT-4 = Expressive One Word Picture Vocabulary Test, 4th Edition (Martin and Brownell, 2011).^{x} Standard score (M = 100, SD = 15); ^{y} Scaled score (M = 10, SD = 3)^{x}.

changes in briefly-presented pictures, and remembering the sequence in which objects had been presented. When required to draw designs from memory after a short delay, she was able to draw an average number of elements from the designs, but her reproductions included some intrusions and some incorrect spatial positioning.

On tests of academic abilities, LM's phonological awareness and her speeded naming of digits and letters were all low-average to average. On reading tests in which all text was presented in the correct orientation, LM's sight-word recognition was low-average for her age and grade-level, as was the speed and accuracy with which she could read short passages of text. If not penalized for printing in mirror image, LM's spelling to dictation was average, and her ability to produce words, phrases, and short sentences was high-average; of note, she printed all letters, words, and sentences in mirror image.

Several tasks were presented to LM to further explore the nature of her mirror writing (Fig. 1). LM printed spontaneously in mirror image with her right, dominant hand only. With this hand, she printed sentences, words and letters in mirror image, whereas with her left hand, she printed sentences, words, and most letters in the correct orientation. Left-handed printing took her much longer to complete (Fig. 1B). On copying tasks, with her right hand she copied all words, all asymmetric letters, some numbers, some unfamiliar shapes, and some line drawings of objects in mirror image. When given a visual cue (such as a coloured asterisk), LM was able to comply, and could print with her right hand in the correct orientation. LM was presented with individual letters printed on a card in either their correct orientation or in mirror-image and asked whether the letter was correct or backward; she made errors on 12 of the 18 letters presented (6/9 of the letters presented in correct orientation were reported to be backward, and 6/9 of the letters presented in mirror-image were reported to be in the correct orientation). Following detailed assessment, LM's parents arranged for occupational therapy support, as none was available in the school setting. In the interim, she participated in further research.

2. Methods

Neuroimaging with fMRI was used to measure LM's brain activity during reading and writing, which was compared to findings in the

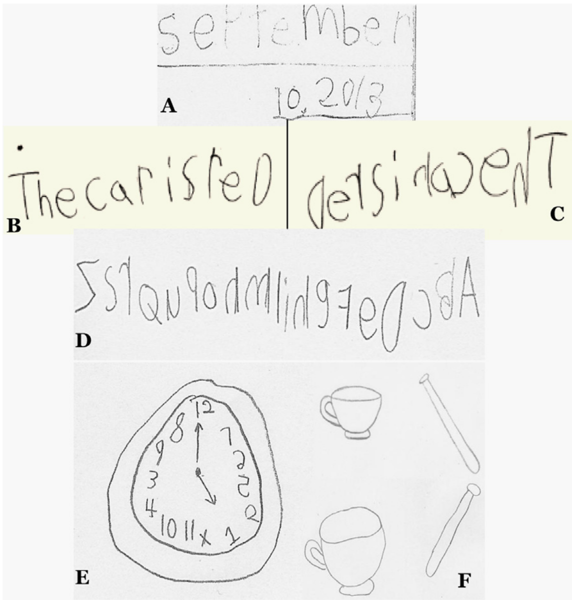

Fig. 1. Writing samples. A) Spontaneous or copied printing from a school work sample produced weeks prior to onset of mirror writing. B) Spontaneous script with the left hand after onset of mirror writing. C) Spontaneous script with the right hand. D) Spontaneous generation of the alphabet. E) Spontaneous generation of a clock face. F) Patient copy (below) of simple line drawings (above).

literature. The functional connectivity of the reading and writing network was also measured with resting-state fMRI, and compared to a control group.

2.1. Participants

Ethics approval was obtained from the Western University Health Sciences Research Ethics Board, and parents of controls and of LM gave informed, written consent prior to participation. Control participants were obtained for the fMRI resting-state analysis from two sources. One source was the publicly available Nathan Kline Institute (NKI) Rockland Sample, which contained N = 5 children aged 6–10 years (NKI ID numbers A00031411, A00032008, A00040556, A00041503, A00043494) who had been scanned with a near-identical resting-state fMRI protocol (http://fcon_1000.projects.nitrc.org/indi/enhanced). The second source was Western University's Psychology Department's Child Development Participation Pool, from which N = 3 children were recruited and scanned at our institution (two female, all right-handed, all aged 7–8 years with typical development of reading and writing skills).

2.2. MRI acquisition

Imaging was performed at the Robarts Research Institute, Western University, London, Canada on a 3 T Siemens Prisma MRI system using a 32-channel head and neck coil. At the beginning of the scanning session, a whole-brain T1-weighted high-resolution structural image was acquired with an MP-RAGE sequence (matrix size 256 × 240 × 160, flip angle = 9°, TR = 2300 ms, TE = 2.98 ms, TI = 900 ms, 1 mm isotropic resolution). Functional MRI scans were acquired using a highly accelerated multiband echoplanar sequence (multiband EPI CMRR release 10b, VD13D; TR = 686 ms, multiband acceleration factor = 4, parallel imaging acquisition iPAT factor = 1) that covered the whole brain, including 36 slices, with an oblique slice plane orientation to exclude the eyes. Further specifications included TE = 30 ms, bandwidth 1500 Hz/px, matrix size 64 × 64, and 3 mm isotropic voxel size, with a 10% gap between slices. During the resting state fMRI scan (5 min), LM was instructed to keep her eyes open. NKI resting state fMRI data was similarly acquired with a multiband EPI sequence with acceleration factor 4, iPAT = 1, TR = 645 ms, TE = 30 ms and 3 mm isotropic voxel size (for full details see http://fcon_1000.projects.nitrc.org/indi/pro/eNKI_RS_TRT/Rest_645.pdf).

2.3. Reading and Writing Tasks for fMRI

During a reading task, normally oriented and mirrored words were presented to LM. In order to keep her attention, she was instructed to press a button using her right index finger when she detected an animal word. Words were chosen based on the recommendation of a neuropsychologist, who provided a list of two to six letter words that LM was able to read in under one second. Words were presented for 2.5 s, with a 0.1 s gap between words. Thirty-six unique words were chosen randomly from this list for every scan (see Supplementary Table S1 for the list of stimuli used). These were presented centrally in white writing on a black background using Matlab (Mathworks, Natick, MA) and the Psychtoolbox (Brainard, 1997), once in mirror form, and once in normal orientation. A block design was used, with six blocks of six mirrored words, six blocks of six conventionally written words, and six rest blocks for baseline analysis. Conditions (mirror, normal, rest) were presented in a counter-balanced order to assure that each condition followed every other condition the same number of times. LM completed three scans of the reading task.

In the writing task, short sentences were presented in both normally oriented and mirrored form, and LM was instructed to copy them onto a lap desk with her right index finger. Sentences were taken from a children's book recommended by LM's mother (Seuss, 1990). Three unique, four-word sentences were chosen for three separate scans (for a total of 9 unique sentences, see Supplementary Table S2). In every trial, a sentence was presented for 15 s, during which LM copied it with her right index finger onto a lap-desk placed on her stomach. She was instructed to use either mirror or normal writing through a visual cue (X) positioned either to the left or right of a blank line underneath the sentence. Writing orientation changed after each trial. There was a seven second gap between trials, which served as a baseline. LM completed three scans of the writing task. During each of the three separate scans, LM was asked to copy each of the three sentences in mirror form twice, and in normal orientation twice (two conditions (normal/mirror), 6 trials per condition (3 sentences presented twice each), each unique sentence presented four times), and sentences were presented in pseudo-randomized order, centrally in white writing on a black background using Matlab (Mathworks, Natick, MA) and the Psychtoolbox (Brainard, 1997). Task performance (compliance to write in the instructed orientation) was monitored using an in-bore video camera. The last scan was excluded from analysis due to excessive motion.

2.4. Reading and writing fMRI analysis

Imaging data were analyzed in Matlab (Mathworks, Natick, MA) with the automatic analysis toolbox (Cusack et al., 2014) and SPM8 (Wellcome Department of Imaging Neuroscience, London, UK). Functional images were converted to NIFTI format, motion corrected using realignment as implemented in SPM, co-registered to the structural T1 image, normalized to the standard Montreal Neurological Institute (MNI) template, and smoothed using a 10 mm full-width half-maximum Gaussian kernel.

A general linear model (GLM) implemented in SPM was used to model brain activity evoked by the reading and writing tasks. For each reading or writing scan, separate block-design regressors were used for mirror orientation versus normal orientation. Time-courses were convolved with the canonical hemodynamic response function. The inter-trial intervals and rest blocks served as the implicit baseline. Contrasts were performed against baseline for each of the four conditions (mirror reading/writing > baseline, normal reading/writing > baseline) as well as for mirror vs. normal letter orientation (mirror > normal

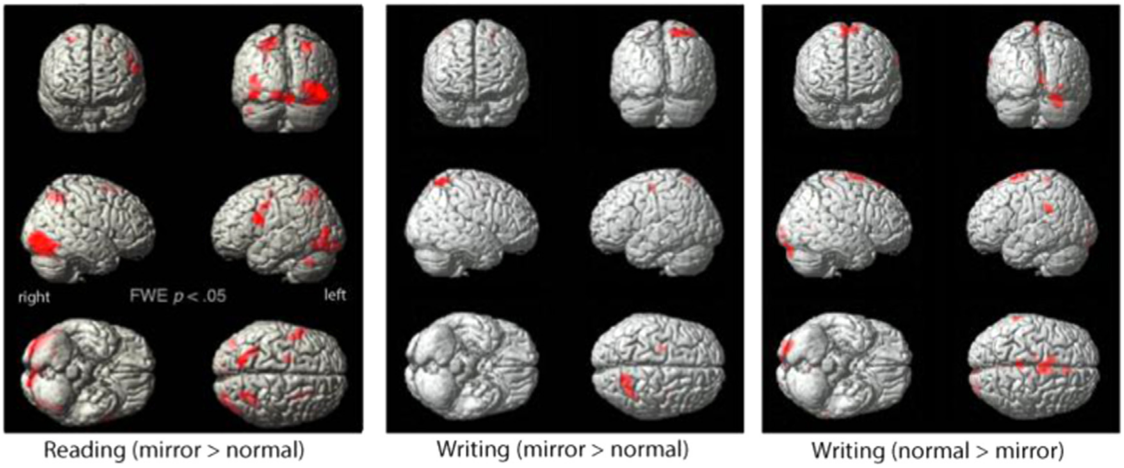

Fig. 2. Areas showing higher activation for mirror vs. normal letter orientation in LM during reading (left) and writing (middle panel), and for normal > mirror for writing (right). No areas responded significantly stronger to normal compared to mirror letter orientation during the reading task. All results are shown at $p < 0.05$ voxelwise FWE-corrected for multiple comparisons.

reading, mirror < normal reading, mirror > normal writing, and mirror < normal writing). Results were voxelwise multiple-comparison (FWE) corrected at $p < 0.05$.

Additionally, activation of eight bilateral regions of interest (ROIs) that are known to be part of the reading and writing network was compared for mirror compared to normal reading and writing by extracting average t-values. ROIs were defined using 4 mm spheres in MNI space using MarsBar, (Brett et al., 2002) and included primary visual cortex (left: −8.7 −92 −1; right: 12.3 −92.6 −1), secondary visual cortex (left: −30.1 −86.8 −3.9; right: 33.4 −85.6 −3.9), the Fusiform Face Area (FFA, 35 −49 −14) (Berman et al., 2010) and its mirrored analogue in the left hemisphere (−43.4 −49 −14), the VWFA (−45 −57 −12) (Vogel et al., 2012) and its homologue in the right hemisphere (49.1 −59.1 −12), Broca's Area (left: −54 12 22; and its mirrored homologue in right hemisphere: 44 11.7 27; (Lee et al., 2012)), Exner's Area (left: −22 −6 52; right: 21.8 −6.6 52 (Sporns, 2011)), the Supplementary Motor Area (SMA, left: −4 8 56; right: 5.4 3.9 56.9) and primary motor cortex (left: −34 −14 62, right: 34.5 −11.3 63.9).

2.5. Resting-State MRI analysis

Subject head motion has a strong effect on noise levels in functional neuroimaging, and when comparing functional connectivity or brain activity between subjects, it is important to rule out differential motion as a confounder. To examine this, for LM and each control, motion was quantified by taking the average of each of the six motion estimates (translation: x – left/right, y – anterior/posterior and z – superior/inferior; and rotation: pitch – chin up/down, roll – top of head left/right, and yaw –nose left/right). Absolute values were used and rotation values (in radians) were scaled to correspond approximately to translation (in millimetres, assuming a head circumference of 53 centimetres, with the radius in millimetres and the rotation value in radians). For the functional connectivity analyses, 200 volumes of data with minimal motion were selected for each child, and a scrubbing model used to remove residual noise and artifacts. Six motion regressors were regressed from voxel time series, and model residuals used for further analyses. Absolute motion magnitude in LM was not significantly different from the control group; Crawford $t\ (7) = -0.51$, critical t for two-tailed significance at $p < 0.05$: 1.895. This observation is important, as previous studies have shown differences in functional connectivity to be easily confounded by motion, especially when comparing patients to control groups.

Brain regions are considered functionally connected if they show correlated changes in spontaneous brain activation through time. Literacy training in general, and mirror discrimination in particular, involves the interplay of visual and motor systems. (Pegado et al., 2014) To quantify functional connectivity across this reading and writing network, the time course of each of the ROIs described above was correlated with that of every other ROI to yield a functional connectivity similarity matrix. The functional connectivity similarity matrix of each control child was then triangulated and compared to the average, triangulated connectivity matrix of all other controls (n-1) using Pearson correlation. LM's connectivity matrix was compared to the average connectivity matrix of all controls. The resulting correlation value is a measure of how similar each child's connectivity within the reading and writing network is to that of the group average. LM's results were statistically compared to those of the control children using a method developed by Crawford et al. for comparing individual patient data to healthy control groups (Crawford et al., 2009).

We then examined in detail the connectivity of the three major nodes specifically associated with reading and writing (VWFA, Broca's and Exner's). Specifically, we quantified the strength with which each node was connected to perceptual (primary visual, secondary visual, FFA) and motor regions (primary motor & SMA). For each major node in each hemisphere (e.g., left VWFA), we calculated the mean connectivity to the target regions [e.g., mean of connectivity to six perceptual regions: left/right (L/R) primary visual; L/R secondary visual; L/R FFA]. Based on the known functions and anatomical locations of the three ROIs most strongly associated with literacy, we hypothesized that VWFA would be more strongly connected to perceptual regions, while Exner's would be more strongly connected to motor regions, and Broca's being equally connected to perceptual and motor regions. To visualise the data, we captured the laterality of the connectivity with the laterality index ((L-R)/(L+R)), and then averaged the overall connectivity across hemispheres. To compare LM to the healthy controls, we again used Crawford-Howell *t*-tests.

3. Results

3.1. Brain activation during reading and writing tasks

During reading, LM's overall pattern of activation with mirror versus normal script was not markedly different from what has previously been observed in healthy children and adults (Fig. 2) (Blackburne et al., 2014). To provide a summary of activation during mirror versus normal reading and writing in the major nodes of the network, we conducted an ROI analysis (Fig. 3A). Hemispheric differences were observed, with

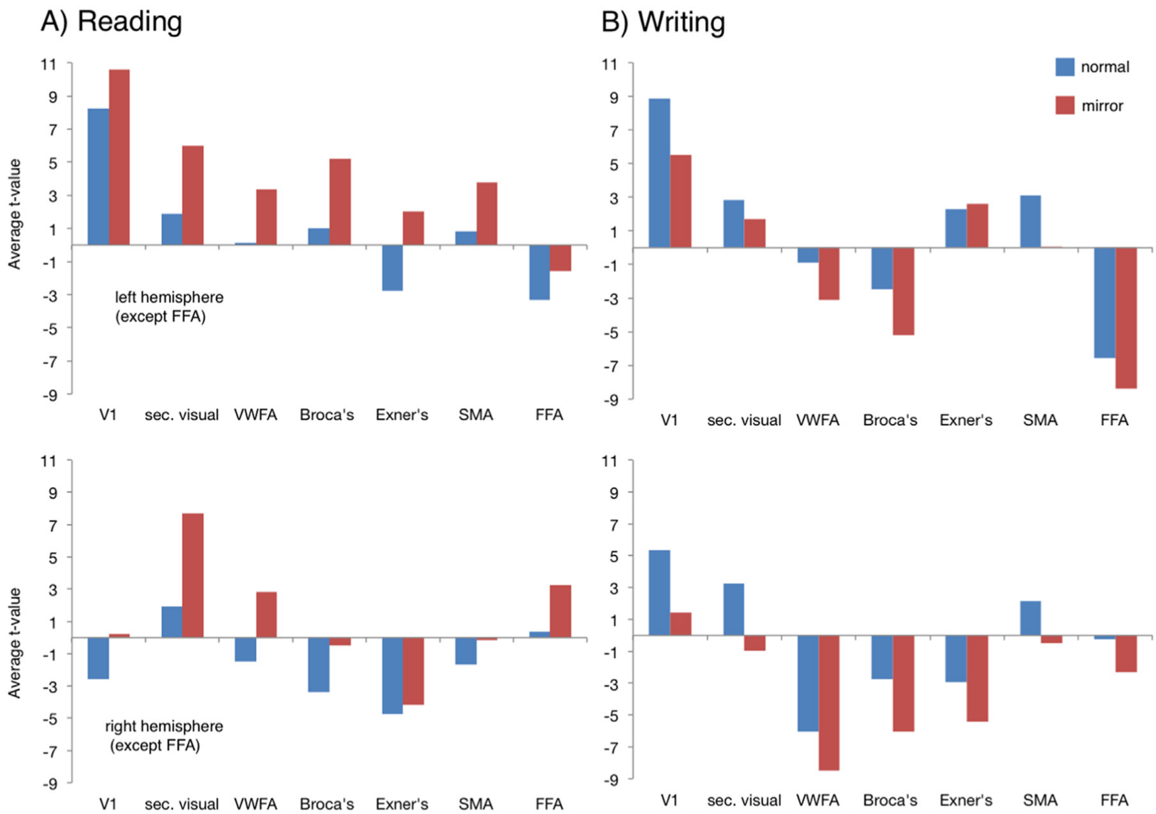

Fig. 3. Activations (t-values) of the reading and writing network ROIs when reading words (A) and writing sentences (B) with normal (blue) compared to mirrored (red) letter orientations, separately for each hemisphere. The FFA, which is right lateralized, is presented with ROIs in the left hemisphere. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

distinctly less activation of right primary visual cortex, right Broca's area, right Exner's area and the right SMA, irrespective of letter orientation. The lack of activation of LM's right primary visual cortex during reading is surprising. Another unexpected result was activation of Exner's area during mirror but not normal reading (Longcamp et al., 2003).

During writing, activation of several brain areas was suppressed for both mirror and normal letter orientations. These areas included the VWFA, its right-sided homologue, Broca's Area bilaterally, right Exner's Area and the FFA. It appeared that activation of the right primary visual cortex was reduced compared to activation in of homologous regions in the left hemisphere, irrespective of letter orientation (Fig. 3B). Additionally, while the VWFA responded strongly to mirrored words, there was essentially no activation to words written in normal script. This is atypical, given the large number of studies that have established the specificity of the VWFA for letters (Dehaene and Cohen, 2011; Dehaene et al, 2010; Ben-Shachar et al., 2011). This lack of activation in LM is difficult to interpret, since she is able to read words written in normal letter orientation, albeit reproducing them in mirrored script. Furthermore, the current results need to be interpreted with caution, as the results from the reading and writing tasks were a case study and no data from typical controls performing the same tasks was available for comparisons.

In summary, unusual patterns of activation were seen in the VWFA and Exner's area, with a lack of activation to normally oriented words during reading and writing. We wished to investigate this system further. Given that reading and writing intrinsically involve the transfer of information between brain regions, the pattern of connectivity may shape LM's behaviour. Thus, we also compared functional connectivity of the reading and writing network in LM with typically developing controls.

3.2. Functional connectivity of the reading/writing network during the resting state

In the resting state, the overall pattern of LM's functional connectivity of the reading and writing network was not significantly different to that of controls (Crawford t $(7) = 1.16$, critical t for significance at $p < 0.05$: 1.895; Fig. 4).

To examine the connectivity of the three major nodes specifically associated with reading and writing, we conducted an ROI analysis. In LM and controls, we characterised each node by its functional connectivity to perceptual (primary visual, secondary visual, FFA) and motor regions (primary motor & SMA). As might be expected, there was a gradient in visual and motor connectivity from the VWFA through Broca's to Exner's (Fig. 5a-c). This pattern was similar for LM and controls, with no significant differences (all p values > 0.1). We then examined the lateralisation of this connectivity. For the relative motor to visual connectivity (Fig. 5f), LM's lateralisation index was similar to controls for VWFA and Broca's areas (Crawford's t $(7) = 0.00$, $p < 0.50$; t $(7) = -0.07$ $p < 0.47$, respectively). However, for Exner's area, a strong difference in lateralisation was seen (t $(7) = -8.31$ $p < 0.0001$), with right Exner's more connected to visual regions and less connected to motor regions versus controls.

3.3. Longitudinal follow-up

One year following the onset of mirror-writing, LM underwent neuropsychological review. She had been receiving private occupational therapy, and had learned strategies for printing conventionally. Under observation, she wrote conventionally with great effort, and used labour-intensive strategies for remembering the proper direction of script. Her printing contained occasional letter reversals, and she continued to reverse numbers. On formal testing of her academic skills, she

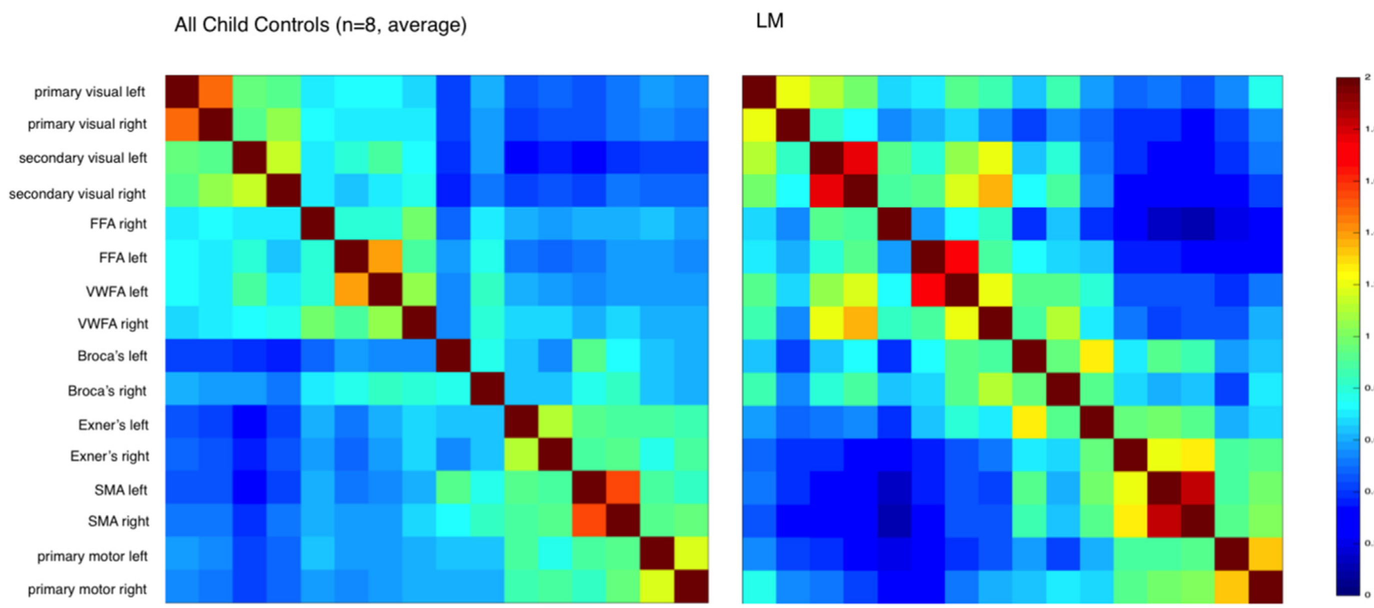

Fig. 4. Functional connectivity across specific brain regions in the resting state. Results displayed as Fisher z-transformed correlations in (A) age-matched control children and (B) in LM.

demonstrated slow gains relative to one-year previously, but the gap between LM and her age-mates persisted (Table 2).

LM also exhibited significant daytime fatigue that manifested as spontaneous napping at school. In addition to requiring accommodations at school, she had difficulty relearning physical skills in gymnastics. Her mother reported a general increase in clumsiness, as well as a need for cues when completing physical tasks, like getting dressed.

4. Discussion

In this study, we used clinical, neuropsychological and imaging approaches to describe an unusual case of sudden-onset, persistent mirror writing in a seven-year-old girl whose initial literary development had been normal. This case is unique for a number of reasons: 1) it represents a sudden-onset of mirror writing in the absence of a detectable neurologic insult, 2) LM's symptoms of involuntary, complete mirror reversal during both spontaneous and copied script occurred with the dominant, right hand only, 3) our patient also mirrored simple, non-linguistic images 4) our patient experienced perceptual problems, below average performance on some visual and memory assessments, and frequent misidentification of letter orientations, along with some difficulty coordinating complex motor tasks, but all in the absence of an identifiable disorder The closest published analogue involved a Japanese woman with sudden-onset, involuntary mirror writing and drawing with her right, dominant hand only (Nakano et al., 2003, 2012). This mirror writing persisted for six years. Unlike our patient, she also had a history of headache. Similar to LM, she also reported perceptual disturbances. Ultimately, her mirror writing and headache remitted at about the same time, and her care team suggested atypical migraine as a possible cause. Clinical MRI in this patient similarly revealed no abnormalities. Functional MRI showed bilateral activation in response to simulated right-handed writing, but predominantly left hemisphere activation during left-handed writing. The authors interpreted the bilateral activation during right-handed writing as a lack of suppression of the left hemisphere leading to mirror writing with the right hand only. Another case report described a woman with persistent mirror writing since childhood, but there was no description of a period of initially normal development (Downey, 1914). Lastly, while Critchley mentioned complete mirror writing in children, he did not provide any details (Critchley, 1926). To our knowledge, our study is the first report of sudden-onset, spontaneous and persistent mirror writing with the dominant right-hand in an emerging reader.

One previous study has assessed how letters in normal and mirrored orientation are processed in the brain of children in early stages of literary acquisition compared to literate adults. Blackburne et al. (2014) proposed that mirrored letters evoke more activation in adults because these visual stimuli are more attention-grasping to proficient readers. The greater activation for mirror versus normal letter orientation reading seen in LM might therefore imply that persistent mirror invariance is not the mechanism responsible for LM's sudden onset of mirror writing. It is noteworthy, however, that unlike the children and adults in the Blackburne study, and in contrast to a large body of research that has established the strong response of the VWFA to letters (Dehaene and Cohen, 2011; Dehaene et al, 2010; Ben-Shachar et al., 2011), LM's VWFA showed no activation to words read in normal letter orientation (Fig. 2). This lack of VWFA activation mimics the equally surprising absence of activation of Exner's area to normal letter orientation.

Literature assessing brain areas involved in children's writing is sparse. Asymmetry between left and right Exner's areas has been described previously in writing tasks (Planton et al., 2017). However, fMRI studies investigating handwriting in healthy adults (Longcamp et al., 2003; Cohen and Dehaene, 2004; Joseph et al., 2003; Beeson et al., 2003; Katanoda et al., 2001; Rektor et al., 2006; Dehaene and Cohen, 2011) suggest that the lack of activation of frontal, parietal and fusiform areas in LM is unusual. However, the extent of activation during writing, irrespective of letter orientation (Supplementary Fig. S1) shows involvement of predominantly visual regions, motor cortex and the cerebellum. It is comparable to that reported by (Richards et al., 2011) for 11-year old children writing novel pseudoletters versus highly practised real letters. Richards et al. also compared good and poor writers, with poor writers showing significantly more activation of occipital regions than good writers when writing novel pseudoletters compared to known real letters. Kushnir et al. (2013) compared practised left-hand mirror writing with right-hand writing of normal letter orientations in a group of eight right-handed adults. Their results showed significantly more activation of left superior and middle temporal gyri and the supramarginal gyrus in normal versus mirror writing. Such differences were not obvious in LM (Figs. 2 and 3). Unlike during reading, there were few differences in activation of the reading and

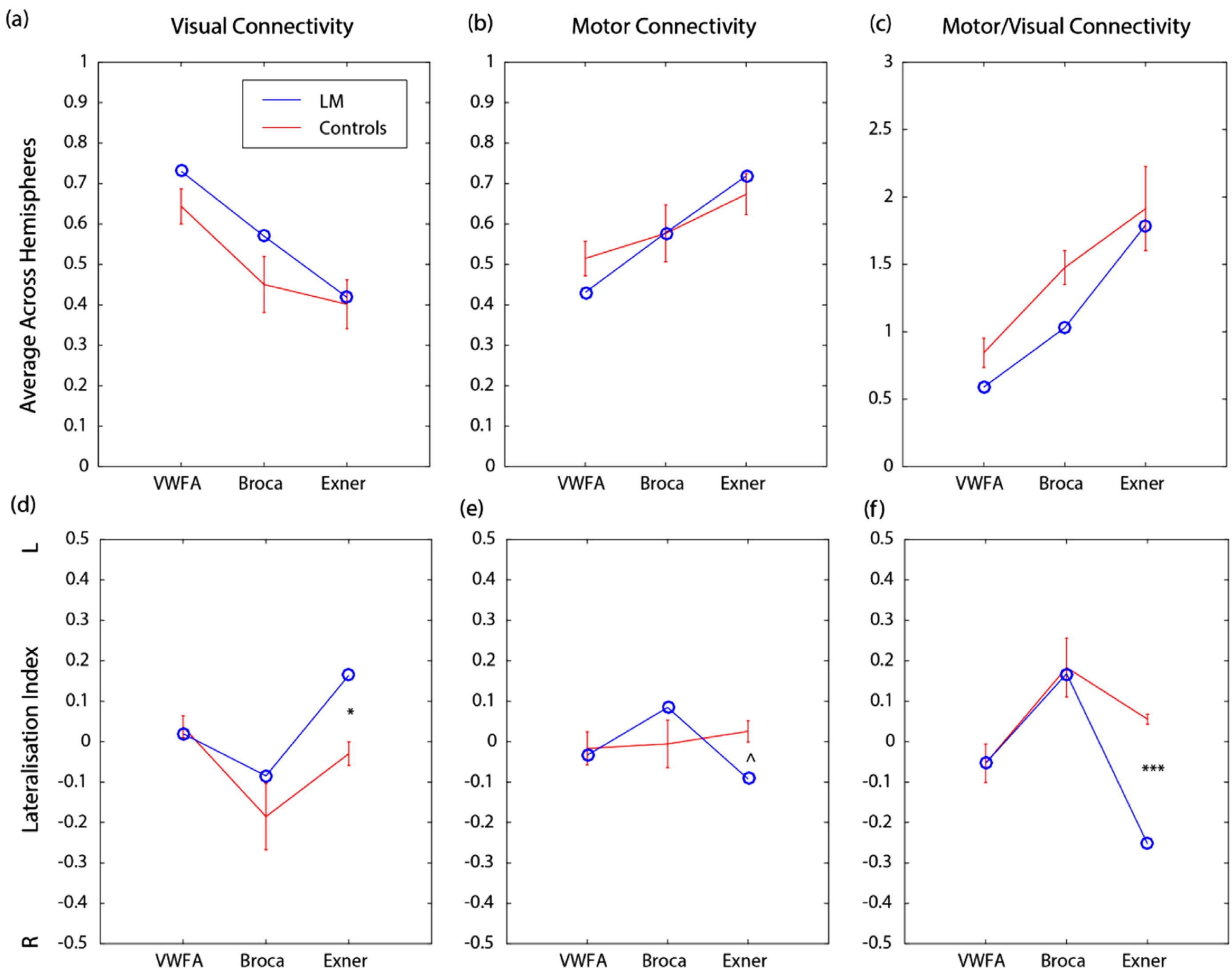

Fig. 5. Functional connectivity of the three language regions to visual (a, d) and motor (b, e) systems, and the ratio between them (c, f). The blue lines and circles show data for LM, and the red lines the mean and standard deviation across the controls. The top row (a-c) shows the average connectivity across hemispheres, which had the hypothesized perceptual-to-motor gradient from VWFA to Exner's. LM also showed this gradient, and we found no evidence she differed from controls. The bottom row (d-f) shows the lateralisation of the connectivity. In this, LM was found to differ notably in Exner's, showing significantly greater connectivity with the visual system on the left. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

Table 2
One year follow-up neuropsychological testing.

	Three-weeks post-onset	One-year post-onset
WIAT-III		
Numerical Operations	89^{x} (Low average)	82^{x} (Low average)
Word Reading	82^{x} (Low average)	81^{x} (Low average)
Oral Reading Fluency		
Accuracy	85^{x} (Low average)	80^{x} (Low average)
Rate	81^{x} (Low average)	88^{x} (Low average)
Spelling	93^{x} (Average)	92^{x} (Average)
WJ-III		
Writing Samples	113^{x} (High average)	106^{x} (Average)

writing network ROIs during normal versus mirror writing (Fig. 3B). Visual areas, however, showed higher activation for normal versus mirror letter orientation. Based on the previous finding of higher occipital activation by poor child writers of novel letter strings (Richards et al., 2011), LM may have had more difficulty with writing normal compared to mirrored letters. This idea is supported by her neuropsychological assessment.

Recent work has framed mirror invariance as an innate property of the visual system that must be actively suppressed in order to read (Borst et al., 2014; Duñabeitia et al., 2011). Skill in doing so appears to emerge gradually over childhood and adolescence (Blackburne et al., 2014). The timing of LM's presentation parallels a proposed shift in brain mechanisms for mirror writing between the ages of six and seven years (Brennan, 2012). However, a failure to suppress mirror invariance is insufficient to account for LM's symptoms. First, LM's resting-state functional connectivity and network architecture were broadly similar to that of age-matched controls, and to results reported elsewhere (Vogel et al., 2012). Additionally, mirror discrimination seemed to be preserved in these regions: LM showed stronger activation to mirror versus normal letter orientation while reading, as has been shown in healthy adults during a similar reading task (Blackburne et al., 2014). Additionally, LM mirror writes with her right hand only, and mirror writes not only when generating text spontaneously, but also while copying. This is unusual with healthy children her age predominantly mirror reversing individual letters when producing them spontaneously, or when writing with their left hand (Fischer and Koch, 2016).

During her neuropsychological assessments, LM showed signs of directional apraxia and trouble remembering (and acquiring) motor skills. Further study of her case could therefore include an investigation of the role of the cerebellum in her presentation, as well as assessment of brain responses during non-language manual tasks. LM also had mild difficulty on visual memory tests and with form constancy. As with writing, copying and drawing objects from memory resulted in mirror reversals and some incorrect spatial positioning. Results obtained with fMRI showed unusual activation patterns of the VWFA, right primary visual cortex and Exner's Area during reading, and functional connectivity analyses revealed altered lateralization of Exner's Area in LM, with right Exner's Area being relatively more connected to visual and less to motor regions than in controls. However, we focused our fMRI analyses on brain regions that constitute a network known to be crucially involved in the process of overcoming mirror invariance during literacy acquisition (Pegado et al., 2014). It is possible that regions outside this network, or other areas of the brain such as the cerebellum or parietal cortex known to also be involved in writing and visual-motor integration also contribute to her symptoms.

Our current medical, psychological, and imaging studies suggest that LM presents a highly unusual case of persistent mirror writing that seems to associated with a deficit in visual-motor integration. Taken together, her symptoms may represent a novel neurodevelopmental disorder.

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Consent

Written, informed consent was obtained from LM's parent for publication of this case report and any accompanying images. Consent for acquisition of control data was also obtained. Copies of the written consent forms are available for review by the Editor-in-Chief of this journal.

Competing interests

None of the authors declares any competing interests.

Authors' contributions

ANP provided neurological consultation, conceived of the study, participated in its design and coordination and critically reviewed the final manuscript. RC designed, and provided scientific oversight to the experiments. AL coordinated and administered experiments, assisted with the literature review, and wrote the experimental section of the manuscript. EV provided neuropsychological consultation, assisted with the literature review, and edited the manuscript. ERF participated in the initial neurological consultation, performed the literature review, and drafted the non-experimental portions of the manuscript. EV, AL and RC wrote the manuscript. All authors read and approved the final manuscript.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.neuropsychologia.2018.05.022.

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