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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