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Impaired functional differentiation for categories of objects in the ventral visual stream: A case of developmental visual impairment

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ABSTRACT

We report the case of a 14-year-old girl suffering from severe developmental visual impairment along with delayed language and cognitive development, and featuring a clear-cut dissociation between spared dorsal and impaired ventral visual pathways. Visual recognition of objects, including faces and printed words, was affected. In contrast, movement perception and visually guided motor control were preserved. Structural MRI was normal on inspection, but Voxel Based Morphometry (VBM) revealed reduced grey matter density in the mesial occipital and ventral occipito-temporal cortex. Functional MRI during the perception of line drawings uncovered impaired differentiation which is normally observed at even younger ages: no local category preferences could be identified within the occipito-temporal cortex for faces, houses, words or tools. In contrast, movement-related activations appeared to be normal. Finally, those abnormalities evolved on the background of chronic bilateral occipital epileptic activity, including continuous spike-wave discharges during sleep, which may be considered as the primary cause of non-specific intellectual disability and visual impairment.

1. Introduction

Although infants already have substantial visual abilities (Gliga and Dehaene-Lambertz, 2007; Frank et al., 2014), full visual development requires extended tuning throughout childhood and into adolescence (Grill-Spector et al., 2008). The various components of the cerebral visual system, and the abilities which they underlie, follow specific developmental trajectories.

The ventral occipito-temporal "what" stream, devoted to the processing of intrinsic objects features (Milner and Goodale, 2008), develops over the first decade, with the progressive differentiation of a mosaic of cortical patches featuring category-selective specialization (for a review see (Grill-Spector et al., 2008)). Thus, while 5–8 year-old children already show well-defined activations in the lateral occipital complex (LOC) to objects, and in the parahippocampal place area (PPA) to places (Scherf et al., 2007), some studies show early preferential activations of the fusiform face area (FFA) to faces (Cantlon et al., 2011) while others do not (Scherf et al., 2007). The PPA then increases in size at least through the age of 11, in parallel with improved visual recognition

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of places (Golarai et al., 2007). Similarly, preferential activation to faces in the FFA positively correlates with age up to ages 12–16, in parallel with improved face recognition (Golarai et al., 2010). Finally, the acquisition of reading is associated with the development of the visual word form area (VWFA) in the left fusiform region (Dehaene and Cohen, 2011). The VWFA is already visible by the age of 7 (Gaillard et al., 2003; Monzalvo and Dehaene-Lambertz, 2013), and its further development parallels the improvement of reading skills (Turkeltaub et al., 2003; Ben-Shachar et al., 2007).

The dorsal occipito-parietal "where" stream, devoted to spatial processing and visual control of actions (Goodale and Westwood, 2004), also develops in an orderly fashion for motion perception and visual-motor control (review in (Braddick and Atkinson, 2011)). In particular motion perception, although present from the first weeks of life, develops steadily up to adolescence (Hadad et al., 2011), with evolving properties of the visual cortex, including area MT/V5 (Wattam-Bell et al., 2010; Rosander and von Hofsten, 2011).

Here we study the case of a young patient who suffered from a severe developmental impairment affecting the perception of visual objects while sparing motion perception and other dorsal stream functions. As compared to the few similar published cases (Ariel and Sadeh, 1996; Joy and Brunsdon, 2002; Eriksson et al., 2003; Gilaie-Dotan et al., 2009, 2011), anatomical and functional imaging allows us to relate this impairment to a probable lack of functional differentiation of the ventral visual stream, which resulted from abnormal electrical activity and cortical development in occipital and temporal visual regions.

2. Material and methods

2.1. Case report

When she first consulted in the neurology department, MJ was a 12-year-old right-handed girl, the first child from genetically unrelated parents. She was born at term (41 wGA) following an eventless pregnancy (birth weight = 2.800 kg (10 p), birth length = 48 cm (−1 SD), birth cranial perimeter = 32.5 cm (−2SD). Her neurological development was considered to be normal (e.g. walking acquired at one year, language before two years). Difficulties with drawing were first noticed at the age of four, associated with some behavioral disorders, especially agitation.

At the age of six, she presented a first episode of nocturnal clonic convulsions. Clinical examination did not reveal any neurological deficit. However, because of her difficulties at school, a qualitative language assessment was carried out. It revealed global difficulties, with a clear-cut dissociation between better oral abilities and severely impaired graphic abilities, affecting both drawing and writing. Cerebral CT-scan was normal. Repeated EEG recordings showed epileptiform activity, consisting in series of spikes lasting from 5 to 10 s, localized in the occipito-temporal region, with variable left, right, or bilateral lateralization. Those anomalies were sometimes, but not always, associated to clinical signs of absence seizure. A treatment with sodium valproate was introduced, and later associated with ethosuximide. Despite this association, the parents reported the persistence of frequent absence seizures, plus occasional clonic seizures.

At the age of eleven, an MRI-compatible vagal nerve stimulation device was implanted (Cyberonics; VNS therapy Guidelines, 2006), leading to a decrease of seizures. Yet, MJ suffered a clonic seizure a few months later, followed by transient confusion, and by more enduring post-ictal psychosis (paranoid delusions with beliefs relative to black magic, auditory and visual hallucinations) (Devinsky, 2008). She was hospitalized in a psychiatry department. Symptoms resolved entirely within less than two months, but were followed by catatonic symptoms which eventually recovered with lorazepam. No other psychotic or catatonic symptom occurred ever since. At the age of twelve, seizures stopped and ethosuximide was discontinued.

It was during her stay in the psychiatry department at the age of 11 that her major visual impairment attracted medical attention, on the basis of MJ's spontaneous every day behavior. Remarkably, the impairment seemed to affect only some aspects of her visual abilities. She was not able to recognize the most usual objects without touching them, and she identified familiar persons only when they started speaking. Actually, due to those difficulties, she had been admitted two years earlier in a special school for blind children.

In striking contrast with her massively impaired recognition abilities, she was able to make bead necklaces, or to play video games involving moving shapes of different colors. She moved around easily even in unfamiliar places, without bumping into obstacles and was able to skillfully skate in the corridors of the hospital, avoiding chairs, ashtrays or tables. She did not report any subjective deficits in visual motion perception.

Despite some difficulties at maintaining central fixation and at inhibiting saccades to peripheral stimuli, a Goldmann kinetic perimetry was performed, showing no visual field defect. She was submitted to the CADET test of visual acuity (Douche and Badoche, 1987), a method based on matching drawings of objects, and hence possibly underestimating her elementary acuity. She scored 4/10 (i.e. an abnormal score) from a far distance (2.5 m) and 8–10/10 (i.e. a normal score) from "reading" distance, suggesting a dissociation between somewhat impaired far distance and preserved near distance visual acuities.

MJ's navigation abilities and her skill with motion-based video games suggested preserved motion perception. This was confirmed when we had an opportunity to perform the Leuven Perceptual Organization Screening Test (L-POST) when MJ was 17 (Torfs et al., 2014; www.gestaltrevision.be/tests). This battery includes 15 subtests, including 3 subtests designed to assess motion perception: kinetic object segmentation, biological motion, and global motion detection. MJ performed normally on the 3 motion subtests, as compared to age-matched healthy participants. By contrast, she was impaired below the 10th percentile in 10 out of 12 shape-oriented tests. Three years elapsed between the bulk of data reported here and the L-POST test. Naturally, MJ was not subject to any rehabilitation of motion perception, and we may assume that her motion vision had not changed in the interval.

Furthermore, MJ showed no clinical signs of ocular apraxia, optic ataxia, astereognosis, right–left confusion, body schema impairment or autotopoagnosia.

The present study was carried out when MJ was 12 to 14-years-old. MJ had been seizure-free since the age of 12. When she was 12, an anatomical MRI scan was performed on a 1.5 T magnet, including T1, FLAIR, diffusion, and T2* sequences. Images were visually analyzed by a senior neuroradiologist blind to MJ's condition, and were considered to be entirely normal, particularly in the visual cortex. PET-scan did not show any abnormalities of cortical perfusion, notably in occipito-temporal regions. Due to alleged minor dysmorphic signs (large forehead, small ears and big mouth), MJ underwent karyotype screening, chromatography of amino acids and organic acids, study of purine metabolism, assessment of lactic acid, pyruvate and ammoniemia. All results were normal. The *FMR1* mutation, the most frequent microdeletions, and congenital disorders of glycosylation were all absent.

MJ underwent several 24-h-long and standard EEG recordings, using 21 scalp electrodes (10–20 system; MR95 Oxford Médelec FMB system). Despite the absence of seizures, there was still bilateral epileptiform activity in the occipito-temporal regions when

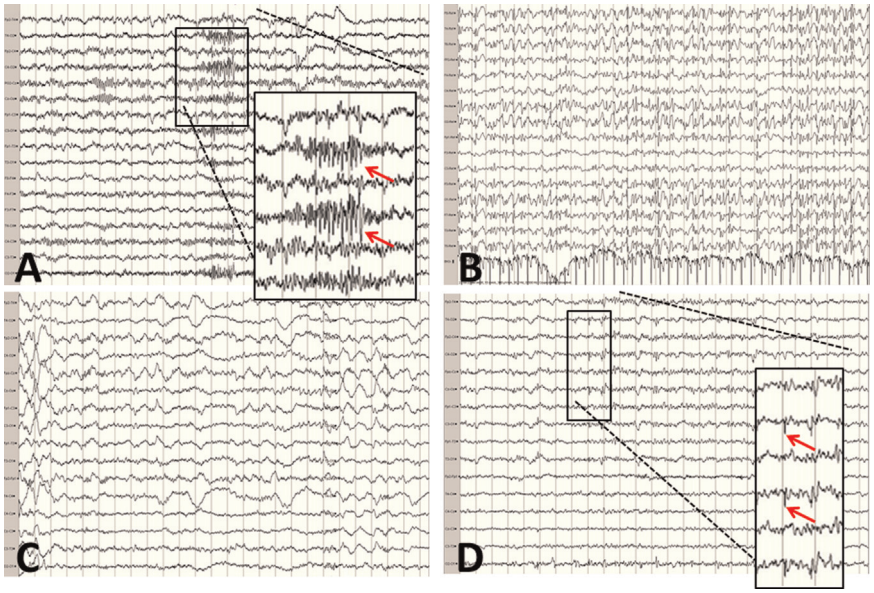

Fig.1. Electroencephalography recordings in patient MJ**.** EEG recordings were made at the age of 9 (panels A and B) and 14 (panels C and D). Illustrations are representative of enduring abnormalities. At the age of 9, there were brief spikes (panel A, red arrows) in bilateral occipito-temporal regions, especially in the right occipital cortex, when MJ was awake; there was also continuous spike-wave activity in slow-wave sleep (panel B) covering almost all of the non-REM sleep. At the age of 14, there were no more abnormalities in slow-wave sleep (panel C), but bilateral occipital spikes (panel D, red arrows) associated with slow waves in REM sleep. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

MJ was awake (Fig. 1A). Moreover there was a continuous spike-wave pattern during almost the whole duration of slow-wave sleep (CSWS; Fig. 1B). The latest overnight EEG recording, performed at the age of fourteen, did not show CSWS, but bilateral occipital spikes associated with slow waves during all phases of REM sleep (Fig. 1C and D).

This clinical pattern was suggestive of a developmental dissociation between an impaired ventral visual stream and a largely spared dorsal stream. This hypothesis was further explored with neuropsychological tests, anatomical and functional brain imaging.

2.2. Methodology

MJ's parents gave their written consent after detailed information had been provided to them. The study was conducted in accordance with the declaration of Helsinski, following approval by the ethics committee of Ile-de-France VII.

2.2.1. Behavioral assessment

MJ was assessed at age 12 and 14. The Wechsler Intelligence Scale for Children – Third Edition (WISC-III) (Wechsler, 1991) was used to evaluate global intelligence.

Object recognition was assessed using visual naming, tactile naming, and face recognition. MJ was asked to name visually presented items: (1) 26 letters, (2) 10 colored patches, (3) drawings of objects without volume rendering (labeled as 2D pictures): 60 line drawings (Snodgrass and Vanderwart, 1980) and 10 colored pictures (Rossion and Pourtois, 2004), (4) drawings of objects with some realistic volume rendering (labeled as 3D pictures), 20 black and white and 20 colored, (5) photographs of objects, 20 black and white and 20 colored, and (6) 20 real familiar objects. On tactile presentation, she was asked to name 10 familiar objects, and 26 plastic letters normally used as pedagogy toys. To assess face perception, we used a subtest of the Kaufman Assessment Battery for Children (K-ABC), in which the child looks at a picture of one or two faces for 5 s, then selects the correct face(s) shown in a different orientation from an array of distractor faces (Kaufman and Kaufman, 1993). MJ was also asked to identify pictures of herself, her mother, father, brother and grandmother.

Dorsal visual functions were evaluated using the Purdue pegboard test (Tiffin and Asher, 1948), a neuropsychological test of manual dexterity and bimanual coordination, involving gross movements of arms, hands, and fingers, and fine motor extremity. The pegboard is a board with two parallels rows of 24 holes, and subjects are asked to place cylindrical metal pegs one by one into these holes. Two further tasks were assessed: (1) reaching and touching small black dots, first with her forefinger, then with the tip of a pen, and (2) grasping three small, three medium, and three big objects (e.g. a safety pin, scissors, a suitcase). This part of evaluation was filmed for subsequent analysis. Finally, MJ was asked to write her first name.

2.2.2. MRI studies

MJ participated in the MRI experiments at the age of 14. We used as controls 30 healthy children (12 girls, mean age 11 years 5 months [9 years 1 month to 14 years]) who were submitted to the same fMRI protocol, using the same scanner and receiver coil, and whose activations were reported in (Altarelli et al., 2013). Children and their parents gave written informed consent, following approval by the local ethics committee.

2.2.2.1. Anatomical MRI. T1-weighted MP-RAGE brain images were acquired on a 3T Siemens MRI scan (acquisition parameters: matrix: $256 \times 256 \times 176$, TR=2300 ms, TE=4.18 ms, TI=900 ms, flip angle=9°, FOV=256 mm, voxel size=$1 \times 1 \times 1$ mm^3). The patient's and 30 controls' anatomical images were studied using voxel-based morphometry, as implemented in the VBM8 add-on (http://dbm.neuro.uni-jena.de/vbm8/) to the SPM8 software (http://www.fil.ion.ucl.ac.uk/spm/), including normalizing to a template space (MNI), segmenting into grey and white matter, modulating to adjust for local volume changes introduced by the nonlinear normalization, Gaussian smoothing (8 mm FWHM), and voxelwise comparison between the patient and controls of grey and white matter density maps with *t*-tests, both with and without declaring age as a variable of no interest. Note that using modulated images avoids further need to correct for different brain size in the statistical model (Ziegler et al., 2014).

2.2.2.2. Functional MRI. To clarify the mechanisms underlying MJ's deficit, we studied the functional properties of the ventral visual stream, using a protocol reported in (Altarelli et al., 2013). MJ underwent 3 fMRI runs (control subjects underwent only one). Each run consisted of 2 blocks for each of 4 categories (faces, tools, houses, and printed words), plus one block of a smoothly rotating checkerboards. Each of those 9 stimulation blocks (duration 15 s), presented in random order, was followed by a fixation block (duration 10.5 s). Each run of object categories comprised 10 pairs of black and white pictures of the same category plus 2 randomly occurring target trials (red star) for which participant had to press a key with their left hand.

160 functional volumes sensitive to brain oxygen-level dependent (BOLD) contrast were acquired with a T2*-weighted gradient echo, echo planar imaging sequence on a 3T Siemens MRI [T_R (time to repeat)=2400 ms, α (flip angle)=81°, T_E (echo time)=30 ms, in plane resolution=3×3 mm^2]. Each volume comprised 40 axial slices of 3 mm thickness with no gap covering all the brain. The first two volumes were discarded from data analysis.

Functional images were analyzed with the SPM5 software (http://www.fil.ion.ucl.ac.uk/spm/). Processing included corrections for EPI distortion, slice acquisition time, and motion; normalization to the MNI anatomical template; Gaussian smoothing (5 mm FWHM); fitting with a linear combination of functions derived by convolving a standard haemodynamic response function with the time series of the stimulus categories, plus their time derivatives, plus six movement regressors. Finally, for all subjects including the patient, individual images were computed for contrasts of interest. Those individual contrast images were then smoothed (8 mm FWHM), and eventually entered in random-effect second-level analyses. Those analyses included studies of the controls' activations (for which we used one-sample *t* tests) and comparisons of the patient *vs.* controls (for which we used two-sample *t* tests, the patient being treated as a sample). Except when stated otherwise, we used a clusterwise threshold of $P < 0.05$ corrected for multiple comparisons across the whole brain, with a voxelwise threshold of $P < 0.001$ for contrasts in control subjects, and $P < 0.01$ for contrasts in MJ or comparing MJ vs. controls.

3. Results

3.1. Behavioral assessment

On the first evaluation with the WISC (MJ was 12 years-old), results were at floor level (Fig. 2, left panel, blue curve) on both performance and verbal IQ tests, when compared to normal scores for her age (Fig. 2 and Table 1). However, if compared to normal standardized scores of the 8-year-old reference population, a clear-cut dissociation emerged between performance and verbal abilities (yellow curve). Most verbal scores reached the level of normal 6-year-olds (green curve), while performance scores still remained at floor level. At the age of 14, after two years of rehabilitation, the same dissociation persisted, with a slight improvement of verbal scores (Fig. 2, right panel). In summary, there was some degree of overall intellectual disability, and a dissociation between massively impaired visual and better preserved verbal scores.

In visual naming tests, her performance substantially differed depending on the types of stimuli. Overall, performance improved with the richness of visual cues afforded by the stimuli (Fig. 3): real objects were identified better than photographs, photographs better than drawings, 3D better than 2D drawings, and colored better than black and white stimuli, thus ranging, at age 14, from 18% to 95% correct responses across conditions. However, even when she successfully identified familiar real objects, it was after a long and effortful scrutiny, sometimes taking her as long as several minutes before coming up with a proposed response. Although the material was not controlled for the study of this parameter, we did not observe indications of an animate vs. inanimate dissociation. Thus when MJ was asked to name black and white 2D pictures at 14 years of age, she made 7/36 (19%) correct answers for inanimate items and 4/24 (17%) for animate items. Naming of color patches was excellent (90% correct).

MJ had not learnt to read: letter naming was extremely poor, both in the visual and in the tactile modality. Over 2 years of rehabilitation between the ages of 12 and 14, MJ had only learnt to write her name, plus ten other isolated letters. Interestingly, she

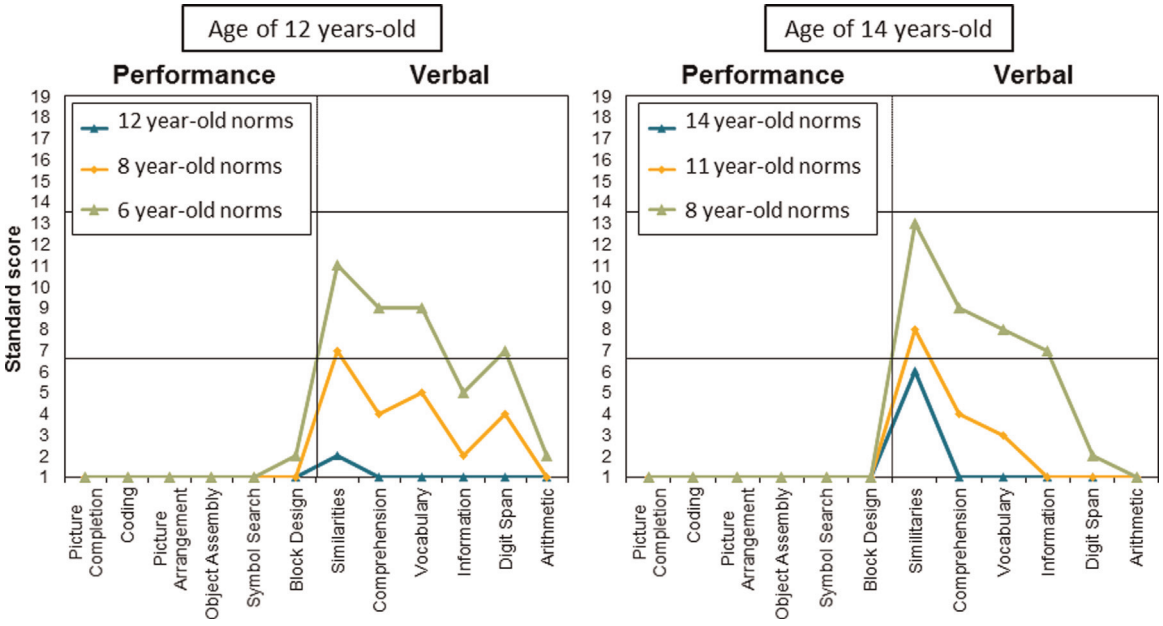

Fig.2. Performance on the WISC-III of patient MJ. MJ was assessed at the age of 12 (left), and 14 (right). Standardized scores above 13 (+1SD) and below 7 (−1SD) are outside the limits of normal variation in the population. MJ's scores were computed with reference to norms for her actual age (blue), and to norms for an age 3 or 4 years below her actual age allowing her to reach at least one normal score (orange), and to norms for an age 6 years below her actual age (green). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

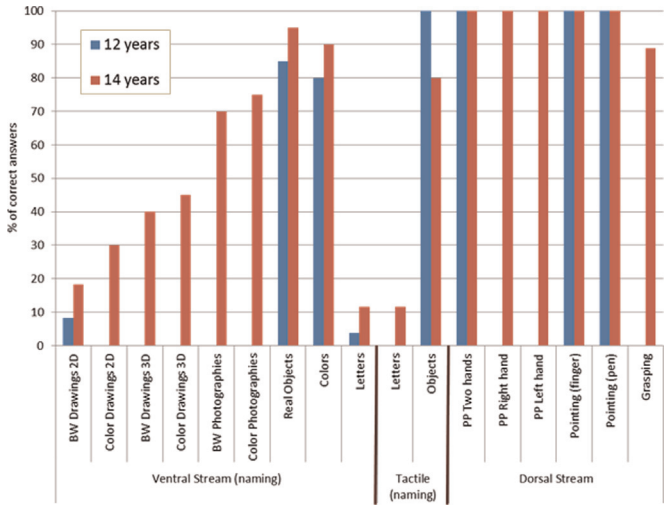

Fig.3. Assessment of visual function of patient MJ. MJ was assessed at age of 12 (blue bars), and 14 (red bars). There was a clear-cut dissociation between impaired ventral stream and spared dorsal stream tasks. Object recognition was better for stimuli with richer affordances. Tactile naming and color naming were spared. BW=black and white; PP=Purdue Pegboard Test. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

was still unable to read the very same letters she could write as she could identify only 3/26 letters.

Faces and Forms recognition on the K-ABC were poor (50% and 9% correct responses respectively; Table 1). Anecdotally, we noted that stimuli featuring prominent cues, such as hair, beard, glasses, or apparent clothes, seemed easier to process. MJ did not recognize the faces of her own father and grand-mother.

In contrast, MJ performed normally in all tests of spatial perception. On the pegboard test, she was normal in both accuracy and speed. Note that this profile further supports the sparing of short range acuity: indeed, the pegboard test may in principle be performed on the basis of tactile exploration, locating target holes through palpation. This procedure however would yield lengthy response times, while MJ showed normal speed. Qualitative inspection of the video recordings shows that her gestures were directly and accurately targeted under visual control. Similarly, accurately reaching small black dots with the tip of a pen also required good visual acuity. Tactile object naming was flawless and fast (Table 1).

3.2. Voxel-based morphometry

The anatomical T1-weighted MRI was normal on visual inspection. We looked for areas of reduced grey matter volume in MJ as compared to controls (Fig. 4). An elongated patch in the right ventral occipito-temporal region, and a cluster in the bilateral cingulate sulcus extending in the paracentral lobule and SMA showed a significant reduction in grey matter in the patient (voxelwise $P<0.001$, clusterwise $P<0.05$ corrected). When lowering the voxelwise threshold to $P<0.005$ (clusterwise $P<0.05$ corrected), we found additional differences in most of the mesial occipital cortex or cuneus, in patchy areas of the left ventral occipito-temporal region, and in the left superior temporal sulcus. The opposite contrast, looking for regions of enhanced grey matter in MJ relative to controls, and comparisons involving white matter density yielded no significant differences.

However, as controls were on average younger than patient MJ, and as there is evidence for a negative correlation of cortical thickness and age in some brain regions (Sowell et al., 2004), we tried to determine whether the grey matter reduction which we observed in MJ would survive after correcting for age. We therefore included age as a covariate in the model comparing the

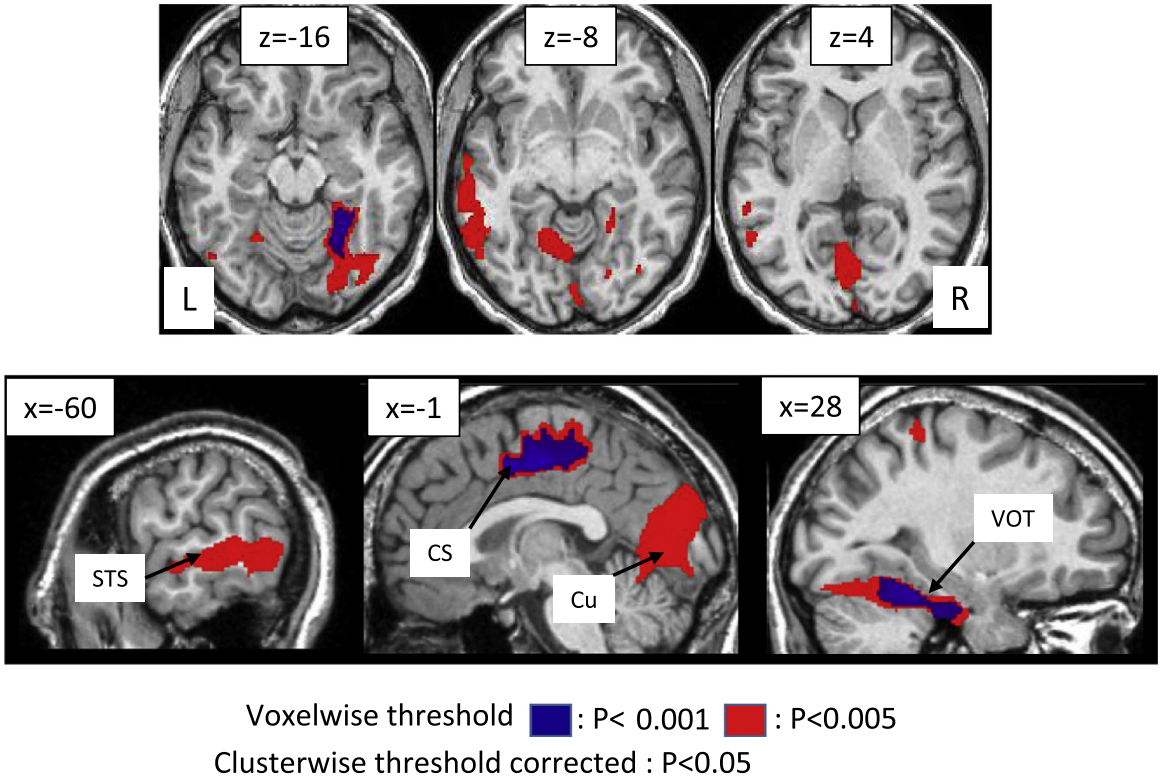

Fig.4. Areas of reduced grey mater density in patient MJ relative to 30 controls. Voxel-based morphometry showed reduced grey matter density in the ventral occipito-temporal cortex (VOT), the cuneus (Cu) the cingulate sulcus (CS) and surrounding areas, the left superior temporal sulcus (STS) (voxelwise $P<0.001$ (blue) and $P<0.005$ (red), clusterwise corrected $P<0.05$). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

patient vs controls. First, we found no significant effect of age, either positive nor negative on cortical grey matter volume. Second, when removing the effect of age by entering it in the model as a regressor of no interest, the differences between the patient and controls remained essentially identical to what was reported above.

Finally, it has been argued that the VBM comparison of a single patient with a group of controls yields an excessive risk of false positive findings, particularly due to "the possibility that any statistically significant difference between a single subject and a control group might reflect *normal* individual variability in neuroanatomy rather than the neuropathology of the specific disease under investigation" (Scarpazza et al., 2013). To directly address this concern, we compared each of the 30 controls to the 29 others, using the same procedure and thresholds as when comparing the patient to the controls. It turned out that not a single control showed any significant reduction in GM density relative to the group. It is thus safe to conclude that the patient, who showed several highly significant clusters of GM reduction, differed significantly from the normal pattern.

3.3. Functional MRI

In this experiment, we looked for functional correlates of MJ's impairment, by studying the processing of stimuli for which she showed the most severe deficit, i.e. line drawings of various categories of objects. We predicted that such stimuli should yield abnormal occipito-temporal activations, most probably with a blurring of the normal category-selective mosaic of cortical regions, i.e. the FFA for faces (Puce et al., 1995; Kanwisher et al., 1997), the VWFA for words (Cohen et al., 2000), the PPA for buildings and scenes (Epstein and Kanwisher, 1998), and the LOC for common objects (Malach et al., 1995).

First, in order to identify the overall regions activated by line drawings in MJ, we contrasted the 4 pooled categories of objects minus rest. This contrast showed bilateral occipital activations (right: MNI 24 −96 21, $Z>8$; left: MNI −24 −99 18, $Z>8$), extending frontwards in the occipito-temporal cortex to $y=-45$, and dorsally up to $z=30$ (Fig. 5A). In control subjects, this contrast revealed similar activations, however extending ventrally to about $y=-30$ (voxelwise $P<0.001$, clusterwise corrected $P<0.05$). We then looked for voxels more activated by this contrast in controls than in MJ (voxelwise $P<0.01$, clusterwise corrected $P<0.05$). In order to exclude potential spurious inhibitions in the patient, the comparison was masked inclusively by the same contrast in controls only (voxelwise $P<0.01$). This comparison yielded no significant difference.

Then, in order to assess the functional specialization of the ventral cortex, we looked for category-specific activations by contrasting each of the 4 categories of pictures minus the 3 others. Those 4 contrasts yielded no category-specific activation in MJ, while in the second-level group analyses in controls, they elicited a typical pattern featuring the left-hemispheric VWFA for words (MNI −54 −63 −18, $Z=4.08$), the right-hemispheric FFA for faces (MNI 42 −48 −18, $Z=5.92$), the bilateral PPA for houses (left: MNI −27 −48 −9, $Z=4.61$; right: MNI 33 −42 −9, $Z=5.17$) and LOC for tools (left: −45 −72 0, $Z=6.12$; right: 48 −69 −6, $Z=5.33$) (Fig. 5B). Note that the lack of functional differentiation across categories in MJ's activations cannot be attributed to a lack of power, as MJ's activations relative to rest were not weaker than in controls, as shown before.

In order to better compare the patient's lack of category-selectivity to the pattern of activation in individual controls, we quantified individual category-specific activations in every participant. To this end, we defined a 20 mm radius sphere around each of the 6 group-level category-specific peak coordinates reported above. For each subject and within each sphere, we computed the number of voxels passing the $P<0.01$ threshold for the relevant contrast testing for category selectivity (e.g. words minus the other 3 categories in the sphere centered on the VWFA). For houses and tools, which were associated to bilateral category-selective regions (the PPA and the LOC, respectively), we added the number of voxels in the left- and right-hemispheric spheres. Finally, we averaged for each subject the number of selective voxels for faces, words, houses, and tools, thus obtaining an individual score indexing the extent of category-selective activations. The mean controls' score was 82 (SEM = 11), and the patient's score was 15. There was one control out of 30 with a score lower than the patient's. We inspected more closely the category-selective activations of this outlier control in the ventral occipitotemporal region, at a voxelwise threshold of $P<0.01$. Interestingly, we found a cluster of 25 word-selective voxels (MNI −57 −42 −15),

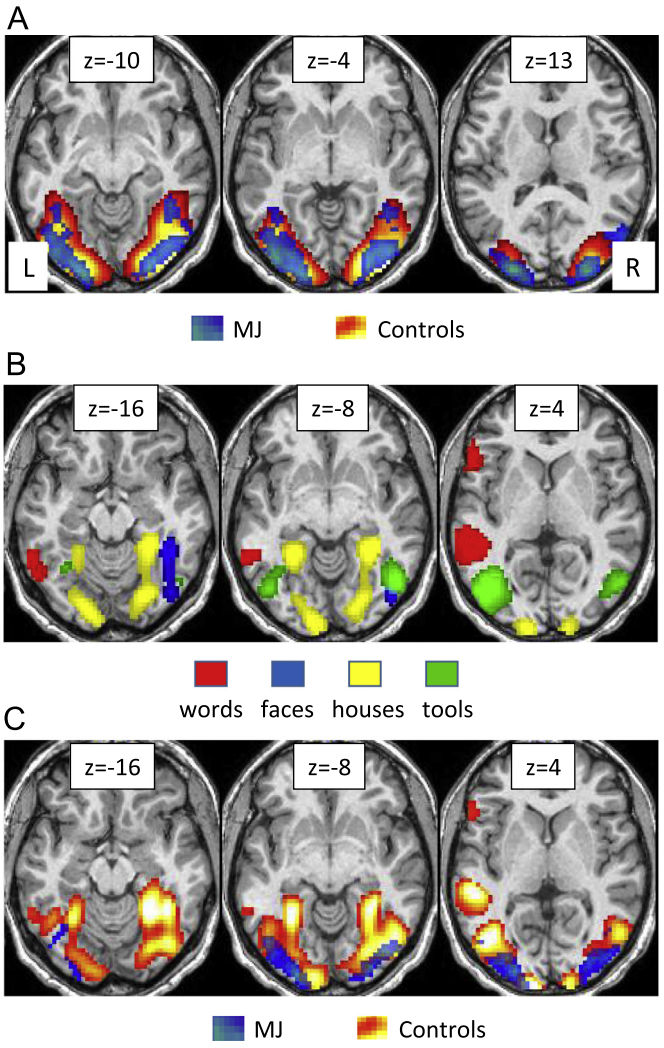

Fig.5. Functional activations in patient MJ and 30 controls. A: Contrast of the 4 pooled categories of objects minus rest in control subjects (hot colors) and in MJ (cold colors), showing that the patient had bilateral occipital activations not different from controls. B: Contrasts of each of the 4 categories of pictures minus the 3 others in control children, showing typical VWFA (red), FFA (blue), PPA (yellow), and LOC (green). In MJ, those contrasts did not reveal any significant category selective activation, even at more liberal thresholds than in controls. C: F-contrast assessing whether activations differed on the whole across object categories, and showing activations across the whole ventral occipitotemporal cortex in controls (hot colors), and only posterior occipital activations in MJ (cold colors). All images are thresholded at clusterwise corrected $P<0.05$; voxelwise $P<0.001$ for controls and voxelwise $P<0.01$ for MJ. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

somewhat anterolateral to the VWFA peak, and a cluster of 37 face-selective voxels (MNI 45 −75 −12), somewhat posterior to the FFA peak and close to the Occipital Face Area (Gauthier et al., 2000). In contrast, at the same threshold, MJ showed no activation cluster larger than 4 voxels. Although those clusters were below the extent threshold, they may suggest that the outlier control had more category-selective activations than MJ, albeit with a somewhat atypical topography. On the whole, although we found one control subject out of 30 (3.3%) with a lack of selectivity comparable to MJ, the patient's pattern of activation remains highly atypical, suggesting a link to her object processing deficit.

In order to assess whether activations differed on the whole across object categories, we computed the F-contrast across the 4 categories (Fig. 5C). In MJ, this contrast only showed bilateral occipital activations posterior to $y=-70$, likely reflecting low-level differences across categories (voxelwise $P<0.01$; left: MNI −18 −99 21, $Z>8$, 468 voxels; right: MNI 24 −96 21, $Z>8$, 388 voxels). In controls, the F-contrast showed much more extensive activations, extending frontwards to $y=-25$, and encompassing all the category-specific regions described above (voxelwise $P<0.001$; left: MNI −42 −69 0, $Z=6.98$, 1698 voxels; right: MNI 39 −48 −18, $Z=7.26$, 1566 voxels).

Finally, in order to identify motion-sensitive regions in controls, we contrasted moving checkerboards minus static line drawings. Although one might have feared that acquiring only one block of visual movement activation in controls would have reduced statistical power, this subtraction revealed mesial posterior occipital activations (MNI −3 −90 −9, $Z=7.57$), and left lateral occipito-temporal activations (MNI −54 −60 −3, $Z=4.72$) and right posterior superior temporal activations (MNI 39 −42 21, $Z=4.38$). The left occipitotemporal matched the location of the motion-sensitive area V5/MT with respect to anatomical landmarks and normalized coordinates (Dumoulin et al., 2000; Malikovic et al., 2007), but the right temporal cluster was dorsal and anterior to the expected location. We reasoned that V5/MT is actually very close to the LOC, which was strongly activated by images of tools, and that subtracting tools-related from movement-related activations might have suppressed V5/MT from the activations. We therefore contrasted moving checkerboards minus static line drawings, excluding tools (Fig. 6). This contrast showed the same activations as before, plus a right lateral occipitotemporal cluster matching the location of area V5/MT (MNI 54 −57 −3, $Z=3.94$). This contrast was assessed in MJ, and showed an essentially normal pattern, with activations in the posterior occipital cortex (MNI 12 −96 0, $Z=5.06$), in the bilateral V5/MT (left: MNI −48 −51 12, $Z=4.54$, 87 voxels, qFDR-corr=0.026; right: MNI 60 −48 −3, $Z=3.71$; MNI 51 −57 12, $Z=2.41$), and in the right posterior superior temporal sulcus (MNI 48 −33 6, $Z=4.31$). Finally the direct comparison of this contrast in controls minus the patient yielded no significant difference.

We may summarize the fMRI results as follows. First, the overall activations induced by complex visual stimuli relative to rest were not quantitatively abnormal in MJ. Second, MJ's ventral visual stream showed a lack of usual categorical selectivity, in good agreement with her visual impairment. Third, activations induced by moving patterns relative to static drawings showed no abnormality.

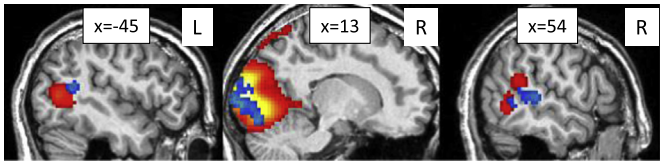

Fig.6. Activations by moving checkerboards minus static objects (tools excluded) in control subjects (hot colors) and MJ (cold colors), showing that the patient had a normal pattern of movement-related activation in the posterior occipital and lateral occipitotemporal cortex. Images are thresholded at clusterwise corrected $P<0.05$; voxelwise $P<0.001$ for controls and voxelwise $P<0.01$ for MJ.

4. Discussion

4.1. Summary

We studied a 12–14-year-old girl suffering from a severe developmental visual deficit. This impairment affected the recognition of all the categories of items that were tested, and included severe prosopagnosia (she was unable to recognize even close members of her family), and severe dyslexia (she was only able to recognize 2 letters). In contrast, there were no indications of impaired motion perception (as confirmed formally at the age of 17 with the L-POST test), nor of visually guided motor control including reaching, grasping, and moving around. This pattern can be roughly summarized as a dissociation between spared dorsal and impaired ventral visual functions.

In good agreement with the behavioral profile, VBM showed a reduced grey matter density in the patient's ventral occipito-temporal cortex, with right-sided predominance, while no abnormalities were detected in her parietal cortex. Bridging anatomical and behavioral abnormalities, functional MRI revealed a lack of category-selective activations in the occipito-temporal cortex which is normally observed at even younger ages (Monzalvo et al., 2012): no FFA, VWFA, PPA or LOC could be identified in patient MJ. In contrast, her movement-related activations did no differ from normal controls, and were similar to those reported in previous studies of the perception of motion (Dumoulin et al., 2000; Hasson et al., 2003), and biological motion (Saygin et al., 2004). Finally, those abnormalities evolved on the background of chronic bilateral occipital epileptic activity, whose causal role should obviously be considered.

4.2. MJ's developmental visual impairment

4.2.1. The role of visual acuity, experience and intellectual disability

Could MJ's recognition deficit be accounted for solely on the basis of reduced visual acuity? At first sight, this account seems implausible considering the high frequency of reduced acuity in infants, contrasting with MJ's exceptional pattern of visual impairment. Thus, uncorrected ametropia may indeed yield mild learning problems, but it never results in such major object recognition deficits as in the present case (Atkinson et al., 2002; Atkinson et al., 2005; Roch-Levecq et al., 2008). Nevertheless, the possibility that reduced acuity played a role in MJ's impairment should be seriously considered. MJ's short range acuity was shown to be within a normal range, based on the CADET test, and fairly preserved acuity was also indirectly supported by the patient's excellent performance on the Purdue Pegboard, the pointing and the grasping tests (Table 1 and Fig. 3). However, those data may not be sufficient to rule out reduced acuity. Indeed, the observation of clinical behavior does not provide any quantitative assessment of acuity, and the CADET test, a procedure mostly used for clinical screening, may not be sufficiently sensitive to detect subtle reductions in acuity. Thus, it remains possible that reduced acuity may contribute to MJ's visual impairment.

Could MJ's deficit be reduced to a lack of visual experience with objects in her short range vision, where acuity was at least fairly good? This account is not credible, as MJ was unable to recognize even items with which she was familiar beyond doubt. Those included the faces of the close relatives who had raised her. Similarly, in spite of repeated attempts to actively teach her to read, she could never learn more than a couple of single letters. Finally, her

Table 1
Neuropsychological findings.

	Tests	MJ's age/age for reference norms	
		12 years/6 years	14 years/8 years
Global efficiency	**WISC**		
	Verbal IQ	**46***/83	**50***/85
	Performance IQ	**46***/**46***	**46***/**46***
	Full scale IQ	**41***/**59***	**45***/**60***
	Verbal comprehension index	**51***/91	**55***/95
	Perceptual organization index	**50***/**51***	**50***/**50***
	Processing Speed Index	**50***/**50***	**50***/**50***
Ventral stream	**Oral naming tests**		
	Letters (/26)	1	3
	Colors (/10)	8	9
	Black and white pictures 2D (/60)	5	11
	Color pictures 2D (/10)	ND	3
	Black and white pictures 3D (/20)	ND	8
	Color pictures 3D (/20)	ND	9
	Black and white photographs (/20)	ND	14
	Photographs (/20)	ND	15
	Real objects (/20)	17	19
	Faces tests		
	K-ABC Faces (/16)	**8***	ND
	Familiar faces (/5)	**3***	ND
	K-ABC Forms recognition (/11)	**1***	ND
Tactile	**Naming tests**		
	Objects (/10)	10	8
	Letters (/26)	ND	3
Dorsal stream	**Spatial tests**		
	Purdue pegboard [score /TR (s)]		
	Two hands (/48)	48/154	48/203
	Right hand (/24)	ND	24/107
	Left hand (/24)	ND	24/161
	Pointing (finger) (/20)	20	20
	Pointing (pen) (/20)	20	20
	Grasping (/9)	ND	8

TR=time of realization; s=second; ND=not done;
* =impaired (< 5th percentile) according to the norms of the test.

inability to recognize familiar manipulable objects such as scissors can also not be attributed to a lack of experience, as she could easily identify the same items haptically.

Finally, could MJ's impairment be reduced to non-specific intellectual disability? Global cognitive testing with the WISC showed, in addition to a dissociation between massively impaired visual and better preserved verbal scores, an overall intellectual disability. This disability could be attributed to the limited education which the patient could receive as a result of her visual deficit and the more diffuse impact of seizures on her cognitive development. We suggest that intellectual disability could not account for the dissociated pattern of visual impairment, and could be considered as an associate deficit.

4.2.2. Cognitive labeling

If we refer to the classical neuropsychological taxonomy, which was developed for classifying acquired visual impairments, MJ would fall in the scope of "apperceptive agnosias", a broad term which has been used since Lissauer (1890) to refer to "any failure of object recognition in which perceptual impairments seem clearly at fault, despite relatively preserved sensory functions such as acuity, brightness discrimination, and color vision" (Farah, 2004). Such impairments often follow brain anoxia due to cardiac arrest or carbon monoxide poisoning (see classical case reports by Benson and Greenberg (1969) and Milner et al. (1991), and reviews in Farah (2004), Serino et al. (2014)). This rough characterization agrees with MJ's behavior when she was 12–14-years-old, and with her impairment on the L-POST tests of mid-level vision when she was 17. As discussed before, MJ's apperceptive agnosia may include or be associated with reduced visual acuity.

4.2.3. Topography of lesions

Previously published patients with developmental deficits, similar to MJ's, showed no brain lesion on visual inspection of MRI scans. Nevertheless, in patient MJ, VBM revealed reduced grey matter volume both in ventral occipitotemporal regions, and in low-level mesial occipital cortex. Those anatomical abnormalities match lesions observed in acquired apperceptive agnosia, which generally affect extensively the bilateral occipitotemporal cortex (see Serino et al., 2014, for a recent review). Careful studies of patients with more restricted lesions suggest that this syndrome may result either from posterior occipital lesions impeding primary levels of visual processing (Serino et al., 2014), or from more anterior lesions affecting category-sensitive sectors of the ventral stream (Konen et al., 2011), or from any combination thereof (De Renzi and Lucchelli, 1993). In the present case, both lower- and higher-level visual cortices were abnormal on VBM. It is thus difficult to disentangle the relative role of those two levels in the genesis of the deficit. Still, within the limits of our functional paradigm, fMRI activations were normal in posterior occipital regions, while they were strikingly undifferentiated in all category-sensitive regions. Thus, although some low-level perceptual deficit cannot be excluded, MJ's visual deficit likely resulted from an impaired processing in mid-level and high-level shape processing regions.

4.3. Other cases of developmental agnosia

MJ's visual impairment was pervasive across all the types of visual stimuli that were tested, spared spatial processing, and developed in the absence of any brain lesion discernible on visual inspection of MRI scans. A couple of published cases share those general features. Patient AV had a medical history close to MJ (Eriksson et al., 2003). Agnosia was noticed at the age of 7, sparing movement and color perception, seizures occurred at about the same age, and EEG showed CSWS in the occipito-temporo-parietal regions. Unfortunately, behavioral tests were limited, and no information is available concerning the anatomical and functional features of AV's visual system. Patient AL had a less selective impairment, given his additional difficulties in localizing, reaching for and manipulating objects (Joy and Brunsdon, 2002). Brain MRI was normal at the age of 4, and no EEG nor functional imaging data were provided.

Finally, patient LG received the most extensive scrutiny. When first studied at the age of 8 (Ariel and Sadeh, 1996), LG showed an object recognition impairment which, like in patient MJ, depended heavily on the quality of stimuli, ranging from black and white line drawings to photographs and real objects (10%, 57% and 78% correct, respectively). He was also severely prosopagnosic. Remarkably though, he learned to read at the age of 2, and read at normal age level when 8 years-old, while MJ could not do better than laboriously identify a couple of letters. Unspecified EEG abnormalities were recorded over both occipital lobes early on, supporting potential similarity to the present case. When 19 years-

old, LG had anatomical MRI, which was normal on visual inspection, no epileptic abnormalities were reported, and he participated in fMRI studies (Gilaie-Dotan et al., 2009, 2011).

When presented with faces, houses, tools, geometric patterns, and moving stimuli, patient LG showed abnormal *deactivation* relative to rest in intermediate retinotopic areas V2–V4, while normal activation was observed in primary visual cortex and anterior sectors of the ventral stream, including the expected location of category-selective areas (Gilaie-Dotan et al., 2009). However the latter region lacked selectivity, as the FFA did not respond preferentially to faces, neither the LOC to objects, while the PPA still responded predominantly to houses. LG was not scanned during the perception of printed words, but considering his very good reading abilities, one may speculate that the specialization of his VWFA may have been spared too. Finally, area V5/MT showed normal sensitivity to movement. This suggests that, in patient LG, a primary dysfunction in intermediate areas V2–V4 prevented the functional development of downstream category-selective areas, mostly those dependent on detailed foveal information. In the present case, patient MJ showed no deactivation within the ventral stream, and the lack of differentiation spared neither the PPA nor the VWFA.

Finally, one should note that, beyond those few carefully studied single cases, more children broadly characterized as suffering from "cerebral visual impairment" may present with similar deficits, as a consequence of various perinatal conditions, or in association with cerebral palsy or hydrocephalus (for a review see Philip and Dutton, 2014).

4.4. The role of abnormal electrogenesis

MJ's EEG recordings revealed bilateral epileptiform activity in the occipito-temporal regions when she was awake, and continuous spike-wave activity during sleep, including typical CSWS until at least the age of 11. Together with the clinical history, this electrical pattern points to deep similarities with the epilepsy-aphasia spectrum, a set of conditions with partial genetic causation (Carvill et al., 2013) whose prominent example is the Landau–Kleffner syndrome (Tsai et al., 2013). As described in the initial report, children with Landau–Kleffner syndrome suffer from "acquired largely receptive aphasia (…) with some association with a convulsive disorder". Despite controversies on the classification of epileptic syndromes (Brazzo et al., 2012), CSWS are among the typical EEG correlates of those disorders (Hughes, 2011). CSWS are mostly located in the temporal region, in agreement with the development of receptive aphasia or auditory agnosia. Once epilepsy is controlled, patients with Landau–Kleffner may suffer from long-term aphasic and other cognitive sequellae (Praline et al., 2003; Nickels and Wirrell, 2008). Thus MJ's condition may be considered as pathophysiologically related to the Landau–Kleffner syndrome, distinguished however by a rare localization affecting the visual rather than the auditory and verbal cortex.

The mechanisms through which epilepsy may impede the development of the visual system are still poorly understood. Still, in Rolandic epilepsy, a less severe condition in the epilepsy-aphasia spectrum, (Besseling et al., 2013) observed a reduced connectivity of Broca's area with the sensory-motor Rolandic network, suggesting that epileptic activity interfered with the establishment of distributed functional networks. Those functional anomalies were paralleled by cortical thinning in the perisylvian cortex of the left hemisphere. Such structural anomalies might be due to epileptic phenomena interfering with the normal proliferation and pruning of connections which subtend cortical development (Overvliet et al., 2013). Again, there is a striking similarity with MJ's reduced grey matter volume, which was located in the occipito-temporal rather than in the perisylvian region.

As a final point of neurological discussion, occipital spikes during REM sleep, as observed in patient MJ's latest EEG recordings, have seemingly not been reported before. This pattern could not be a result of the treatment with lorazepam, which was introduced shortly before the EEG recording. Indeed, while lorazepam may lead to a reduction of REM sleep with prolonged REM latency (Röschke et al., 2000), it does not induce spiking activity (Trompeo et al., 2011). Neither can those spikes be related to the psychotic episode suffered by MJ (Poulin et al., 2003). REM sleep disorders in psychotic patients only include shortened REM sleep latency with frequent sleep onset REM periods (Lamont et al., 2010). One may only speculate that this abnormal electrical activity contributed to the development or prolongation of MJ's cognitive deficits, by interfering with the normal role of REM sleep in memory (Poe et al., 2010).

In conclusion, we studied a young patient suffering from severe developmental visual deficit. The primary cause of her impairment could be found in interlinked chronic epileptic activity and abnormal cortical development in her occipitotemporal region. This activity interfered with the development of her ventral visual stream, resulting in reduced grey matter volume, and in a lack of differentiation of category-sensitive areas.

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