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Homozygous LAMC3 mutation links to structural and functional changes in visual attention networks

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ABSTRACT

The occipital lobe contains a substantial part of the neural machinery involved in visual perception. Mutations in the LAMC3 gene have recently been shown to cause complex bilateral occipital cortical gyration abnormalities. However, to what extent these structural changes impact visual behavior is not known. We recorded responses for two screening test batteries targeting visual function (Leuven - Perceptual Organization Screening Test, Cortical Vision Screening Test) and measured eye fixation performance in a visual attention experiment from a patient with homozygous LAMC3 gene mutation. Using voxel-based morphometry (VBM) we quantitatively assessed the extent of structural changes brought on by the genetic mutation by comparing mean cortical curvature, cortical thickness, and gray matter volume in 34 cortical areas between patient and an age-, sex-, and education-matched control group. Anatomical connectivity between these cortical areas was investigated by a structural covariance analysis. Visual screening-, and behavioral results revealed that the patient's impairments were predominantly in visuo-spatial attention. Consistent with this, VBM and structural connectivity results revealed significant structural changes in cortical regions subserving attentional functions. We conclude that the LAMC3 gene mutation affects cortical areas *beyond* the occipital lobe and primarily those visual functions that involve heavily distributed networks – such as visuo-spatial attention.

Introduction

The structure and function of the brain are tightly interrelated. Collocated neurons are frequently involved in similar functions (e.g. visual maps, tonotopic maps, spatial maps) and may exhibit similar gene expressions patterns (Zeng et al., 2012). To what extent this structure-function relationship develops due to experience, self-organization mechanisms, or genetic codes is not well understood. A particular difficulty in studying these mechanisms arises from the fact that they tend to heavily interact in the course of development. On rare occasions however, nature presents a unique opportunity to study one of these three mechanisms selectively (Özçelik and Onat, 2016). Specifically, patients with congenital cortical malformations, where a structural abnormality can be linked to the mutation of a single recessive gene (Barak et al., 2011; Gulsuner et al., 2011; Özçelik et al., 2010) provide not only a unique insight into how a single gene can influence the development of cortical structure but also tie single gene expression to human behavior and cognition. In these rare cases, the individual must be homozygous for the gene in question, which renders the investigation of consanguineous populations especially fruitful (Özçelik et al., 2010). Here, we report the case study of such an individual.

The patient (NG 367-1) (Barak et al., 2011) has a single mutation in the LAMC3 gene coding for the (γ3) chain of the laminin family proteins, which play a crucial part in cell differentiation, migration, and adhesion

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(Hamill et al., 2009). This gene mutation has been linked by Barak et al. (2011) to a loss of secondary and tertiary gyri of the occipital lobe, leading to prominent bilateral smoothening and thickening of the cortex (see Fig. 1). No further cortical changes had been reported, and there was no quantitative assessment of structural abnormalities by Barak et al. (2011). The occipital lobe is a critical component in visual function as it contains neural machinery subserving nearly every aspect of visual perception. However, despite the pronounced structural abnormalities in the occipital areas, especially in the object recognition area LOC (lateral occipital complex) (Grill-Spector et al., 2001), the patient had not noticed any difficulties related to vision, nor did Barak et al. (2011) report any problems in the patient's visual behavior. This outcome has been quite surprising, given the tight link of cortical structure and function. Patients with extensive cortical malformation usually suffer from mental retardation, and delay in cognitive or motor functions (Bilguvar et al., 2009; Jansen and Andermann, 2005). Yet, it is possible, that potential visual impairments of our patient had gone unnoticed, as in the case of A.T. (Michel and Henaff, 2004) who, following an eclamptic attack had pronounced bilateral occipital lesions, reported to have no perceptual deficits. Yet, it was later discovered that A.T. suffered from hemispatial neglect.

Here, we examined visual cognition and perception of this patient in detail. We report the results of several high-, and mid-level vision test batteries along with an experiment, that measured the patient's ability to maintain her fixation in the presence of distractors. Intact visual function in the presence of congenital structural abnormalities would point to powerful compensatory mechanisms due to brain plasticity. Conversely, compromised visual function associated with structural abnormalities would point to a link between *LAMC3* expression, cortical structure and visual behavior. In order to link behavioral results to cortical structure, we *quantitatively* assessed and compared mean curvature, cortical thickness and gray matter volume between patient (NG 367-1) and a matched control group using voxel-based-morphometry, and performed structural covariance analysis to explore the possibility that the structural changes due to the *LAMC3* mutation are not limited to occipital areas.

Materials and methods

Participants

Patient

The patient, a 37-year-old (at the time of study) female, has prominent bilateral smoothing and thickening of the lateral occipital cortex. This structural abnormality has been tied to a mutation in the laminin γ3 gene: *LAMC3* (Barak et al., 2011). The patient has been found to be neurologically intact with average intelligence (Barak et al., 2011). She is very cooperative, shows a general positive affect and presents socially and emotionally appropriate behavior. Perimetric examination administered by an ophthalmologist showed bilateral superior and lower nasal defects in the right eye, and peripheral constriction more prominent in the superior nasal field on the left (see Supplementary Fig. S1). Low-level vision screening with the Rosenbaum Pocket Vision Screener showed acuity in the near normal range, and color vision was normal according to the Ishihara color test (see Table 1). The patient's pursuit was saccadic and not smooth. She did not detect movement of a target (pen held by the physician) in her visual periphery. Only when the target entered more central regions of her visual field she noticed its movement.

The patient has completed 12 years of schooling and has been working for a government organization. Due to staring and blinking spell seizures that started at age 10 the patient has been prescribed valproic acid, levetiracetam, pregabaline and topiramate. The patient gave written consent prior to participating in this study and was compensated for her time of participation. The study was in accordance with the declaration of Helsinki and was approved by the Research Ethics Committee at Bilkent University. Testing times were kept short since the patient tired easily and her neurologists recommended her not to exert herself for long durations at a time due to her epilepsy.

Healthy controls

Control participants were recruited through an advertisement management system at Bilkent University. Twelve sex, age, and education years-matched (mean age 37.17 ± 3.69 years) healthy individuals participated in the *structural MRI study*. Two of these were subsequently

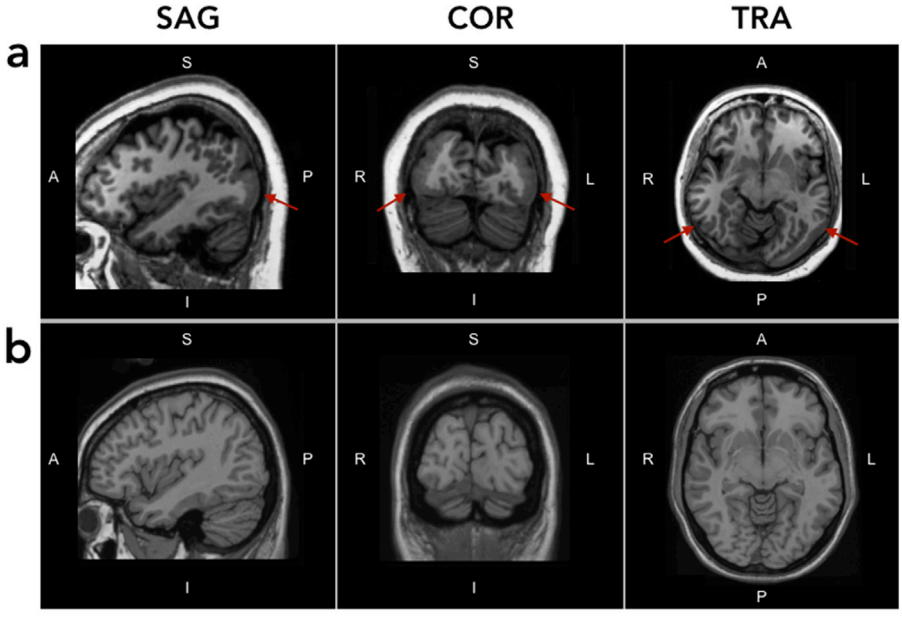

Fig. 1. T1-weighted images of (a) the patient's brain and (b) corresponding views of the Colin brain (Holmes et al., 1998). Depicted from left to right: sagittal, coronal, and transversal views. L: left, R: right, A: anterior, P: posterior, S: superior, I: inferior.

Table 1
Assessment of visual abilities. Shown are raw scores and interpretations of several standard and custom-made test that measure early and higher visual processes and visual cognition. It is apparent that the patient has predominantly problems in visuo-spatial attention, but has also some deficits in visual motion perception, and visual memory.

Test	Raw Score	Norms/Comments
Early Visual Processing		
Acuity *Rosenbaum Pocket Vision Screener*	L20/30	
	R20/30	Within normal range
Color vision *Ishihara color plates*	14/14	Normal
Early Visuo-perceptual Processing		
Shape discrimination *CORVIST*	8/8	Within normal range
Shape ratio discrimination (Efron) *L-POST*	4/5	8.7th %tile, impaired
Size discrimination *CORVIST*	2/2	Within normal range
Shape detection *CORVIST*	4/4	Within normal range
Fine shape discrimination *L-POST*	4/5	13.2th %tile, normal limits
RFP contour integration *L-POST*	4/5	13.9th %tile, normal limits
RFP texture surfaces *L-POST*	4/5	11.8th %tile, normal limits
Figure ground segmentation *L-POST*	5/5	56.6th %tile, normal limits
Object Perception		
Face perception *CORVIST*	8/8	Within normal range
Recognition of missing parts *L-POST*	4/5	11.6th %tile, normal limits
Recognition of objects in isolation *L-POST*	5/5	50.7th %tile, normal limits
Embedded figure detection *L-POST*	3/5	13.1th %tile, normal limits
Recognition of objects in scene *L-POST*	5/5	54.2th %tile, normal limits
Processing of Visual Motion		
Kinetic object segmentation *L-POST*	3/5	1st %tile, impaired
Global motion detection *L-POST*	3/5	6.8th %tile, impaired
Biological motion *L-POST*	4/5	29.2th %tile, normal limits[1]
Visuo-spatial Attention & Perception		
Scattered dot counting *CORVIST*	3/4	Impaired
Dot counting *L-POST*	3/5	1.8th %tile, impaired
Crowding close *CORVIST*	2/2	Within normal range[2]
Crowding wide *CORVIST*	0/2	Impaired
Dot lattices *L-POST*	3/5	6.4th %tile, impaired
Fragmented numbers *CORVIST*	8/8	Within normal range
RFP fragmented outline *L-POST*	4/5	6.4th %tile, impaired
Benton's Judgment of Line Orientation Test	0/30	Patient cannot pass trial phase, impaired
Maze tracing	3/4	With difficulty and only after tracing with hand
Locate dot on line	2/3	With great difficulty and delays (up to 15 s)
Locate dot in/out of figure	1/3	Impaired (Supplementary Fig. S2)
Clock drawing	4/6	Mild visuo-spatial errors (Supplementary Fig. S2)
Cookie theft picture	16 IUs	No indication of simultagnosia (Supplementary Note N1)
Fixation performance *(Experiment)*	N.A.	More affected by peripheral distractors than controls
Visual Memory		
Benton's Visual Retention Test	0/10	Impaired (Supplementary Fig. S2)
Visual Activities Questionnaire (VAQ)	N.A.	Problems in Visual Attention, Peripheral Vision, & Motion (Supplementary Note N2)

excluded from the study since their data were obtained with a different pulse sequence and head-coil (12-channel). Image acquisition protocols and pulse sequence parameters (e.g. flip angle, TR, TE times) have been shown to affect image quality in structural scans (Han et al., 2006; Kempton et al., 2011; Li and Mirowitz, 2004), which in turn changes the segmentation of brain tissues by software routines (e.g. Freesurfer) and thus complicates the interpretation of morphometric results (Clark et al., 2006). Eight sex- and education years-matched (mean age 37.5 ± 16.46 years) healthy individuals participated in the *eye-movement experiment.* All participants gave informed consent prior to participating in the study and were paid for their participation.

Assessment of visual function by neuropsychological tests

Previous investigations indicated relatively normal retinotopic organization of early visual areas (Barak et al., 2011). However, retinotopic mapping is but one aspect of visual function, thus we examined visual cognition and perception in the patient in detail using several visual tests and an experiment. Table 1 gives an overview of the tests, and each is described briefly next.

Cortical Vision Screening Test (CORVIST). The CORVIST (James et al., 2001) focuses on several aspects of visual processing, including object recognition and visuo-spatial attention. We administered 7 of 10 subtests, excluding the tests of visual acuity, color vision and general reading skills, which were assessed previously. Impaired performance on a given subtest indicates a particular affected cortical location.

Leuven Perceptual Organization Screening Test (L-POST). The L-POST was used to assesses various aspects of mid-level visual perception including object perception, attention, and perceptual grouping (Torfs et al., 2014). Scores were calculated as percentile in comparison to a population of 1501 people from every background, age and education level.

Cookie Theft Picture. This test measures various cognitive abilities including visuospatial attention (Goodglass and Kaplan, 1983). The patient was asked to describe the picture. We assessed total number of information units (UIs) produced according to the scoring theme proposed by Giles et al. (1996).

Locating dots with respect to lines, figures, or mazes. To further assess visuospatial attention, we produced simple drawings of undulated lines and shapes similar to those described and used by Michel and Henaff (2004) and asked the patient, depending on the task, to indicate on which line a dot was located, to say whether the dot was inside or outside a shape, or to indicate the exit of a maze (see Supplementary Fig. S2).

Benton's Visual Retention Test. A visual memory test that asks participants to reproduce simple line drawings from memory, one at a time (see Supplementary Fig. S2) (Benton, 1945).

Clock Drawing Test. A standard test that measures visual neglect (Goodglass and Kaplan, 1983). The patient was asked to draw a clock and to draw the hands such that they indicate the time to be 10 min after 11 (see Supplementary Fig. S2). The drawing was scored according to the scheme by Shua-Haim (1996).

Benton's Judgment of Line Orientation Test. A standard test of visuo-spatial skills where participants are asked to match the angle and orientation of two oriented lines. Performance has been linked to the functioning of the right parietal lobe (Benton et al., 1978).

The Visual Activities Questionnaire (VAQ). The VAQ (Sloane et al., 1992) was used to assess several aspects of visual processing including visual acuity, peripheral vision, color vision, and dark and light adaptation. Translation of the items to Turkish was verbally administered at the

[1] In a separate informal investigation, we noted that the patient had problems in perceiving biological motion at larger stimulus sizes.

[2] The reason why the patient might have performed within normal range might be because she did not follow (or was not able to follow) fixation instructions.

time of testing, and the patient's answers were noted by the administrator.

Assessment of eye-movements in the presence of visual distractors

Experimental design and analysis

The experiment took place in a quiet and dimly lit room to optimize pupil and corneal reflection detection by the eye tracker. Each participant's head was stabilized using a chin rest. All participants performed four eye-tracking conditions in randomized order in one experimental session: *Fixation-only (F)* - in order to assess general fixation ability, *Rapid serial visual presentation task* (*RSVP)* - to assess if engaging in a rapid serial visual presentation at the central mark affects fixations, *Task-irrelevant peripheral distractors (IPD)* and *Task-relevant peripheral distractors (RPD) tasks* - to assess how well fixation can be maintained in the presence of task-irrelevant and task-relevant peripheral distractors, respectively. The conditions lasted approximately 12 min in total including 420 trials in RSVP (20 of which included targets), 108 trials in IPD and RPD conditions. In the F condition participants were asked to fixate at the center of a fixation mark. In the remaining conditions (RSVP, RPD, IPD), the task was to respond by pressing "x" button on the keyboard as soon as a target was detected while maintaining their fixation at the center of the fixation mark. Fig. 2 illustrates possible trial sequences of RPD, IPD, and RSVP tasks. Stimuli in RPD, IPD, and RSVP conditions were all letters except that the target in the IPD condition was number "2". Trials in RPD started with a fixation mark presented for 120 ms and followed by a cue "x" either in black or white (indicating target trial) colored font, for 100 ms at 8.71° visual angle eccentricity in one of four possible directions. It is immediately followed by a letter in black colored font in the same location, and it is presented for 200 ms. Trials in the IPD condition were same as those in the RPD except that as no cues preceded targets. Targets in the IPD condition were displayed in white colored font for 200 ms. The experimental code was written in MATLAB using Psychtoolbox (Brainard, 1997). Eye-movements were recorded with an ASL Eye-Trac6 D6 Desk Mounted Optics. To assess fixation performance, we compare mean deviation (in degrees visual angle) from fixation in horizontal and vertical directions, and percent correct and reaction time in the patient and control group. Analysis for reaction time was done in SPSS and fixation data was analyzed using MATLAB.

Structural MRI measurements

Image acquisition

High-resolution three-dimensional MPRAGE, T1-weighted anatomical images (TR = 2600 ms, TE = 3.02 ms, flip angle = 8, FOV = 256 × 224 mm^2, voxel size 1 × 1 × 1 mm^3, number of slices = 176, acceleration factor (GRAPPA) = 2) were acquired using a 3 T scanner (Magnetom Trio, Siemens AG, Germany) with a 32-channel phase-array head coil for the patient and 10 healthy control participants.

Preprocessing

T1-weighted images were processed with the Freesurfer analysis package (http://surfer.nmr.mgh.harvard.edu). Preprocessing included intensity normalization, removal of non-brain tissue, subcortical segmentation, and identification of gray matter/white matter boundary based on the performed cortical reconstruction and volumetric parcellation. The cortex was then parcellated into units based upon the sulcal and gyral surface structure of the Desikan Killiany Atlas (Desikan et al., 2006).

Voxel-based morphometry

Mean curvature (MCU), cortical thickness (CTH), and gray matter volume (GMV) were computed for each control participant and the patient and for each unit of parcellation. GMV (mm^3) values were corrected for the volume of the cranium (intracranial volume). We then used the distribution of control participant scores (for each unit of parcellation) to determine the 99% confidence intervals (CI) for control group mean MCU, CTH and (normalized) GMV scores using sampling with replacement in a nonparametric bootstrapping procedure (Efron, 1979). We also conducted one sample t-tests comparing patient and control group scores. To correct for a false-positive inflation at multiple comparisons we employed the FDR procedure by Benjamini and Hochberg (1995). If the patient's mean score (for MCU, CTH or GMV) lies outside the corresponding estimated control group confidence interval, *and* the one sample *t*-test comparing patient score and controls is significant at the P_{FDR} criterion of at least $P_{FDR} < 0.05$, we report a given region to be significantly different between patient and controls. For convenience we also provide the local gyrification index (LGI), which is a metric that is closely linked to MCU (Luders et al., 2006), and an intuitive index frequently used in clinical research. The method to compute the LGI is implemented in Freesurfer based on a method developed by Schaer et al. (2008). LGI data analysis followed the same statistical procedures that were outlined for the voxel-based morphometry indices.

Structural covariance analysis

Structural covariance analysis' main use is to help understand disease-related changes in topographical organization. The first step in standard structural covariance analysis is to create separate correlation matrices (e.g. Pearson's correlation coefficient) of cortical thickness or gray matter volume values in ROIs for at least two groups of participants. After correlation matrices are binarized by a thresholding procedure, the two groups are compared to each other to see how the resulting structural networks are different. In our study, it is not possible to follow the standard analysis procedures since we have only a single observation from the patient. Therefore, we followed a different procedure as explained in Kim et al. (2016). They suggest that vertex-wise sampled cortical thickness data can be considered as a distribution for each ROI for an individual participant. Therefore, it is possible to generate individual structural networks by calculating the z-score for each pair of ROIs. Based on this procedure, and using cortical thickness, we created individual structural covariance networks for the patient and for each healthy control participant. The covariance between two ROIs was calculated using z-scores, and the individual covariance matrices were created based on the magnitude of the z-scores. We then generated a

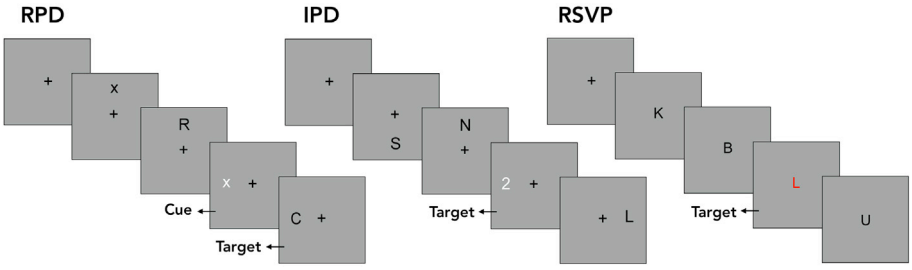

Fig. 2. Sample trials in eye-movement experiment. Shown are three of the four experimental conditions, and respective possible trial sequences: RPD - task relevant peripheral distractors, IPD - task irrelevant peripheral distractors, RSVP - rapid serial visual presentation task. The black cross denotes the location of the fixation mark. It was located at the center of the screen. See text for further details.

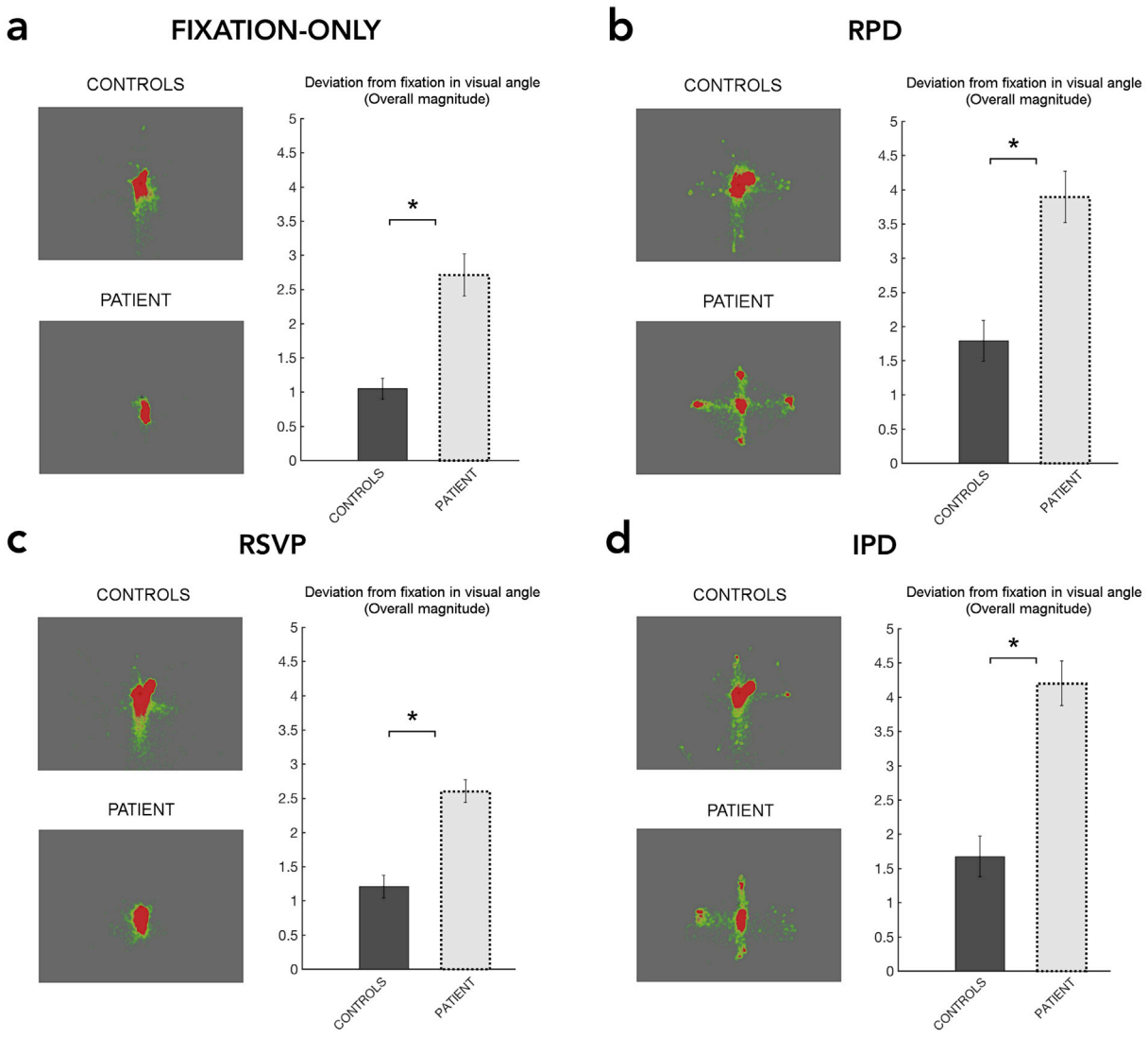

Fig. 3. Fixation performance of patient and controls in the eye-movement experiment. Shown in Fig. 3 are fixation data of patient and control group for all experimental conditions: a: Fixation-only, b: RPD – task relevant peripheral distractors, c: RSVP – rapid serial visual presentation task, and d: IPD – task irrelevant peripheral distractors. Heat maps denote cumulative densities of fixation points on a scale from light green (fewer fixations) to deep red (more fixations). Corresponding absolute deviations from the central fixation mark are shown for patient (light gray bars) and control group (dark gray bars) in degrees visual angle. Errorbars of control group show inter-individual variance in the corresponding experimental condition.

mean connectivity matrix of control group. The mean connectivity matrix of the control group and the connectivity matrix of the patient were binarized by applying a threshold (z-value = 1.96) corresponding to the 95% confidence interval. In a final step, the binarized matrices were compared to each other in order to reveal potential dissimilarities of connectivity of ROIs between the patient and the control group.

Results

Visual functional outcomes

Table 1 shows raw scores and norms for each administered test. The patient's performance was within the normal range for tests of early visual-, and visuo-perceptual processing and object perception. There were, however, marked impairments for tests of visuo-spatial attention and perception, as well as some impairment of visual motion perception and memory.

Fig. 3 illustrates the patient's difficulty to maintain fixation compared to the control group in the eye-movement experiment, however, this difficulty was exacerbated in the presence of peripheral distractors (task relevant and irrelevant). A 2 (group: patient, controls) x 4 (condition: F, RSVP, RPD, IPD) ANOVA on fixation deviation magnitudes[3] (computed as the absolute distance from central fixation) yielded a significant main effect of group (F (1,1816) = 317.25, $p < 0.001$), a significant main effect of condition (F (3,1816) = 39.26, $p < 0.001$), and a significant interaction (F (3,1816) = 9, $p < 0.001$). The interaction was driven by differences in how task difficulty affected fixation patterns of patient and controls.

Table 2 shows behavioral scores of the patient and (mean) control group in the eye-movement experiment. Assessment of task performance in reaction time (RT, in seconds) by one-sample t-tests showed significantly longer reaction time of patient compared to controls in RSVP and

[3] The ANOVA was conducted on fixation deviation magnitudes using eye data (fixation) of each time unit per participant. Consequently, the degrees of freedom are based on the number of observations (fixations) of the participants, not the sample size.

Table 2
Behavioral results of eye-movement experiment. Mean scores of the control group are shown along with one standard error of the mean.

	RSVP		IPD		RPD	
	% correct	RT[a]	% correct	RT[a]	% correct	RT
Patient	75	0.490	100	0.758	70	0.482
Controls	100	0.439 ± 0.02	97 ± 1.92	0.632 ± 0.03	87 ± 8.18	0.446 ± 0.06

[a] Statistically significant at $p < 0.05$.[4]

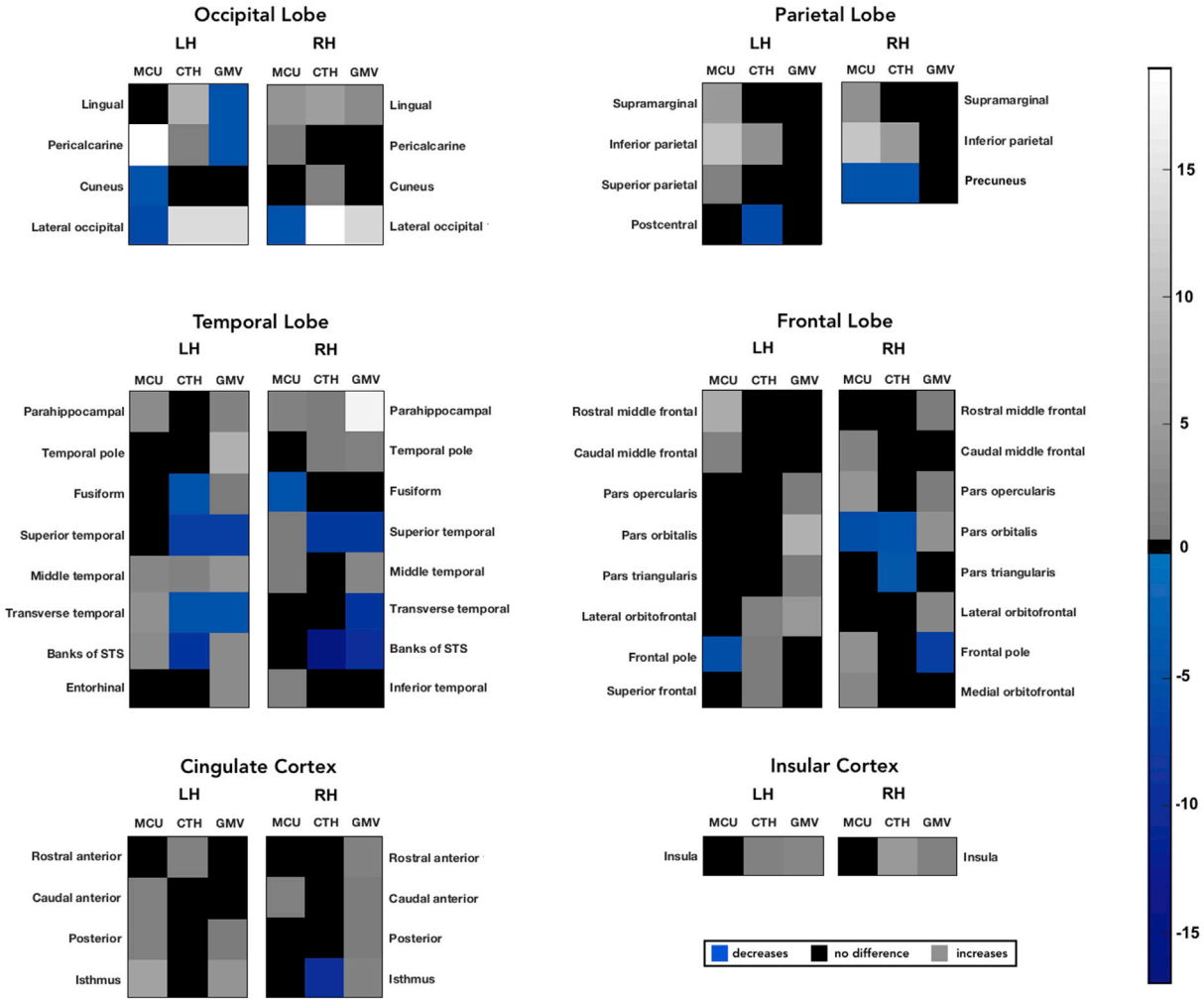

Fig. 4. A graphical overview of increases and decreases in mean curvature (MCU), cortical thickness (CTH) and gray matter volume (GMV). We computed change by dividing the difference between patient score and the respective control group 99% CI limit (upper or lower) by the standard deviation of the mean estimate of the respective bootstrapped group data. A black square means that differences between patient score and control group was not significant. Gray colors imply that the patient's score was significantly above the control group value, and blue colors that was significantly below. This representation highlights the most profound changes in MCU (first column), CTH (second column) and GMV (third column) in both left (LH) and right hemispheres (RH). Supplementary Tables 1 and 2 provide corresponding numerical values. Supplementary Tables 3 and 4 provide raw score ranges of healthy control participants. Also, see Supplementary Fig. S3 for an additional representation of the results by z-scores. Opposite changes in gray matter volume and cortical thickness (e.g. pericalcarine cortex or fusiform gyrus) - though at first counterintuitive can be explained by the mostly independent computation of these indices. In fact, gray matter volume (but not thickness) is strongly related to surface area. See Supplementary Table 9 and Supplementary Fig. S5.

IPD (t (7) = −2.840, $p = 0.025$; t (7) = −3.922, $p = 0.006$ respectively). However, the patient's task performance assessed in % correct was not markedly different from the controls.

[4] Participants in the eye-movement experiment were not age-matched (including four older- and three younger participants). See Supplementary Note N3.

Cortical structural changes

Morphometry analysis

Morphometric analysis shows that structural changes are not limited to occipital areas, but occur throughout the entire brain. We computed *structural change* by dividing the difference between patient score and the respective control group 99% CI limit (upper or lower) by the standard deviation of the mean estimate of the respective bootstrapped group data. Shown in Fig. 4 is a graphical overview of these changes in MCU,

Table 3
Affected regions involved in visual and attentional processes. Listed are cortical areas (left column), defined after Desikan et al. (2006), that are significantly different in at least one of the morphometric scores (mean curvature, cortical thickness, or gray matter volume) between patient and control group, *and* that are known to play a prominent role in vision and attention (right column). Supplementary Tables 1 and 2 provide corresponding numerical values. Supplementary Table 8 lists subcortical structures involved in attentional processes that are significantly different in *structure volume* in the patient.

Affected Cortical Area	Role in Vision/Attention
Occipital Lobes	
Pericalcarine	Early visual processing, e.g. spatial frequency, orientation, motion (Grill-Spector and Malach, 2004)
Cuneus	Early visual processing (Grill-Spector and Malach, 2004)
Lingual Gyrus	
Left	Attention to the global aspect of form (Fink et al., 1996)
Right	Visual orienting (Salmi et al., 2007)
Lateral Occipital Cortex	Object perception (Grill-Spector et al., 2001)
Parietal Lobes	
Precuneus	Visuo-spatial imagery (Cavanna and Trimble, 2006)
Inferior Parietal	Spatial attention: modulation of early visual areas via feedback connections (Greenberg et al., 2012) Visual motion (area V3A) (Braddick et al., 2001)
Left	Attentive control on current task goals (Singh-Curry and Husain, 2009)
Right	Responding to salient new information in the environment (Singh-Curry and Husain, 2009)
Left Superior Parietal	Attentional modulation of neural activities of the visual cortex (Han et al., 2004)
Supramarginal Gyrus	Sustained and visuo-spatial attention (Corbetta et al., 2008)
Temporal Lobes	
Parahippocampal Gyrus	Visual memory encoding (Brewer et al., 1998) Spatial orientation (Maguire et al., 1998)
Superior Temporal Sulcus (STS)	Biological motion (Saygin, 2007)
Banks of the STS	Visual motion processing (Braddick et al., 2001)
Inferior Temporal Gyrus	Object recognition (Desimone et al., 1984)
Fusiform Gyrus	Face perception (Kanwisher et al., 1997)
Temporal Pole	Integration of attention and visual information (Langevin et al., 2015)
Entorhinal Cortex	Involves in attentional modulation (Oswald et al., 2001)
Frontal Lobes	
Superior Frontal	Prevention of reflexive eye movements in overt attention control tasks (Guitton et al., 1985), includes human frontal eye fields FEF (Paus, 1996) Part of dorsal fronto-parietal attention network (Corbetta et al., 2008)
Middle Frontal	Attentional reorienting (Japee et al., 2015), links ventral and dorsal attention networks (Corbetta et al., 2008)
Inferior Frontal[5]	Part of ventral fronto-parietal attention network (Corbetta et al., 2008) Response inhibition or delay (cognitive control) (Aron et al., 2004)
Cingulate Cortex	
Caudal Anterior	Boosts attention toward relevant events in cued attention tasks (Weissman et al., 2004)
Rostral Anterior	Regulates attention to threat or competing stimuli (Bishop et al., 2004; Klumpp et al., 2012)
Posterior	Regulates balance between internally and externally directed attention (Leech et al., 2012) Memory and visuo-spatial functions (Maguire et al., 1998)
Insular Cortex	Task-level control, focal attention (Menon and Uddin, 2010; Nelson et al., 2010)

CTH and GMV. This representation highlights the most profound changes. Supplementary Tables 1 and 2 provide corresponding numerical values. Supplementary Table 5 shows corresponding results for the local gyrification index, which were largely consistent with the MCU results.

Table 3 lists significantly abnormal regions in the patient that are known to play a specific role in visual or attentional processing.

[5] Includes Pars Orbitalis, Pars Triangularis, and Pars Opercularis.

Structural covariance analysis

Consistent with the morphometry results, we find that changes in anatomical connectivity are not limited to the occipital region of the patient, but can be seen throughout the brain (see Fig. 5). Notably, the structural connectivity differences between the patient and the control group were larger in the right, than the left hemisphere. We highlight next the connectivity profiles of cortical regions with the largest changes in connectivity in the patient. See Fig. 5 for a graphical representation of all connectivity profiles, and Supplementary Note N4 for a comprehensive description of all changes.

Cortical areas with the largest alterations in their connectivity to other brain regions were the superior parietal cortex and postcentral gyrus in the parietal lobe, the temporal pole and entorhinal cortex in the temporal lobe, as well as the lateral occipital cortex and the pericalcarine cortex in the occipital lobe.

Specifically, in the parietal lobe superior parietal cortex showed changes in the anatomical connectivity with several regions, including superior frontal gyrus (LH), rostral anterior cingulate cortex (RH), lateral occipital cortex (LOC) (LH, RH), inferior temporal gyrus (LH), and the insula (RH). Also, connectivity of postcentral gyrus with superior frontal gyrus (RH), rostral anterior cingulate cortex (RH), LOC (RH), and insula (RH) were altered in the patient.

The temporal pole showed changes in connectivity with several regions including supramarginal gyrus (LH) and inferior parietal cortex (LH, RH) in parietal lobe; pars-opercularis and orbitalis (LH), precentral gyrus (LH) and orbitofrontal cortex (LH) in frontal lobe; isthmus- (LH), posterior- (LH), and rostral anterior cingulate cortices (RH) in cingulate cortex; LOC (LH) in occipital lobe; and superior temporal gyrus (LH, RH), fusiform gyrus (LH, RH), inferior- and middle temporal gyrus (RH) in temporal lobe.

Moreover, entorhinal cortex showed altered connectivity with the regions including supramarginal gyrus (LH, RH) and precuneus cortex (LH) in parietal lobe; pars opercularis (LH), middle frontal gyrus (RH) and precentral gyrus (RH) in frontal lobe; isthmus cingulate cortex (RH) in cingulate cortex; lingual gyrus (LH, RH) and LOC (LH) in occipital lobe; and banks of superior temporal sulcus (STS) (LH) in temporal lobe.

In the occipital lobe, LOC showed altered connectivity with pars triangularis (RH), cuneus cortex (RH), pericalcarine cortex (RH), banks of STS (RH) and transverse temporal cortex (RH). Pericalcarine cortex also showed changes in connectivity with several regions, inferior parietal cortex (LH) in parietal lobe; superior frontal gyrus (RH), pars opercularis (LH) and frontal pole (LH) in frontal lobe; rostral- (LH) and caudal (RH) anterior cingulate cortices in cingulate cortex; and superior temporal gyrus (LH, RH), inferior temporal gyrus (LH), fusiform gyrus (LH) and the banks of STS (RH) in temporal lobe.

Taken together, these structural findings appear to be consistent with the functional outcomes reported above, pointing primarily to structural differences in cortical attentional networks, as will be discussed next.

Discussion

We assessed visual function, brain morphometry and structural connectivity in an individual with homozygous *LAMC3* mutation. Our goal was to gain insight into how this single gene can influence the development of cortical structure and to tie single gene expression to human visual behavior and cognition. Overall, the structural abnormalities associated with the *LAMC3* mutation are not limited to the occipital lobe (Barak et al., 2011), but extend to parietal, temporal, frontal, cingulate, and insular cortices. The deficits found in the visual assessment including test batteries and eye-tracking measurements are largely consistent with the structural changes we observed, in that they point to the possibility of deficits in attentional processing.

Specific functional outcomes associated with LAMC3 mutation

Overall, the behavioral results strongly point to impairments

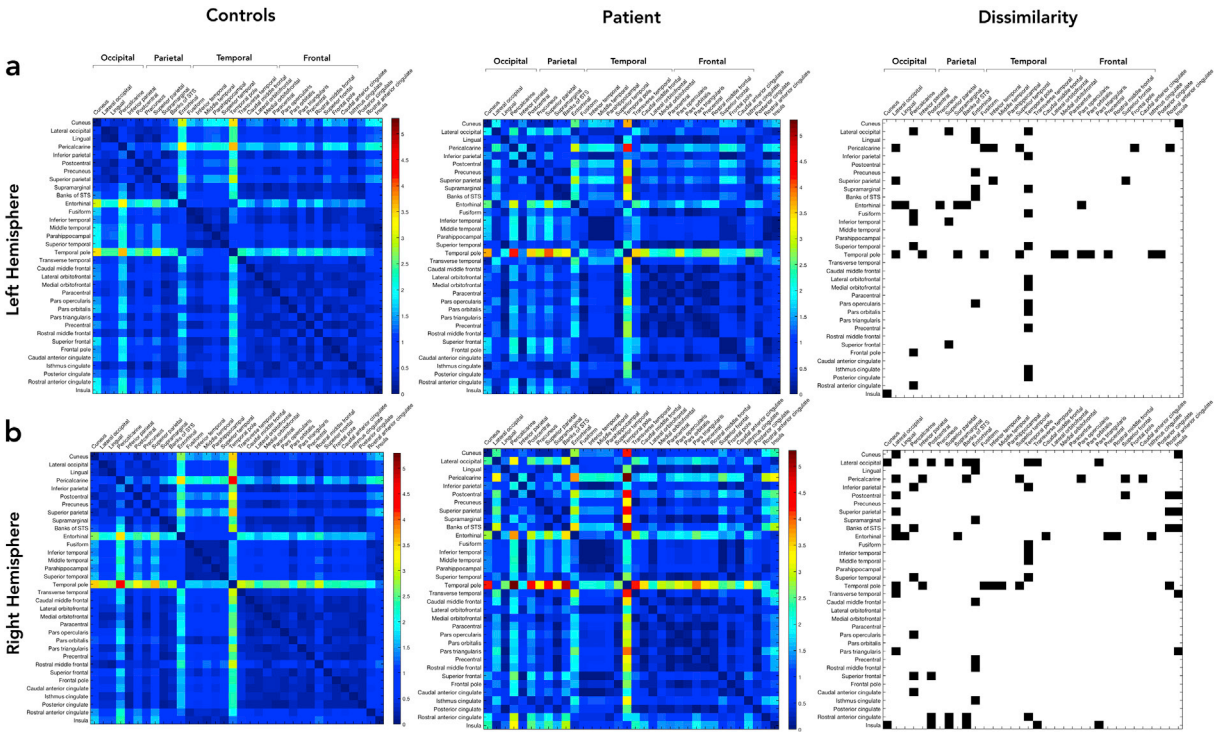

Fig. 5. Structural connectivity networks of patient and controls. Shown are structural connectivity networks of controls (first column) and patient (second column) in (a) left- and (b) right hemisphere. Dissimilarity matrices of the resulting networks (last column) are generated by comparing the binarized matrices (of controls and patient) with a threshold corresponding the 95% CI. See text and Supplementary Note N4 for description of the results.

primarily in endogenous attentional processes. Results of visual neuropsychological test batteries (CORVIST and L-POST) and the VAQ indicate that the patient had great difficulty with tasks that require visuo-spatial attention. She also showed impairments in spatial orienting and a proneness to visual distractors in the eye-movement experiment, as well as in the processing of global motion, indicating problems in sustained attention (Reynolds, 2015), since both types of task involve maintaining focus and resisting distraction. Despite impairments in global motion detection, the patient was able to detect biological motion without problems. This dissociation might occur because local and global motion information are thought to be processed by distinct cortical mechanisms (Chang and Troje, 2009). Thus, biological motion detection might be possible through local mechanisms which may compensate for the problems in global motion processing (Van Boxtel and Lu, 2013).

Although we also found marked impairments in visual memory (e.g. Benton's Visual Retention Test) we suggest that these might be linked to the problems in visual attention since attention has been shown to be an important determinant in the information processing of several domains from perception, to action to memory (Amso and Scerif, 2015). For example, it has been suggested that visuo-spatial information is encoded in memory by a direct modulation of attention (Cowan, 2000; Feng et al., 2012; McElree, 1998). Therefore, limited or impaired attentional mechanisms may impose restrictions on the encoding process of visuo-spatial memory (Awh and Jonides, 2001; Cowan, 1995; Engle, 2002). Moreover, a growing body of literature indicates that attention and memory processes may share common cortical circuits, especially in the tasks that require visuo-spatial skills (Feng et al., 2012; Fusser et al., 2011; Kastner and Ungerleider, 2000). Thus, the patient's performance in Benton's Visual Retention Test, which involves visual memory and visuo-spatial skills (Amieva et al., 2006), may be impaired due to her deficits in visuo-spatial attention.

Structural changes throughout the brain

Morphometry. Our morphometric assessment revealed that structural abnormalities in the patient were not limited to the occipital cortex, but extended to parietal, temporal, frontal, cingulate and insular cortices. These results are consistent with a recent study that used a *qualitative* assessment to reveal the effects of a novel nonsense LAMC3 gene mutation on cortical structure, and found that structural abnormalities included other brain regions in addition to the occipital lobes (Zambonin et al., 2017).

Consistent with the functional outcomes reported in the previous section, morphometric assessment of the brain yielded several severely affected cortical regions that are part of the *dorsal fronto-parietal attention network* and are known to play a role in endogenous attentional processes including intraparietal sulcus, superior parietal cortex and superior frontal gyrus (including FEF, Paus, 1996) (Corbetta et al., 2008; Corbetta and Shulman, 2002). Also cortical regions that are part of the *ventral attention network*, which plays a role in exogenous processes showed structural changes, e.g. middle and inferior frontal gyrus (pars orbitalis, pars opercularis, pars triangularis), inferior parietal cortex and superior temporal sulcus (Corbetta et al., 2008; Corbetta and Shulman, 2002). Dorsal-, and ventral attention networks make reciprocal connections via middle frontal gyrus (MFP) (Corbetta et al., 2008; Japee et al., 2015), therefore the patient's impairments in visuo-spatial attention and spatial orienting may be caused by structural abnormalities in either network, or in the convergence point of these networks (MFP).

Connectivity. Consistent with the morphometry results, we find that anatomical connectivity *within* cortical areas that are involved in the *dorsal fronto-parietal attention network* (connectivity between superior frontal gyrus and superior parietal cortex) was altered in the patient compared to the control group. This would be consistent with the patient's difficulty not only in performing goal-driven, voluntary attention-related tasks, but also in regulating visuo-spatial attention during the task (Wu et al., 2016). Indeed, structural abnormalities specifically in the

right parietal lobe (e.g. supramarginal gyrus, inferior parietal cortex in the patient) have been associated with impairment of visuo-spatial attention (Han et al., 2004) and sustained attention (Berger and Posner, 2000), regardless of the underlying cause – be it degenerative disease, psychopathology, abnormality of development or stroke.

Also, in the dorsal fronto-parietal attention network, the right superior parietal cortex showed altered connectivity with insula and rostral anterior cingulate cortex, which are regions involved in task-level control and focal attention, and regulation of attention to competing stimuli, respectively (Bishop et al., 2004; Klumpp et al., 2012; Menon and Uddin, 2010; Nelson et al., 2010). This finding pertaining to the right parietal regions might explain the patient's impaired fixation performance, especially in the presence of distractors, in the eye-movement experiment as well as her inability to perform tasks that involve visuo-spatial skills, such as Benton's Judgment of Line Orientation Test and Benton's Visual Retention Test (Benton et al., 1978; Benton, 1985; Ungerleider and Mishkin, 1982).

Interestingly, connectivity *within* regions involved in the *ventral attention network* did not show any changes in the patient compared to the control group, as did the convergence point of the attention networks, MFP. However, regions in both attention networks showed altered connectivity with visual areas in the patient, including the connectivity of the superior parietal cortex, and pars triangularis with LOC, and the connectivity of the superior frontal gyrus, superior temporal gyrus, pars opercularis, and inferior parietal cortex with pericalcarine cortex. This finding might account for the patient's impaired performance in the eye-movement experiment and in tasks that require visuo-spatial attention since visuo-spatial attention processing may involve the connectivity of both networks with the visual areas (Pantazatos et al., 2012; Umarova et al., 2009).

Additional cortical regions subserving attentional functions showed drastic changes in connectivity with the areas that are part of ventral- and dorsal attention networks. These regions include postcentral gyrus (visual orienting of attention) (Corbetta, 1998; Hietanen et al., 2006), entorhinal cortex (attentional modulation) (Oswald et al., 2001), insular cortex (task-switching, focal attention, and control) (Menon and Uddin, 2010), and temporal pole (integration of attention and visual information) (Langevin et al., 2015). These cortical regions also showed altered connectivity with the visual areas, including LOC with postcentral gyrus, entorhinal cortex and temporal pole, and insula with cuneus cortex.

Taken together, all findings point to the possibility that the patient's problems in visual attention may be due to her structural abnormalities and aberrant connectivity patterns in cortical regions known to subserve attentional processes. Whether or not these structural changes are a direct effect of the *LAMC3* mutation or rather an indirect effect of a change in cumulative development of visual processing (Amso and Scerif, 2015) by the mutation, cannot be distinguished. Nevertheless, either directly or indirectly *LAMC3* mutation can be linked to impairments in visual attention. Possible developmental mechanisms underlying this dysfunction are discussed next.

Cortical development and visuo-spatial attention

Our results suggest that the *LAMC3* mutation is associated with structural changes *throughout the brain* - including parietal, temporal, frontal, cingulate, and insular cortices - and are not limited to occipital cortical gyration abnormalities (Barak et al., 2011). Complex patterns of-, and extensive structural changes are common to several neurodevelopmental disorders, as are clinical manifestations in motor or cognitive functions such as in memory and attention (Gathercole and Alloway, 2006; Marchand-Krynski et al., 2017). Unfortunately, there is no consistent and replicated evidence that shows that the direction of gray matter changes (increase or decrease in volume and thickness) are directly related to attention (Takeuchi et al., 2017). What is suggested instead, is that neurodevelopmental factors that govern cortical maturation are the primary factors in forming the relationship between cortical thickness and spatial attention (Amso and Scerif, 2015; Westlye et al., 2011). Strikingly, some of the observed structural changes in our patient, in particular those in cortical thickness resemble that of ADHD patients (Makris et al., 2006; Silk et al., 2016), in particular the increased gray matter volume in posterior cingulate cortex, the altered connectivity in the dorsal fronto-parietal attention network, and the dysfunction of visual-spatial abilities (Nakao et al., 2011).

However, not all neurodevelopmental disorders that are associated with complex structural brain changes *also* result in strong impairments in visual/visuo-spatial attention. For instance, Rett syndrome, which is caused by a MECP2 gene mutation, leads to structural abnormalities throughout the brain (Carter et al., 2008) similar to those caused by the *LAMC3* mutation. However, the structure of the occipital lobe and visual processing is relatively preserved in these patients (Carter et al., 2008; Jain et al., 2010). Similarly, Autism Spectrum Disorder (ASD) is a pervasive genetically-based developmental disorder (Sadybekov et al., 2017), in which the occipital lobe appears to be the least affected area in terms of its structural organization (Nickl-Jockschat et al., 2012), and visuo-spatial skills are intact or even enhanced in ASD (DeRamus et al., 2014; Sahyoun et al., 2010). Notably, individuals diagnosed with these disorders exhibit seizures (Carter et al., 2008; Murdoch and State, 2013) as in the case of our patient, but do not show strong visual/visuo-spatial attention deficits. This indicates that seizures by themselves do not necessarily result in impairment of visual/visuo-spatial attention. Thus, the *LAMC3* mutation appears to be special in terms of its association with impairments in visual/visuo-spatial attention, clinically distinguishing itself from some of the well-known neurodevelopmental disorders (Carter et al., 2008; DeRamus et al., 2014; Farzin et al., 2011; Sahyoun et al., 2010).

Genetic Expression. LAMC3 is expressed in nearly all cortical and subcortical structures during development, but its expression peaks between late gestation (24–38 post-conceptual weeks) and late infancy (6–12 post-natal months) (Barak et al., 2011). Strikingly, this period covers the timing of the development of sustained attention (between 4 and 6 months of age) as well as the development of top-down executive attention, which continues even throughout adolescence (Amso and Scerif, 2015). Thus, a change in LAMC3 gene's prominent expression during the development of attentional functions in the brain could be one of the reasons that underlies the specific visual/visuo-spatial attention impairment of our patient. Moreover, we found that *LAMC3 expression in healthy adults* was low to moderate in nearly all of the cortical and subcortical areas (Hawrylycz et al., 2012; Zeng et al., 2012) that had an abnormal structure or connectivity pattern in our patient (see Supplementary Table 7), which further supports the idea that changes in *LAMC3* expressions in these regions could provide an explanation for the observed structural and functional changes.

Indirect effects of the LAMC3 mutation. Alternatively, the patient's structural and functional abnormalities in visuo-spatial attention may be due to changes in the cumulative development of visual processing (Amso and Scerif, 2015). That is, an early impairment in cortical organization of visual areas may impose changes in the local structure, connections and top-down modulation of visual information processing. This impairment may in turn affect structure, function, and connectivity of the visual attention networks. Our patient with LAMC3 gene mutation has profound and extended congenital changes in lower and higher visual processing areas that may have adversely affected her cumulative structural and functional development of the visual processing. This might have thus resulted in the structural, perceptual and cognitive impairments, especially in visuo-spatial attention, that go beyond the occipital cortex.

Spared visual abilities. The structural abnormalities in ventral areas (fusiform gyrus) and lateral occipital complex lead us to expect that the patient might have difficulties in object and face recognition (Grill-Spector et al., 2001; Kanwisher et al., 1997). Surprisingly however, she did not show any impairment in tasks probing these abilities. This might suggest that there are compensating mechanisms at work. For example,

one could argue that decreases in surface curvature (and thus decreases in gray matter surface area) might be linked to increases in white matter volume. However, we found no systematic relationship (increase or decrease) between mean curvature and white matter volume changes (see Supplementary Table 6, and Supplementary Fig. S4). Other compensatory mechanisms, however, might be possible, such as an increased efficiency of neural processing (Li et al., 2009). This could be the subject of future investigations.

Taken together, our results imply that the homozygous mutation of *LAMC3* primarily affects visual functions that involve heavily distributed networks – such as visuo-spatial attention. It also points to a remarkable ability of the brain to re-organize itself in order to maintain or attain vital 'normal' visual functions in the face of a compromised cortical architecture.

Limitations

Case Studies. The patient is in several ways a unique individual, and there are known methodological challenges for case studies. Significant differences may emerge from individual variability in neuroanatomy only and they may not reflect the main effect of the disorder/condition under investigation (Scarpazza et al., 2013). Moreover, the likelihood of detecting significant difference between a single-subject and a group of controls has been shown to be higher in frontal and temporal cortices compared to occipital and parietal cortices (Scarpazza et al., 2013). In order to address these limitations, we use bootstrapping to generate conservative 99% confidence intervals and followed an FDR procedure (Benjamini and Hochberg, 1995) to correct for false-positive inflation at multiple comparisons for each morphometry estimate for the control group. In addition, we provide the range of control group raw scores for each estimate.

Medications. Neurodevelopmental abnormalities caused by gene mutations commonly cause epilepsy and related seizures (Barkovich et al., 2012; Guerrini et al., 2003; Mischel, 1995; Raymond et al., 1994; Wenzel et al., 2001). The patient had been followed by her neurologist due to ongoing partial seizures occurring once in a month, and she had been on medication with a combination of valproic acid, levetiracetam, pregabalin, and topiramate. She did not report any problems after starting these medications, and was able to continue to perform all personal tasks and as an employee. Previous studies suggested that long-term use of these medications may cause adverse effects, such as impairments in vision (Zaccara et al., 2011), and in cognitive functions, such as attention (Martin et al., 1999), and memory (Sgobio et al., 2010). Thus, the particular medical/medication history of the patient might act as a confound which complicates the interpretation of our findings. However, more recent studies suggest that these particular medications might not necessarily adversely affect cognition. For example, Jellett et al. (2015) showed that valproic acid and ongoing seizures do not cause any cognitive impairment in intractable epilepsy beyond those caused by the underlying brain malformation. Moreover, neither levetiracetam nor pregabalin has been associated with severe neuropsychological and psychiatric side effects (Ciesielski et al., 2006; Helmstaedter and Witt, 2008; Mecarelli et al., 2004; Zhou et al., 2008). In fact, some studies reported improved cognitive function in patients with epilepsy in response to levetiracetam intake (Piazzini et al., 2006; Zhou et al., 2008). While long-term use of pregabalin may induce mild cognitive impairments, such an impairment had only been observed in individuals who used the maximum dosage of pregabalin, *and* who, concurrently, had subjective neurotoxicity complaints (Salinsky et al., 2010). Our patient used a much lower dosage of pregabalin, than individuals reported in Salinsky et al. (2010) and did not have any concurrent neurotoxic complaints.

The heterogeneity of medications' effects among patients is not well understood. For example, the use of topiramate has been shown to lead to mild to moderate impairments in verbal fluency and working memory, yet there are substantial individual differences in response to topiramate intake (Cirulli et al., 2011), even after environmental factors are taken into account (Goldstein et al., 2007). One possibility is that genetic differences between individuals contribute to this variation (Cirulli et al., 2011; Goldstein et al., 2007; Ray et al., 2009), yet a clear understanding of genetic mechanisms is still lacking.

The particular combination of medications that patient NG 367-1 uses is rather rare, thus finding a similarly medicated group of otherwise healthy controls has been impossible. Thus, we cannot completely rule out a potential influence of these medications on our results. However, the side effects of the medications are very well-known, and our patient did not report any problems related to memory or any other cognitive function. Instead, the few complaints she had regarding her cognitive abilities were related to spatial attention. Consistent with this, our functional assessments indicate predominantly deficits in visual/visuo-spatial attention, and the observed structural changes in the attention networks support this result. Thus, we believe that it is not likely that the patient's medications were the cause of the functional and structural changes in visual/visuo-spatial attention.

Conclusion

This study provided a unique opportunity to single out the contribution of a single gene to visual development and function in humans. Homozygous mutation of *LAMC3* can be linked to structural and functional changes in visual attention networks. Moreover, the patient's intact low-level visual-, face- and object recognition abilities suggest that critical visual functions can be attained with a compromised cortical architecture. By what mechanisms this is accomplished is the subject for future research.

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KD, HB and BMU conceived the original study. SS and TK conducted initial ophthalmologic and neuropsychological assessments. YT and FSU administered the L-POST and CORVIST, and interpreted the results. YT also conducted Cookie Theft Picture, Benton's Visual Retention Test, Benton's Line Orientation Test, Clock Drawing, Maze Tracing and Dot Locating tests. BMU and KD designed the behavioral studies. BMU collected and analyzed all behavioral and anatomical data with support from PD, and FSU. KKO provided support for the labeling of the morphometry data. Statistical analyses were done by BMU and KD. BMU and KD wrote the manuscript with feedback from HB, TO, KKO, SS, and TK. TO provided additional guidance throughout the study.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.neuroimage.2018.03.077.

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