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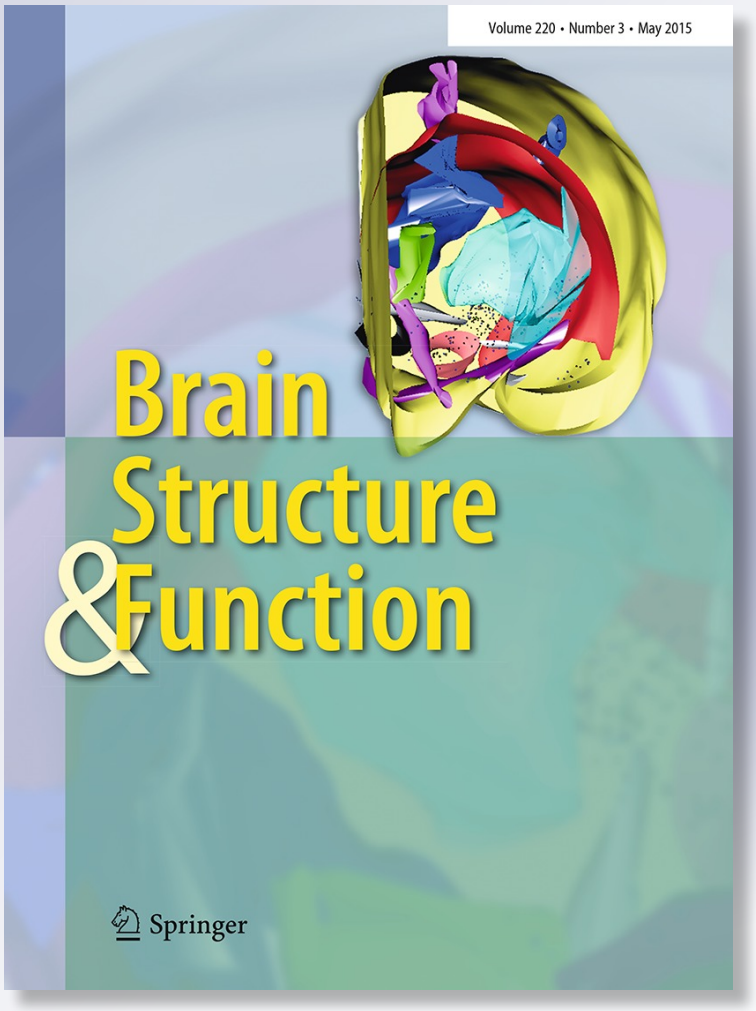

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SHORT COMMUNICATION

Anosognosia for obvious visual field defects in stroke patients

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Abstract Patients with anosognosia for visual field defect (AVFD) fail to recognize consciously their visual field defect. There is still unclarity whether specific neural correlates are associated with AVFD. We studied AVFD in 54 patients with acute stroke and a visual field defect. Nineteen percent of this unselected sample showed AVFD. By using modern voxelwise lesion-behaviour mapping techniques we found an association between AVFD and parts of the lingual gyrus, the cuneus as well as the posterior cingulate and corpus callosum. Damage to these regions appears to induce unawareness of visual field defects and thus may play a significant role for conscious visual perception.

Keywords Anosognosia · Visual field defect · Consciousness · Visual perception · Stroke · Human

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Introduction

The phenomenon of denial of a loss of vision in patients with bilateral damage of the occipital lobe is named Anton's syndrome (Anton 1899). After a bilateral occipital lesion causing complete blindness this syndrome describes the peculiar behavior of patients which deny their loss of vision and are convinced that their vision functions normally.

Whereas bilateral occipital strokes and cortical blindness—and anosognosia for cortical blindness (Anton's syndrome) respectively—are extremely scarce (Milandre et al. 1994) anosognosia for a visual field defect (AVFD) is more frequently observed. One previous study indicated that 62 % of the patients with visual field defects due to ischemic stroke presented with AVFD (Celesia et al. 1997). Other data reported an even higher incidence rate up to 88 % (Bisiach et al. 1986).

Only very few studies addressed the anatomical brain regions associated with AVFD. Heterogeneous observations were reported. Previous studies indicated that retrorolandic and parieto-occipital areas were associated with AVFD (Bisiach et al. 1986; Koehler et al. 1986). In contrast, a further study did not find a relationship between anatomical regions and AFVD (Celesia et al. 1997). To clarify these heterogeneous observations and to analyze whether there are brain regions specifically related to a loss of conscious visual perception we applied for the first time

a statistical lesion-behaviour mapping (VLBM) analysis (Rorden et al. 2007) in a large sample of 54 patients with acute stroke and visual field defects (VFD).

Methods

We investigated 54 patients who were oriented to all qualities [31 female (57 %), 23 male] with VFD due to acute stroke affecting the territories of the middle or the posterior cerebral arteries documented by Magnetic Resonance Imaging (MRI) 7 days [standard deviation (SD) 2.9 days] on average after stroke onset. None of the patients presented with a previous stroke or other lesion of the central nervous system. Forty-one patients suffered from hemianopia (76 %) and 13 from quadrantanopia (24 %) (see Table 1). Patients who were not alert, not oriented, not cooperative, or had severe aphasia as well as patients with a psychiatric history, dementia and eye-disease were excluded. Thus, five patients had to be excluded from the study. The patients gave informed consent for their participation in the study, which was approved by the local ethics committee and thus was performed in accordance with the ethical standards laid down in the 2013, 7th Declaration of Helsinki.

Visual acuity was tested using a commonly applied vision chart (®Börm Bruckmeier Verlag 2002, Germany). Anosognosia for visual field defect was examined using a German translation of the anosognosia scale suggested by Bisiach et al. (1986).

- Grade 0: the disorder is spontaneously reported or mentioned by the patient following a general question about their complaints;
- Grade 1: the disorder is reported following a question about a possible visual field defect;
- Grade 2: the disorder is acknowledged only after demonstrations through routine neurological confrontation techniques; thus, the patients were asked to signal as soon as they perceived the examiner's waving fingers moving inward from beyond the boundaries of each visual field quadrant. Demonstrations were achieved first by explaining to the patient the difference between the intact quadrant respective intact visual field compared to the side of the pathological quadrant respective pathological visual hemifield. Secondly, the patient was asked to count stationary fingers presented sequentially in each visual field quadrant;
- Grade 3: no acknowledgement of the disorder can be obtained.

Following the revised diagnosis criteria for this scale (Baier and Karnath 2005) patients who mentioned their defect spontaneously (grade 0) or following a question about a possible visual field defect (grade 1) were not considered as having AVFD. Patients who denied of having any visual problems despite the fact that they were specifically asked (grade 2) and patients who insisted of having no visual field defect despite a demonstration of the disorder (grade 3) were considered as having anosognosia of visual field defect.

Table 1 Demographical and clinical data of all patients with visual field defects split for the anosognosia scale grading

	No AVFD		AVFD	
	Grade 0	Grade 1	Grade 2	Grade 3
Number	32	12	6	4
Hemisphere lesioned				
L/R	13/19	6/6	3/3	0/4
Time since lesion (days)				
Median (range)	6 (2–12)	5 (2–10)	9 (4–15)	9 (5–11)
Age (years)				
Median (range)	68 (28–84)	75 (29–92)	67 (51–78)	73 (33–83)
Paresis of contralesional side				
Median (range)	5 (0–5)	4 (2–5)	5 (3–5)	3 (2–3)
% present	28	58	67	100
Visual acuity				
Median (range)	0.8 (0.5–1.0)	0.8 (0.7–1.0)	0.8 (0.7–1.0)	0.8 (0.7–1.0)
Spatial neglect				
Mean CoC (SD)	0.048 (0.043)	0.035 (0.037)	0.047 (0.416)	0.105 (0.127)
Visual field defects				
Hemianopia % present	66	92	83	100
Quadrantanopia % present	34	8	17	0

AVFD anosognosia for a visual field defect, *CoC* center of cancellation (Rorden and Karnath 2010)

Visual field defects were assessed by the standard neurological confrontation technique. The patients were asked to signal as soon as they perceived the examiner's waving fingers move inward from beyond the boundaries of each visual field quadrant. Spatial neglect was tested with the Bell's test (Gauthier et al. 1989). We calculated the Center of Cancellation (CoC) (Rorden and Karnath 2010). CoC scores greater than 0.081 for right brain damage and smaller than −0.086 for left brain damage patients, respectively, were taken to indicate neglect behaviour (cf. Rorden and Karnath 2010; Suchan et al. 2012). Six patients showed neglect. There was no difference between the anosognosia ($n = 2$) and the non-anosognosia group ($n = 4$) with regard to neglect (Fisher's exact test $p = 0.306$).

All patients had circumscribed left or right-hemispheric brain lesions due to ischemic stroke demonstrated by MRI. We used diffusion-weighted imaging (DWI) within the first 48 h post-stroke and T2-weighted fluid-attenuated inversion-recovery (FLAIR) sequences when imaging was conducted 48 h or later after stroke onset.

The boundaries of the lesions were delineated directly on the individual MRI scans by using MRIcron software (Rorden et al. 2007). Both the MRI scan and the lesion shape were then mapped into stereotaxic space using the normalization algorithm provided by SPM5 (http://www.fil.ion.ucl.ac.uk/spm/). For determination of the transformation parameters, cost-function masking was employed (Brett et al. 2001). The extension and location of the lesion shapes were controlled by a second examiner.

To evaluate the relationship between lesion location and AVFD, we first performed a subtraction analysis (Rorden and Karnath 2004). This was followed by a VLBM analysis using the Liebermeister test-statistic implemented in the MRIcron toolset (Rorden et al. 2007). We controlled for multiple comparisons by using permutation correction. All results presented in the following survived a 5 % cut-off threshold. To identify the anatomical structures affected we applied the WFU PickAtlas version 2.3 implemented as a toolbox in SPM5 as well as the probabilistic maps of visual cortex by the Juelich group, using the SPM Anatomy Toolbox (Eickhoff et al. 2005).

Results

Ten (=19 %) of the 54 patients with visual field defects showed AVFD; seven had right-sided lesions, and three had left-sided lesions (Fig. 1). Six of these ten individuals were rated denial grade 2, i.e., they recognised their deficit only after demonstration; four subjects were rated denial grade 3, i.e., they remained unaware of their visual field deficit even after demonstration of the deficit by the examiner. Forty-four patients were classified not having AVFD. Of the ten patients with AVFD, five patients indicated phosphenes, whereas only two patients had photopsias. With regard to the occurrence of phosphenes and photopsias in the patients without AVFD (seven patients with phosphenes and two patients with photopsias) a difference between the two groups was seen with regard to phosphenes ($\chi^2 = 0.02$) but not to photopsias ($\chi^2 = 0.09$).

Figure 2a, b illustrates the results of the subtraction analyses for the patients with right-sided and with left-sided lesions. For the right-sided lesion patients, the subtraction analysis indicated that the white matter of the calcarine sulcus ($x = 17$, $y = -58$, $z = 16$), parts of the precuneus ($x = 5$, $y = -72$, $z = 16$), the posterior cingulate ($x = 5$, $y = -73$, $z = 13$), the cuneus ($x = 11$, $y = -93$, $z = 8$; $x = 12$, $y = -94$, $z = 2$), the corpus callosum ($x = 15$, $y = -40$, $z = 11$) as well as the lingual gyrus ($x = 15$, $y = -65$, $z = -3$; $x = 17$, $y = -54$, $z = -3$; $x = 17$, $y = -54$, $z = 6$) were more frequently affected by patients with AVFD compared to patients without AVFD. In patients with left-sided lesions, in particular the lingual gyrus ($x = -7$, $y = -89$, $z = -11$; $x = -16$, $y = -63$, $z = -7$) but also parts of the middle occipital gyrus ($x = -27$, $y = -69$, $z = 0$) were mainly affected by patients with AVFD.

Since the number of patients with AVFD following left-sided lesions was very low ($n = 3$) and no evidence for specific differences in lesion location for AVFD following left- versus right-hemispheric lesions had been observed in a previous study (Celesia et al. 1997) we pooled the data of all patients for a final statistical analysis by flipping the left-sided lesions to the right hemisphere. Figure 2c shows the result of this VLBM analysis using the Liebermeister test (Rorden et al. 2007). It indicated that lesions extending from the posterior cingulate ($x = 9$, $y = -53$, $z = 12$) to the corpus callosum ($x = 14$, $y = -41$, $z = 18$) as well as a small lesion area affecting the lingual gyrus ($x = 9$, $y = -86$, $z = -5$); assigned to V1 and to V2 with a probability of 70 % each (Eickhoff et al. 2005) were structures associated significantly with AVFD.

Discussion

Our analysis revealed that AVFD is associated with anatomical regions within the lingual gyrus, the cuneus, as well as the posterior cingulate and corpus callosum. The data suggest that the conviction about one's integrity of the visual system in the absence of visual perception does not depend on damage of a single structure in primary visual cortex but rather on several regions within and outside of primary visual cortex.

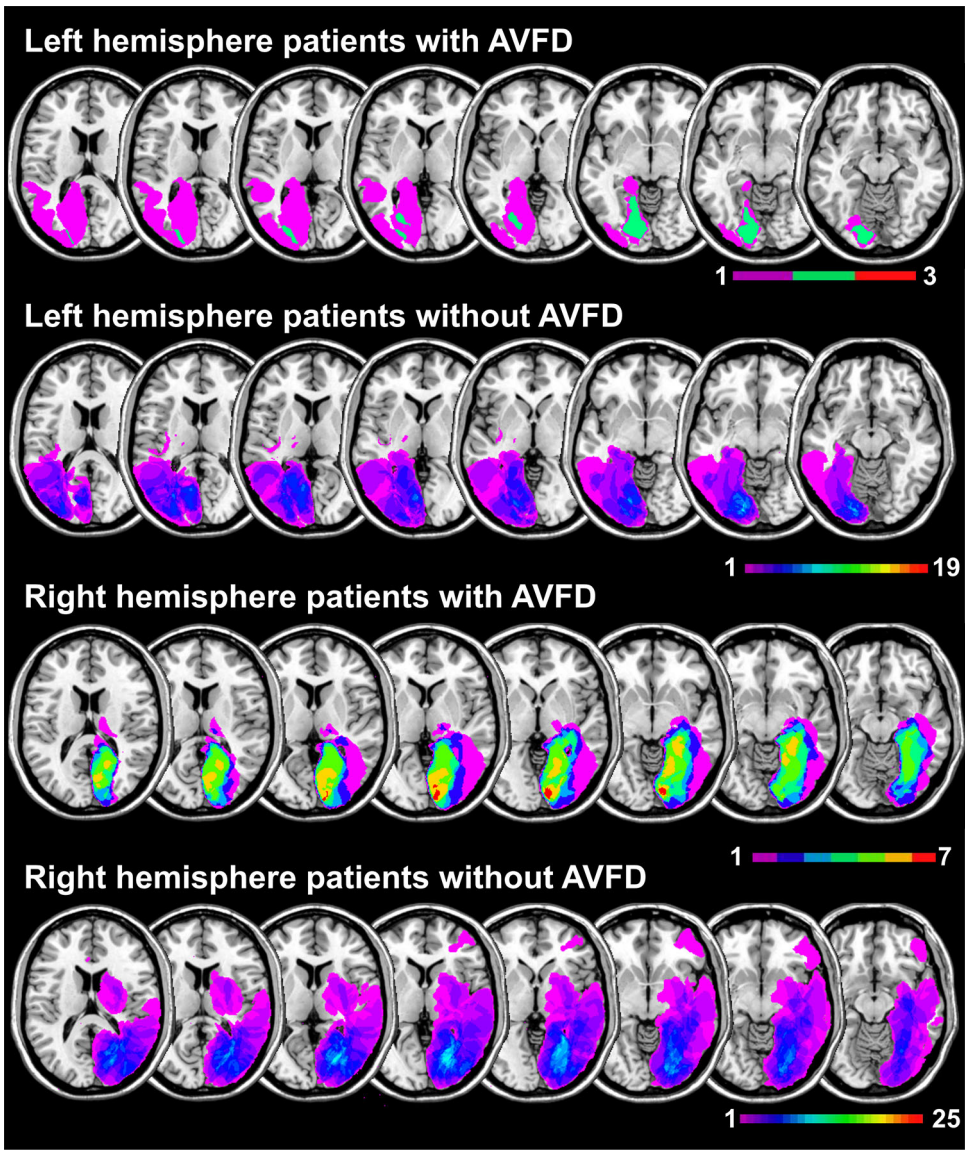

Fig. 1 Simple overlaps plots of the groups of left hemisphere patients with anosognosia for a visual field defect (AVFD), left hemisphere patients without AVFD, right hemisphere patients with AVFD, and right hemisphere patients without AVFD. The number of overlapping lesions is illustrated by different colours coding increasing frequencies from *violet* ($n = 1$) to *red* ($n = \max.$)

Differences between the present and previous lesion analysis data on this issue (Celesia et al. 1997) might be due to the fact that the latter study still used a paper-and-pencil rather than a statistical voxel-based approach. The current findings support previous functional MRI data arguing that visual consciousness is based on a network process in which primary nodes are located in the medial occipital lobe (lingual gyrus) and secondary nodes within parietal and limbic cortices (Stoerig and Barth 2001; Pins and Ffytche 2003). An fMRI study of a single patient with left-sided extinction following a stroke affecting the infero-posterior parietal cortex (leaving striate and extrastriate occipital cortex intact) revealed further evidence that parietal regions such as the cuneus may play a role in visual awareness (Vuilleumier et al. 2001). The authors observed that awareness of faces presented in the left visual half-field evoked an increase of activity in the right V1, bilateral cuneus and fusiform gyrus as well as the left superior parietal cortex.

These previous observations and the present data would be in line with the notion that activity in V1 alone—although necessary for normal visual perception—is not sufficient for visual awareness (Rees et al. 2002).

With regard to the occurrence of AVFD previous studies have indicated that more than two-third of the patients tested were not aware of their visual deficit (Celesia et al. 1997; Bisiach et al. 1986; Koehler et al. 1986). Our data implicate that the incidence of AVFD in acute stroke patients might be lower than previously believed. Based on the revised criteria for diagnosing anosognosia with the scale of (Bisiach et al. (1986); Baier and Karnath 2005) we revealed an incidence of 19 % for AVFD in an unselected sample of continuously admitted patients with acute stroke and a lesion involving the

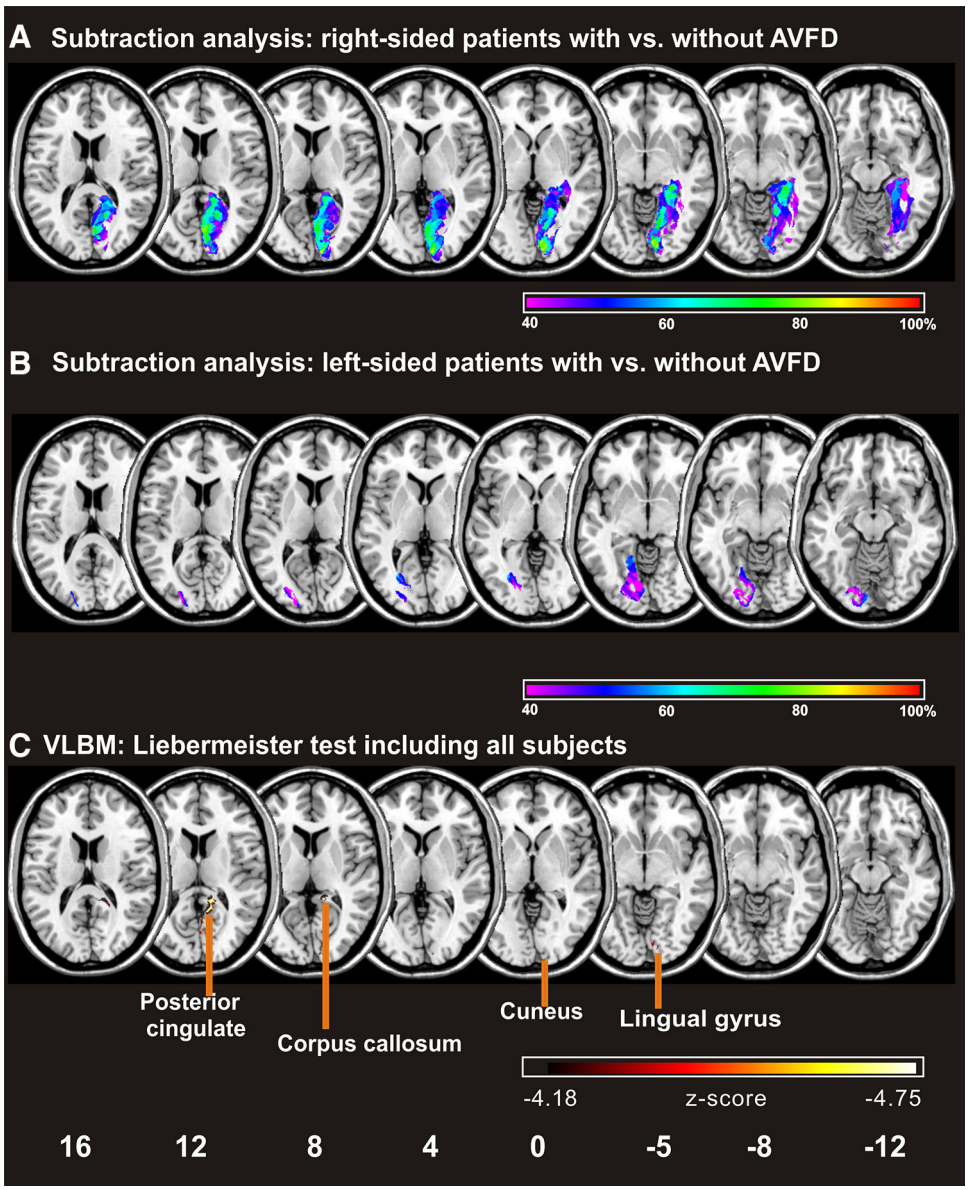

Fig. 2 **a** Subtracted superimposed lesions of the seven right-sided patients with anosognosia for a visual field defect (AVFD) minus those right-sided patients without AVFD. The percentage of overlapping lesions of the anosognosia patients after subtraction of controls is illustrated by different colors coding increasing frequencies beginning at *violet* (40 %) to *dark red* (100 %) which reflects the relative frequency of damage. **b** Subtracted superimposed lesions of the three left-sided patients with anosognosia for a visual field defect (AVFD) minus the 19 left-sided patients without AVFD. The percentage of overlapping lesions of the anosognosia patients after subtraction of controls is illustrated by different colors coding increasing frequencies beginning at *violet* (40 %) to *dark red* (100 %) which reflects the relative frequency of damage. **c** Statistical voxelwise lesion-behavior mapping (VLBM) analysis plot comparing all 54 patients (without and without AVFD; the left-sided lesions were flipped to the right hemisphere). Presented are all voxels that survived a correction for multiple comparisons using a 5 % permutation cut-off

visual pathways. One explanation for the discrepancy in incidence of AVFD thus might be different criteria to diagnose AVFD: Our revised criteria do not classify patients having anosognosia if they do not mention their defect spontaneously following a general question about their complaints but immediately when the examiner addresses the deficit (e.g. hemianopia). Baier and Karnath (2005) have shown that this behaviour is not due to anosognosia but rather due to the fact that such stroke patients spontaneously concentrate on other co-existing defects with a subjectively higher impact. This is in clear contrast to patients who insist that the function is undisturbed, even when the examiner addresses the defect (Baier and Karnath 2005).

A second explanation for the discrepancy in incidence of AVFD might be due to the fact that Celesia et al. (1997) used Goldmann perimetry whereas we used bedside confrontation technique. Thus, we cannot entirely conclude that our lower number of patients found with AVFD might be due to our bedside assessment. However, while the finger confrontation technique is definitely not sensitive enough to detect small visual field defects it appears reliable in detecting large defects such as the loss of one visual half-field or one entire quadrant. Finally, it is possible that the different time periods between stroke-onset and clinical testing might have contributed to the differences in incidence observed in the present and the previous studies. For example, the clinical testing in the study by Celesia et al. (1997) was within 24 h after stroke-onset, while testing in the present study was within the first week after stroke-onset.

What might be the physiological mechanism inducing the denial of a visual field defect, i.e. the inability to consciously recognize a visual field defect? It has been suggested that the conviction of normal vision in patients with Anton's syndrome might be based on a hyperfunction status of the visual memory system (Ffytche et al. 2010). This status might be induced by the brain lesion. In line with such a notion is the observation of hyperperfusion in occipito-temporal regions measured by single photon emission computed tomography in a single patient with seizures due to vascular lesions of the left medial occipital cortex. This patient demonstrated no awareness of his hemianopia in the period between the seizures (Spatt and Mamoli 2000). The conclusions drawn from this single observation should be regarded with care. Nevertheless, transferred to the hypothesis stated above the present data could indicate that lesion to the cortical regions identified might evoke the postulated hyperperfusion. Interestingly, it was reported that other visual phenomena such as palinopsia, i.e., the perseveration of a previously perceived image, might indeed be associated with perilesional hyperperfusion (Hayashi et al. 2002). However, future perfusion studies are required to empirically test this hypothesis. Another explanation of AVFD might be due to "filling in" processes, i.e. the completion of missing information across the visual field defect, resulting in that the subject does not (consciously) experience the defect (Ramachandran and Gregory 1991; Cohen and Legargasson 2005). Interestingly, the fact that phosphenes were associated with AVFD might point towards this hypothesis. On the other hand, whereas "filling in" seems probable for scotomas it is rather unusual for large field defects such as hemianopia or quadrantanopia (Celesia et al. 1997).

In conclusion, the present data appear to support the notion that AVFD is associated with lesion of specific anatomical regions including parts of the lingual gyrus, the cuneus as well as the posterior cingulate and corpus callosum. It is possible that these regions represent a network involved in conscious visual perception.

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Conflict of interest The authors report no conflicts of interest.

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