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The Relation Between Migraine, Typical Migraine Aura and "Visual Snow"

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Objective.—To assess the relationship between the phenotype of the "visual snow" syndrome, comorbid migraine, and typical migraine aura on a clinical basis and using functional brain imaging.

Background.—Patients with "visual snow" suffer from continuous TV-static-like tiny flickering dots in the entire visual field. Most patients describe a syndrome with additional visual symptoms of the following categories: palinopsia ("afterimages" and "trailing"), entopic phenomena arising from the optic apparatus itself (floaters, blue field entoptic phenomenon, photopsia, self-light of the eye), photophobia, nyctalopia (impaired night vision), as well as the non-visual symptom tinnitus. The high prevalence of migraine and typical migraine aura in this population has led to the assumption that "visual snow" is caused by persistent migraine aura. Due to the lack of objective measures, alternative diagnoses are malingering or a psychogenic disorder.

Methods.—(1) The prevalence of additional visual symptoms, tinnitus, and comorbid migraine as well as typical migraine aura was assessed in a prospective semi-structured telephone interview of patients with "visual snow." Correlations were calculated using standard statistics with $P < .05$ being considered statistically significant. (2) Areas with increased brain metabolism in a group of "visual snow" patients in comparison to healthy controls were identified using [^{18}F]-2-fluoro-2-deoxy-D-glucose positron emission tomography and statistical parametric mapping (SPM8 with whole brain analysis; statistical significance was defined by $P < .001$ uncorrected for multiple comparisons).

Results.—(1) Of 120 patients with "visual snow," 70 patients also had migraine and 37 had typical migraine aura. Having comorbid migraine was associated with an increased likelihood of having palinopsia (odds ratio [OR] 2.8; $P = .04$ for "afterimages" and OR 2.6; $P = .01$ for "trailing"), spontaneous photopsia (OR 2.9; $P = .004$), photophobia (OR 3.2; $P = .005$), nyctalopia (OR 2.7; $P = .01$), and tinnitus (OR 2.9; $P = .006$). Typical migraine aura was associated with an increased likelihood of spontaneous photopsia (OR 2.4; $P = .04$). (2) After adjusting for typical migraine aura, comparison of 17 "visual snow" patients with 17 age and gender matched controls showed brain hypermetabolism in the right lingual gyrus (Montreal Neurological Institute coordinates 16-78-5; $k_E = 101$; $Z_E = 3.41$; $P < .001$) and the left cerebellar anterior lobe adjacent to the left lingual gyrus (Montreal Neurological Institute coordinates -12-62-9; $k_E = 152$; $Z_E = 3.28$; $P = .001$).

Conclusions.—Comorbid migraine aggravates the clinical phenotype of the "visual snow" syndrome by worsening some of the additional visual symptoms and tinnitus. This might bias studies on "visual snow" by migraineurs offering study participation more likely than non-migraineurs due to a more severe clinical presentation. The independence of entoptic phenomena from comorbid migraine indicates "visual snow" is the main determinant. The hypermetabolic lingual gyrus confirms a brain

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dysfunction in patients with "visual snow." The metabolic pattern differs from interictal migraine with some similarities to migrainous photophobia. The findings support the view that "visual snow," migraine, and typical migraine aura are distinct syndromes with shared pathophysiological mechanisms that need to be addressed in order to develop rational treatment strategies for this disabling condition.

Key words: visual snow, migraine, aura, [18F]-2-fluoro-2-deoxy-D-glucose positron emission tomography

Abbreviations: OR odds ratio, VS visual snow, [18F]-FDG PET [18F]-2-fluoro-2-deoxy-D-glucose positron emission tomography

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Patients with "visual snow" (VS) describe a visual disturbance that consists of tiny dynamically flickering dots in the entire visual field resembling the "static" or "snow" of a badly tuned analogue television. The symptoms are continuous and can persist over years. Persistent visual disturbance is mentioned sporadically in the literature without larger systematic studies.[1-3] Patients are often diagnosed as having persistent migraine aura, malingering, or psychogenic disorder because objective measures for the condition are not available to date. A recent study of a substantial cohort of subjects with VS confirmed that the visual disturbance is often associated with migraine and migraine aura. However, not every patient with VS has a history of migraine. Further, VS starts only rarely with migraine aura, and the phenotypical description as well as the clinical course of VS by no means resembles typical migraine aura, which is in general homonymous, often presents with moving zigzag lines, and typically lasts less than 60 minutes. This suggests that VS is a unique condition different from migraine aura.[4-6] Importantly, VS should be seen as a syndrome since it is almost always associated with additional visual complaints including palinopsia, entoptic phenomena that arise from the optic apparatus itself (ie, floaters, blue field entoptic phenomenon, self-light of the eye and photopsia),[7] poor night vision (nyctalopia), and photophobia. A large proportion of VS patients has bilateral continuous tinnitus.[5]

To investigate the role of migraine and typical migraine aura mechanisms underlying VS, we sought to assess whether the presence of migraine or aura is associated with different phenotype of the *VS syndrome*. We prospectively recorded accompanying visual and auditory symptoms in a large cohort of

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patients with VS and correlated these symptoms with comorbid migraine and typical migraine aura. To assess potential pathophysiological correlates, we further studied brain metabolism in patients with the hypothesis that VS is associated with regional hypermetabolism distinct from previous findings in migraine.[8,9]

Clinical data of a subgroup of the study population have been previously presented in a report on the detailed phenotype[5] and in preliminary form.[10,11]

SUBJECTS AND METHODS

The study was approved by the Institutional Review Board (# 11-07270 and # 11-07431) and the radiation safety committee (58605-RU-04-URH) of the University of California, San Francisco. Patients were recruited via advertisements in social media with the support of a self-help group on VS (Eye on Vision Foundation; http://www.eyeonvision.org/). After being contacted by the patient, eligibility was assessed during telephone interviews.

Clinical Data.—*Telephone Interview*.—After being approached by the patient, verbal consent was obtained and subjects with self-suspected VS underwent a semi-structured telephone interview. The following items were covered during the interview:

1. Demographics (age, gender) and handedness.
2. Patients were asked to describe their current visual symptoms in their own words. Based on that information and additional open questions, a diagnosis of VS was made and associated visual symptoms were recorded as described recently.[10] In brief, VS was defined as dynamic, continuous, tiny dots in the entire visual field (similar to "TV static" or "TV snow") lasting longer than 3 months (criterion A).[5] Other symptoms were palinopsia ("afterimages" and "trailing" of moving objects), entopic phenomena (phenomena arising from the structure of the visual system itself including (1) excessive floaters in both eyes; (2) excessive blue field entoptic phenomenon, ie, uncountable little gray/white/black dots or rings shooting over the visual field in both eyes when looking at homogeneous bright surfaces, such as the blue sky; (3) self-light of the eye, ie, colored waves or clouds when closing the eyes in the dark; and (4) spontaneous photopsia, ie, bright flashes of light),[7] photophobia, and nyctalopia (impaired night vision). Due to its high prevalence in subjects with VS,[5] the presence or history of tinnitus was also covered during the interview despite being a non-visual symptom.
3. Headache history was assessed according to the International Classification of Headache Disorders – 2nd edition.[6] Migraine aura was only diagnosed when typical features were present, which are unilaterality (homonymous), development over 5 minutes, duration for less than 60 minutes, reversibility, zigzag lines, and scotoma.[4,6]

Data Analysis.—SPSS (v20, IBM Corp., Armonk, NY, USA) was used for the statistical analysis of the clinical data. Standard descriptive statistics were applied. If appropriate, data are presented as mean ± standard deviation. Nominal data were compared using chi-square or Fisher's exact test, ratio data using *t*-test. Statistical significance was defined as $P < .05$.

Functional Brain Imaging.—All subjects participating in the positron emission tomography (PET) study gave written informed consent. Inclusion criterion was VS with at least 2 additional visual symptoms as defined previously.[5] Control subjects did not have VS, associated visual symptoms, tinnitus, a history of frequent migraine attacks (more than 1 every 2 months), or of migraine aura. Exclusion criteria for both groups were ophthalmological pathology other than refraction anomalies, any lifetime history of intake of hallucinogenic drugs, and pregnancy in women. Each subject underwent a detailed personal interview with a focus on visual symptoms, migraine history including typical aura and general past medical history. On the scanning day, each subject had a fasting period of at least 6 hours prior to the acquisition of a high-resolution T1-weighted anatomical MR image (MPRAGE sequence) on a General Electric Signa HDxT 3.0 Tesla scanner (GE Healthcare, Fairfield, CT, USA). Afterwards, a [^{18}F]-2-fluoro-2-deoxy-D-glucose PET ([^{18}F]-FDG PET) scan was acquired using standard parameters, with injection of 10 mCi via an antecubital vein and 45 minutes distribution period in a dark room with eyes closed, on a

GE Discovery VCT PET/CT scanner (GE Healthcare) in three-dimensional (3D) mode with septa retracted. Images were reconstructed by 3D iterative reconstruction into 47 image planes (separation 3.27 mm) and into a 128 by 128 image matrix (pixel size: 2.1×2.1 mm^2). The structural magnetic resonance imaging (MRI) was coregistered to the PET using SPM8 (Wellcome Department of Imaging Neuroscience, http://www.fil.ion.ucl.ac.uk/spm). The coregistered MRI was automatically segmented into gray matter, white matter, and cerebrospinal fluid and normalized into standard stereotaxic space. The spatial normalization parameters from this step were applied to spatially normalize the PET image. Final voxel size was $2 \times 2 \times 2$ mm^3. PET images were then smoothed with a Gaussian Kernel of 12 mm full-width at half maximum. The group of VS patients was compared with controls using a 2-sample *t*-test with masking of non-brain tissue (whole brain explicit mask generated with WFU PickAtlas from Advanced Neuroscience Imaging Research Laboratory, Department of Radiology of Wake Forest University School of Medicine, http://fmri.wfubmc.edu/), and using proportional scaling. Due to the high prevalence of typical migraine aura in patients with VS,[11] the presence of migraine aura was used as a covariate of no interest. According to the clinical manifestation of VS, we suspected hypermetabolism in VS patients. We therefore assessed brain areas with *increased* metabolism in VS patients compared with controls in a voxel-wise fashion. In line with previous studies on migraine,[12,13] we considered voxels reaching a significance threshold of $P < .001$ uncorrected for multiple comparisons to be significant.

RESULTS

Clinical Data.—Of the 142 patients who contacted the Headache Center at the University of California, San Francisco, 120 subjects (mean age 31 ± 12 years; 62 female) met criterion A for "visual snow,"[5] ie, presence of dynamic, continuous, tiny dots in the entire visual field lasting longer than 3 months.

Additional Visual Symptoms.—Palinopsia with "afterimages" from stationary scenes was present in 84%, and with "trailing" in 58%. Excessive floaters were the most common entoptic phenomenon with a prevalence of 83%. Second most common was the blue field entoptic phenomenon (76%). Spontaneous photopsia and consistent self-light of the eye occurred in half of patients. About two thirds of patients had photophobia and nyctalopia. In addition to these visual symptoms, 64% of patients noted continuous bilateral and mainly high-pitched tinnitus (Table 1).

Table 1.—Additional Symptoms in Patients With "Visual Snow"

	All Visual Snow Patients N = 120	
Palinopsia ("afterimages")	101	84%
Palinopsia ("trailing")	69	58%
Floaters	99	83%
Blue field entoptic phenomenon	91	76%
Self-light of the eye	64	53%
Spontaneous photopsia	64	53%
Photophobia	86	72%
Nyctalopia	76	63%
Tinnitus	77	64%

Association of Additional Symptoms With Migraine and Typical Migraine Aura.—The presence of migraine was associated with an increased prevalence of the additional symptoms palinopsia (odds ratio [OR] 2.8 for "afterimages" and OR 2.6 for "trailing"), spontaneous photopsia (OR 2.9), photophobia (OR 3.2), nyctalopia (OR 2.7), and tinnitus (OR 2.9). Spontaneous photopsia was more prevalent in patients with typical migraine aura (OR 2.4, Table 2).

Functional Brain Imaging.—Seventeen patients (10 female, mean age ± standard deviation 31 ± 7 years) with VS and at least 2 additional visual symptoms were recruited for the imaging study. Seven had VS as long as they could remember. Mean age of onset in the remaining was 25 ± 8 years. Fourteen (82%) had a history of migraine. Five of those had migraine with typical aura, and 1 had typical migraine aura without history of migraine.[6] All 3 patients without history of migraine had a positive family history of migraine. Besides headache, past medical history included depression, Graves' disease, hypothyroidism, acne, and attention deficit hyperactivity syndrome, each present only in 1 subject. The current regular medication as well as the past medication

Table 2.—Correlations Between Additional Symptoms in Patients With "Visual Snow" and Comorbid Migraine and Typical Migraine Aura (Statistics: Chi-Square Test)

	Patients With "Visual Snow" N = 120							
	Migraine				Typical Migraine Aura			
	Yes n = 70	No n = 50	*P*	OR (95% CI)	Yes n = 37	No n = 83	*P*	OR (95% CI)
Palinopsia ("afterimages")	63	38	.04	2.8 (1.0; 7.8)	34	67	.12	—
Palinopsia ("trailing")	47	22	.01	2.6 (1.2; 5.5)	25	44	.14	—
Floaters	60	39	.27	—	30	69	.79	—
Blue field entoptic phenomenon	53	38	.97	—	28	63	.98	—
Self-light of the eye	38	26	.81	—	20	44	.92	—
Spontaneous photopsia	45	19	.004	2.9 (1.4; 6.2)	25	39	.04	2.4 (1.0; 5.3)
Photophobia	57	29	.005	3.2 (1.4; 7.2)	30	56	.13	—
Nyctalopia	51	25	.01	2.7 (1.2; 5.8)	26	50	.29	—
Tinnitus	52	25	.006	2.9 (1.3; 6.2)	27	50	.18	—

—, NA.

trials for VS are shown in Table 3. All subjects stated having normal ophthalmological exams except for some refraction anomalies. The 17 controls had the same age and gender distribution (10 female, 31 ± 7 years). Since history of migraine and typical migraine aura were exclusion criteria for controls, they differed significantly from VS patients in respect of history of migraine ($P < .001$, Fisher's exact test) and history of typical migraine aura ($P = .02$, Fisher's exact test).

The voxel-wise [^{18}F]-FDG PET group comparison evidenced hypermetabolism of the right lingual gyrus (Montreal Neurological Institute coordinates: 16-78-5; cluster size $k_E = 101$; $Z_E = 3.41$; $P < .001$) and a trend for the anterior lobe of the left cerebellum (Montreal Neurological Institute: -12-62-9; $k_E = 152$; $Z_E = 3.28$; $P = .001$) (Figure) in patients with VS when compared with healthy controls after adjusting for the presence of typical migraine aura.

DISCUSSION

"Visual snow" (VS) is a disabling disorder with patients complaining about TV-snow-like tiny flickering dots in the entire visual field. The symptoms can be continuous and might persist over years. In a recent study, almost all patients with VS had additional visual symptoms, such as palinopsia, entoptic phenomena (floaters, blue field entoptic phenomenon, and others), nyctalopia (impaired night vision), photophobia, and tinnitus suggesting that VS is likely a clinical syndrome.[5] In our study population, the majority of patients with VS had comorbid migraine (58%), and 31% had typical migraine aura. This high comorbidity, when compared with the general population,[14] has led to the assumption that VS might represent persistent migraine aura as often discussed in the initial case series,[1-3] although the clinical presentation is clearly different from typical migraine aura.[5]

Here, we sought to understand whether the VS syndrome manifests differently in patients with migraine or typical aura. For that, a cohort of VS patients was carefully phenotyped in respect to the clinical presentation and comorbidities. We found that VS patients, who also have migraine according to International Classification of Headache Disorders – 2nd edition[6] had a significantly higher likelihood of having palinopsia, photophobia, nyctalopia, and tinnitus. Of the entoptic phenomena, ie, visual perceptions arising from the optic apparatus itself,[7] only spontaneous photopsia was more prevalent in VS patients with migraine history, while floaters, blue

Table 3.—Current Regular Medication and Past Treatment Trials for "Visual Snow" in 17 VS Patients Who Took Part in the [18F]-FDG PET Study

	Current Medication	Medication for "Visual Snow"		
		Generic Name	Duration	Effect
1	—	—	—	—
2	—	Sertraline, fluoxetine	6 months	None
3	—	—	—	—
4	Dexlansoprazole, bupropion, zolpidem, topiramate, dicyclomine	—	—	None
5	Methimazole	Fluoxetine, verapamil, lamotrigine	—	None
	—	Sertraline	—	Worsening
6	—	Amitriptyline, propranolol	2 months	None
7	—	—	—	—
8	—	Naproxen	—	Improvement
	—	Sertraline, clonazepam	—	None
9	Throid (porcine), vitamin D, fexofenadine	—	—	None
10	—	—	—	—
11	—	—	—	—
12	—	—	—	—
13	Minocycline	—	—	None
14	—	—	—	—
15	—	—	—	—
16	—	—	—	—
17	—	—	—	—

—, no current medication and/or no medication tried for "visual snow" in the past.

field entoptic phenomenon, and self-light of the eye were equally distributed. Three major conclusions might be drawn from this: First, the presence of migraine might aggravate the manifestation of the VS syndrome by worsening some, but not all additional visual symptoms. Second, our study population was recruited via a self-help group, and it is possible that patients with a more severe clinical manifestation are more eager to participate in a research study. Therefore, a more severe manifestation of the VS syndrome in migraineurs indicates that the high prevalence of migraine in our VS study population might be subject to a selection bias suggesting that the relevance of migraine for VS pathophysiology might be overrated as well. In contrast, the presence of typical migraine aura, ie, the putative correlate of cortical spreading depression[15] that presents with a homonymous, centrifugally moving scintillating scotoma shaped in zigzag lines,[16,17] does not substantially alter the distribution of the additional visual symptoms in the VS syndrome. Typical migraine aura may thus not influence the VS phenotype suggesting that the high prevalence of aura is less subject to selection bias than migraine. Although VS is clearly not persistent migraine aura,[5] typical migraine aura might share some pathophysiological background with the VS syndrome. Third, the impressive entoptic phenomena floaters, blue field entoptic phenomenon, and self-light of the eye are present in VS patients independently of a history of migraine, suggesting that these symptoms are probably not mediated or facilitated by a migrainous mechanism. In contrast, they might depend solely on the presence of VS.

Some of the additional visual symptoms in patients with VS can also be found in migraineurs. This might, at least in part, explain how a migrainous, but not typical migraine aura, comorbidity might potentiate these symptoms in VS patients. For migraineurs without VS, the higher prevalence of palinopsia when compared with healthy controls seems to be of minor relevance since it affects only 14.2% of the group and occurs only episodically.[18]

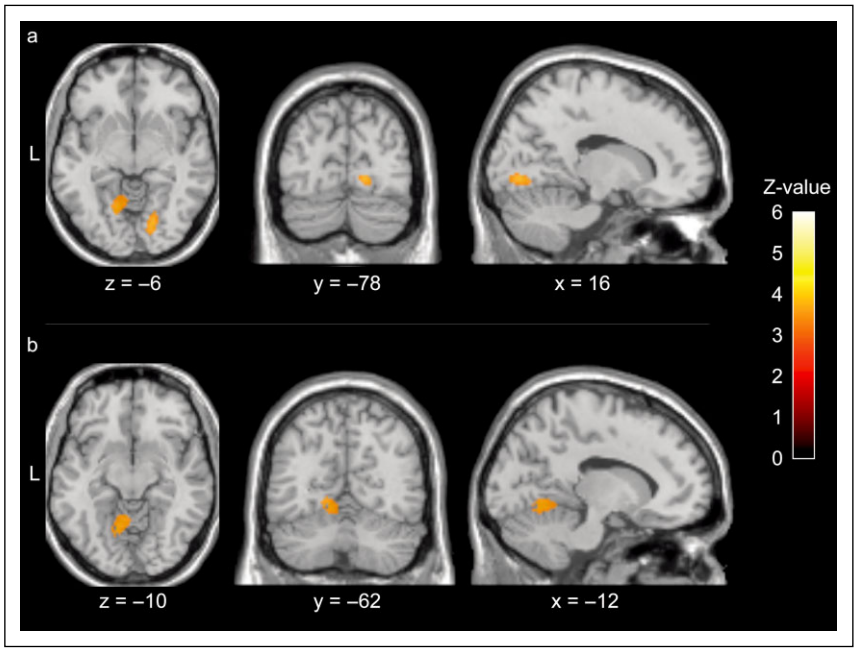

Figure.—When comparing the brain metabolism of patients with "visual snow" to healthy controls in [^{18}F]-FDG PET using a paired *t*-test in SPM8, the right lingual gyrus (in [a]; Montreal Neurological Institute 16-78-5; k_E = 101; Z_E = 3.41; *P* < .001) and the anterior lobe of the left cerebellum (in [b]; Montreal Neurological Institute -12-62-9; k_E = 152; Z_E = 3.28, *P* = .001) were metabolically more active in patients with "visual snow." The figure was thresholded at *P* ≤ .001.

However, this predisposition to palinopsia in migraineurs might perpetuate mechanisms of palinopsia in VS resulting in a higher prevalence and continuous presence.[5] For the key migraine symptom photophobia,[6] recent studies have suggested a pain-mediated increase in light sensitivity.[19] In VS, such mechanism is unlikely due to the low prevalence of chronic headache in patients with *continuous* VS and photophobia.[5] In contrast, photophobia as a symptom of the VS syndrome might be perpetuated by comorbid migraine in a non-pain-mediated manner. This is less clear for tinnitus, which is not a classical migrainous symptom[20] although migraine attack-associated episodes of tinnitus have been reported.[21] Tinnitus could be interpreted as noise within the acoustic system. The similarity to "TV-snow," ie, "TV-noise," has previously led to the interpretation that tinnitus might be the clinical correlate of the affection of the acoustic system by VS-like mechanisms.[5] In our study, tinnitus was also more prevalent in VS patients with comorbid migraine and thus behaved like the additional visual symptoms supporting that the VS syndrome might indeed include the non-visual symptom tinnitus.

In [^{18}F]-FDG PET, the right lingual gyrus and the anterior lobe of the left cerebellum were metabolically more active in patients with VS when compared with healthy controls. This first objective correlate of VS strongly suggests the VS syndrome is a neurological condition. This has important consequences for communication with patients, who have been frequently diagnosed as having a psychogenic disorder or as being malingerers. The relevance of the (trend) hypermetabolism of the left cerebellum is unclear. The cerebellum's key function for vision is extraocular motility.[22] Only little is known about its role in visual perception, but cerebellar disease has been associated with difficulties in depth perception[23] or with a phenomenon called upside-down vision.[24,25] When analyzed visually, this area seems to extend laterally and rostrally to the left lingual gyrus (Figure) possibly reflecting the relatively low spatial resolution of PET. Such bilateral hypermetabolism in the lingual gyrus might be a signature of hyperactivity of the visual system in VS. Interestingly, the same area showed hyperperfusion in [^{15}O]-water PET during high luminous stimulation in migraineurs[26] and during low light stimulation in spontaneous

migraine attacks indicating relevance for the migrainous phenomenon photophobia.[27] To put our finding into a broader neurobiological context, it has to be stated that the lingual gyrus is also involved in visual memory[28] and different higher order functions of vision, such as the perception of color,[29] the identification of facial expressions of emotions,[30] or grapheme-color synesthesia.[31] This broad involvement of the lingual gyrus in visual post-processing including photophobia during migraine attacks indicates that VS might also be a disorder of visual post-processing.

One limitation of the imaging part of the study is the higher prevalence of migraineurs in the VS group in comparison with the control group. This could potentially bias the results by showing an effect from migraine rather than from VS – or by "masking" VS correlates in PET by the presence of migraine in the VS group. To address this issue, future studies with pure VS patients without history of migraine or with migraineurs without VS as controls would be necessary. However, we believe that the hypermetabolism in our patients is VS related and not a migraine effect since not all subjects with VS had a history of migraine and, importantly, several recent studies were not able to show hypermetabolism in *interictal* migraineurs in comparison with controls despite including only migraineurs.[8,9,32] In addition, it is unlikely the metabolism data were biased by the higher number of patients with history of migraine aura in the VS group since only one third of VS patients had comorbid aura. Further, the analysis was adjusted for migraine aura and none of our subjects had experienced an episode of typical migraine aura during the distribution period of the tracer or during the scanning.

CONCLUSION

In a substantial cohort of patients with the "visual snow" (VS) syndrome, migraine is associated with an increased prevalence of the additional symptoms of palinopsia, photopsia, photophobia, nyctalopia, and tinnitus suggesting a more severe phenotype, although not with entoptic phenomena. VS patients with migraine might thus be more interested in participating in studies on VS than patients without migraine, creating a bias of migraine prevalence in such studies and an overestimation of the relevance of migraine for VS pathophysiology. In contrast to migraine, comorbidity of typical migraine aura did not alter the phenotype of the VS syndrome. The high prevalence of typical migraine aura in VS patients therefore is not associated with a worsening of the additional visual symptoms and thus not with an overestimation of aura prevalence in VS. This might indicate a pathophysiological overlap of VS and typical migraine aura despite the distinct clinical presentation. [^{18}F]-FDG PET revealed an objective correlate for VS symptoms. The unique pattern of hypermetabolism in the lingual gyrus in patients with VS has not been shown for *interictal* migraineurs alone. VS is thus a syndrome distinct from migraine, although the hyperperfusion of this area *during* migrainous photophobia indicates a potential pathophysiological overlap of both conditions and possibly reflects the perpetuation of the additional visual symptoms in VS patients by comorbid migraine. Understanding this overlap in more detail will be crucial to develop treatment strategies for this disabling neurological disorder in the future.

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Headache. 2015 Nov-Dec;55(10):1436-41. doi: 10.1111/head.12628. Epub 2015 Aug 26.

Visual Snow in Migraine With Aura: Further Characterization by Brain Imaging, Electrophysiology, and Treatment--Case Report.

Unal-Cevik I[1], Yildiz FG[2].

Author information

Abstract

OBJECTIVE: This study aims to investigate characteristics of visual snow accompanied by migraine and special interest on occipital bending, electrophysiological properties, and response to treatment.

BACKGROUND: Visual snow is characterized by continuous dynamically flickering dots in the visual field. Most patients also have comorbid migraine. Cortical hyperexcitability is a feature of migraine. Recent studies indicate an association between occipital bending with psychiatric disorders such as depression. Here, we demonstrate a patient with visual snow, migraine with aura, left occipital bending, and cortical hyperexcitability. Treatment response to lamotrigine was objectively assessed by repetitive pattern reversal visual evoked potentials (rVEP).

METHODS: A 25-year-old woman with a 10-year history of migraine with aura (2-3 attacks/week) admitted for 1-year history of visual snow. She reported continuous bright and colorful lights, palinopsia, floaters, nyctalopsia, and photopsia. Brain magnetic resonance imaging (MRI) was performed. Visual habituation response was assessed before and after lamotrigine treatment by rVEP.

RESULTS: Brain MRI revealed left occipital bending. On rVEP study, there was potentiation response. After lamotrigine treatment, the patient had no more complaints of visual snow, was able to sleep, and the frequency of migraine decreased to 2 attacks/month. Electrophysiologically, the cortical hyperexcitability was improved.

CONCLUSIONS: The visual snow and loss of habituation ability in migraine associated with occipital bending can be improved with lamotrigine treatment. This report may provide new insights on "visual snow" pathophysiology in migraine.

KEYWORDS: anticonvulsant; cortical excitability; headache; magnetic resonance imaging; occipital bending; repetitive pattern-reversal visual evoked potential

PMID: 26307008 DOI: 10.1111/head.12628

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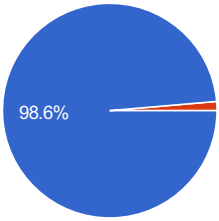
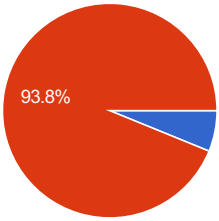
Summary

Do you have visual snow?



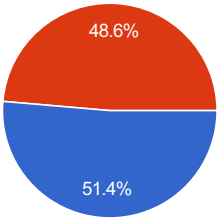
Yes	**288**	98.6%
No	**4**	1.4%

Do you know of anyone in your family with Visual Snow?



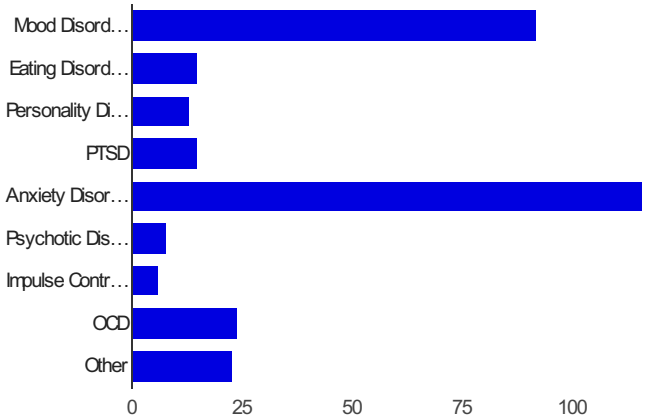
Yes	**18**	6.2%
No	**274**	93.8%

Do you have any known mental issues/disorders



Yes	**150**	51.4%
No	**142**	48.6%

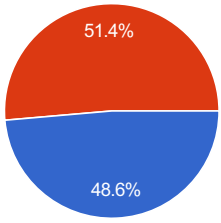
If yes above, please indicate which disorder you may have.



Mood Disorder(depression,Bipolar)	**92**	59%
Eating Disorder(binge eating disorder,bulimia)	**15**	9.6%
Personality Disorder	**13**	8.3%
PTSD	**15**	9.6%
Anxiety Disorder	**116**	74.4%

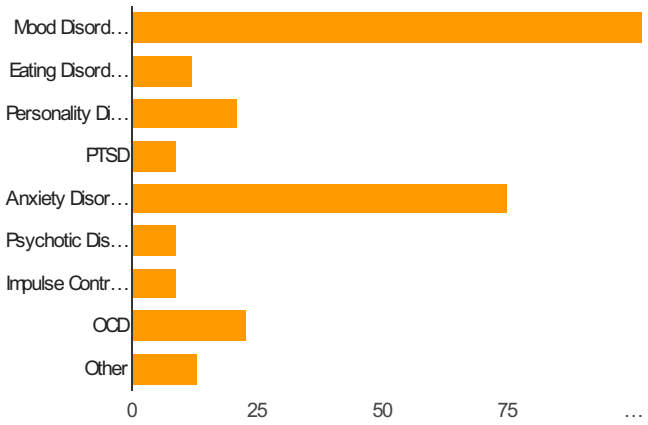
Psychotic Disorder(hallucinations)	**8**	5.1%
Impulse Control Disorder	**6**	3.8%
OCD	**24**	15.4%
Other	**23**	14.7%

Does anyone in your family have a mental disorder?



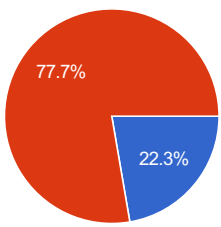
Yes	**141**	48.6%
No	**149**	51.4%

If yes above, please indicate which disorder he/she/they may have.



Mood Disorder(depression,Bipolar)	**102**	73.4%
Eating Disorder(binge eating disorder,bulimia)	**12**	8.6%
Personality Disorder	**21**	15.1%
PTSD	**9**	6.5%
Anxiety Disorder	**75**	54%
Psychotic Disorder(hallucinations)	**9**	6.5%
Impulse Control Disorder	**9**	6.5%
OCD	**23**	16.5%
Other	**13**	9.4%

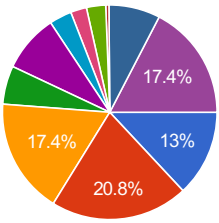
Do you have pulse type visual snow or broadband visual snow?



Pulse Type	**64**	22.3%
Broadband	**223**	77.7%

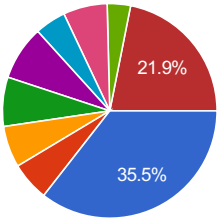
If you have floaters, How many distinct floaters would you say you have in your vision? (If able, please take the time to try to see and count them now)

1	**27**	13%
2	**43**	20.8%
3	**36**	17.4%
4	**12**	5.8%



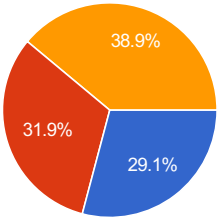
5	**18**	8.7%
6	**7**	3.4%
7	**5**	2.4%
8	**6**	2.9%
9	**1**	0.5%
10	**16**	7.7%
0	**36**	17.4%

How is your vision?



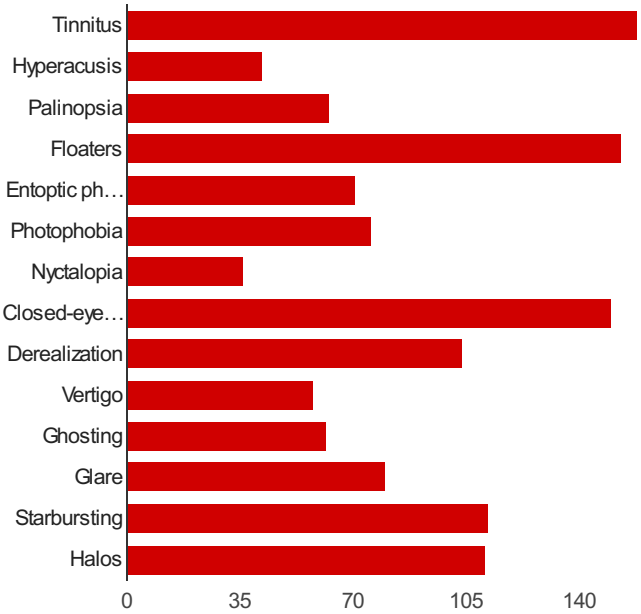
20/20	**91**	35.5%
20/15	**15**	5.9%
20/10	**16**	6.3%
20/25	**19**	7.4%
20/30	**21**	8.2%
20/35	**12**	4.7%
20/40	**17**	6.6%
Better than 20/10	**9**	3.5%
Worse than 20/40	**56**	21.9%

Do you think that the visual snow impairs your visual acuity?



Yes	**83**	29.1%
No	**91**	31.9%
Only at night	**111**	38.9%

Do you have any other symptoms such as the following? Please See http://www.visualsnow.eu/symptoms/ for descriptions.

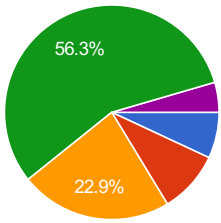


Tinnitus	**158**	60.3%
Hyperacusis	**42**	16%
Palinopsia	**63**	24%
Floaters	**153**	58.4%
Entoptic phenomena	**71**	27.1%
Photophobia	**76**	29%
Nyctalopia	**36**	13.7%
Closed-eye hallucinations	**150**	57.3%
Derealization	**104**	39.7%
Vertigo	**58**	22.1%
Ghosting	**62**	23.7%
Glare	**80**	30.5%
Starbursting	**112**	42.7%
Halos	**111**	42.4%

If you experience migraines, what type of migraine do you experience?

Cluster Headaches	**38**	34.2%
Ocular Migraines	**49**	44.1%

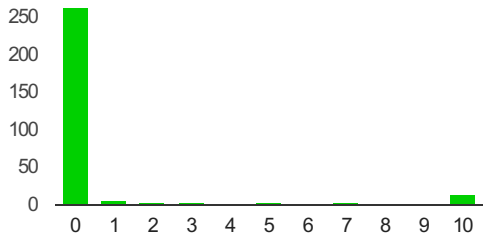
Migraine with Aura	**61**	55%



Tropical (wet, rain forest, monsoon)	**20**	6.9%
Dry (arid)	**27**	9.4%
Mild (Mediterranean, marine)	**66**	22.9%
Continental	**162**	56.3%
Polar	**13**	4.5%

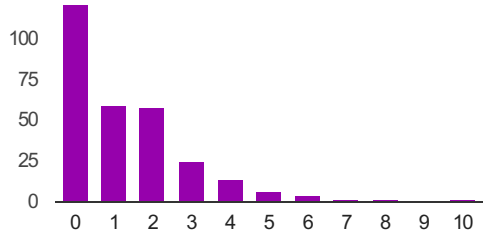
Drug Use

How many cigarettes do you smoke per day?



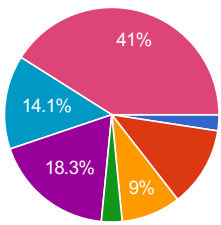
0	**262**	90.3%
1	**5**	1.7%
2	**3**	1%
3	**2**	0.7%
4	**1**	0.3%
5	**2**	0.7%
6	**1**	0.3%
7	**2**	0.7%
8	**0**	0%
9	**0**	0%
10	**12**	4.1%

How many cups of caffeine product do you have per day?



0	**121**	41.7%
1	**59**	20.3%
2	**58**	20%
3	**25**	8.6%
4	**14**	4.8%
5	**6**	2.1%
6	**4**	1.4%
7	**1**	0.3%
8	**1**	0.3%
9	**0**	0%
10	**1**	0.3%

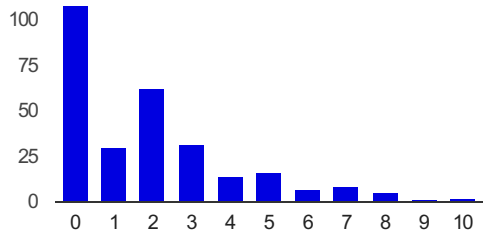
How often do you consume alcohol?



6-7 days a week	**7**	2.4%
1 day a week	**35**	12.1%
2-3 days a week	**26**	9%
4-5 days a week	**9**	3.1%
1 day a month	**53**	18.3%
2 days a month	**41**	14.1%
Never	**119**	41%

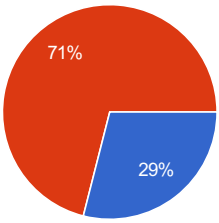
How many drinks of alcohol do you consume when you drink?

0	**108**	37.6%



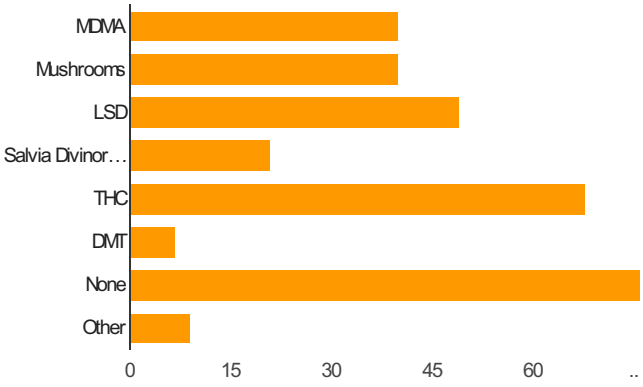
1	**30**	10.5%
2	**62**	21.6%
3	**32**	11.1%
4	**14**	4.9%
5	**17**	5.9%
6	**7**	2.4%
7	**9**	3.1%
8	**5**	1.7%
9	**1**	0.3%
10	**2**	0.7%

Have you ever used psychedelics?



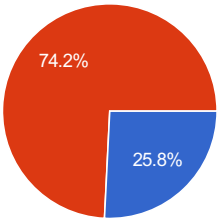
Yes	**84**	29%
No	**206**	71%

What psychedelics have you used?



MDMA	**40**	24.5%
Mushrooms	**40**	24.5%
LSD	**49**	30.1%
Salvia Divinorum	**21**	12.9%
THC	**68**	41.7%
DMT	**7**	4.3%
None	**76**	46.6%
Other	**9**	5.5%

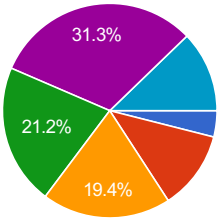
Have you taken an SSRI (Selective serotonin re-uptake inhibitors) drug?



Yes	**74**	25.8%
No	**213**	74.2%

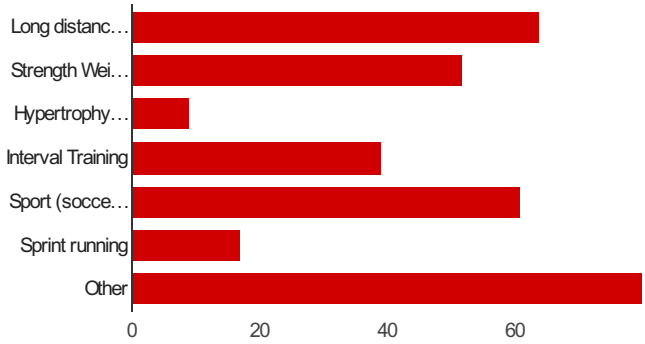
General Health

How often do you exercise?



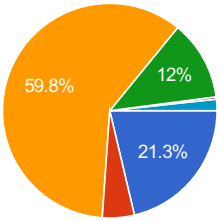
Greater than 6 times a week	**11**	4%
Once a month	**33**	11.9%
Once a week	**54**	19.4%
Never	**59**	21.2%
2-3 times a week	**87**	31.3%
4-5 times a week	**34**	12.2%

What type of exercise do you do?



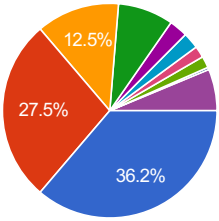
Long distance running	**64**	28.7%
Strength Weightlifting	**52**	23.3%
Hypertrophy Weightlifting	**9**	4%
Interval Training	**39**	17.5%
Sport (soccer, football, hockey, etc.)	**61**	27.4%
Sprint running	**17**	7.6%
Other	**80**	35.9%

How is your BMI?



Overweight	**62**	21.3%
Obese	**14**	4.8%
Healthy	**174**	59.8%
Underweight	**35**	12%
Extremely Obese	**1**	0.3%
Extremely Underweight	**5**	1.7%

How many hours on average do you spend outside per day?



1	**104**	36.2%
2	**79**	27.5%
3	**36**	12.5%
4	**24**	8.4%
5	**8**	2.8%
6	**7**	2.4%
7	**5**	1.7%
8	**5**	1.7%
9	**0**	0%
10+	**1**	0.3%
0	**18**	6.3%

Affecting Visual Snow

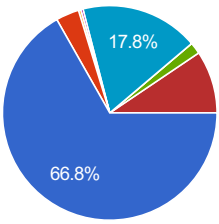
If you have tried anything that has made your visual snow or related symptoms(please indicate which symptoms) better then please write about how here.

No
no
N/A
No.
None
Sleep
Taking a medicine to lower blood pressure seemed to do some help, but probably anxiety related.

How did you get visual snow?

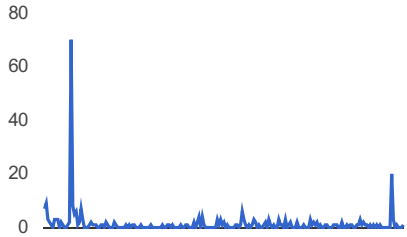
Born with it
Always had it
Birth
I've always had it
Unknown
Always had it.
I've had it as long as I can remember

How did you get visual snow(few options/short answer)?



From Birth	**191**	66.8%
After Psychedelic drug use	**10**	3.5%
Lyme Disease	**1**	0.3%
Auto-immune disease	**0**	0%
Dehydration	**1**	0.3%
Random(suddenly had it)	**51**	17.8%
Brain damage (such as concussion)	**0**	0%
After taking prescription drugs	**5**	1.7%
Other	**27**	9.4%

Number of daily responses



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The Relation Between Migraine, Typical Migraine Aura and "Visual Snow"

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Objective.—To assess the relationship between the phenotype of the "visual snow" syndrome, comorbid migraine, and typical migraine aura on a clinical basis and using functional brain imaging.

Background.—Patients with "visual snow" suffer from continuous TV-static-like tiny flickering dots in the entire visual field. Most patients describe a syndrome with additional visual symptoms of the following categories: palinopsia ("afterimages" and "trailing"), entopic phenomena arising from the optic apparatus itself (floaters, blue field entoptic phenomenon, photopsia, self-light of the eye), photophobia, nyctalopia (impaired night vision), as well as the non-visual symptom tinnitus. The high prevalence of migraine and typical migraine aura in this population has led to the assumption that "visual snow" is caused by persistent migraine aura. Due to the lack of objective measures, alternative diagnoses are malingering or a psychogenic disorder.

Methods.—(1) The prevalence of additional visual symptoms, tinnitus, and comorbid migraine as well as typical migraine aura was assessed in a prospective semi-structured telephone interview of patients with "visual snow." Correlations were calculated using standard statistics with $P < .05$ being considered statistically significant. (2) Areas with increased brain metabolism in a group of "visual snow" patients in comparison to healthy controls were identified using [^{18}F]-2-fluoro-2-deoxy-D-glucose positron emission tomography and statistical parametric mapping (SPM8 with whole brain analysis; statistical significance was defined by $P < .001$ uncorrected for multiple comparisons).

Results.—(1) Of 120 patients with "visual snow," 70 patients also had migraine and 37 had typical migraine aura. Having comorbid migraine was associated with an increased likelihood of having palinopsia (odds ratio [OR] 2.8; $P = .04$ for "afterimages" and OR 2.6; $P = .01$ for "trailing"), spontaneous photopsia (OR 2.9; $P = .004$), photophobia (OR 3.2; $P = .005$), nyctalopia (OR 2.7; $P = .01$), and tinnitus (OR 2.9; $P = .006$). Typical migraine aura was associated with an increased likelihood of spontaneous photopsia (OR 2.4; $P = .04$). (2) After adjusting for typical migraine aura, comparison of 17 "visual snow" patients with 17 age and gender matched controls showed brain hypermetabolism in the right lingual gyrus (Montreal Neurological Institute coordinates 16-78-5; $k_E = 101$; $Z_E = 3.41$; $P < .001$) and the left cerebellar anterior lobe adjacent to the left lingual gyrus (Montreal Neurological Institute coordinates -12-62-9; $k_E = 152$; $Z_E = 3.28$; $P = .001$).

Conclusions.—Comorbid migraine aggravates the clinical phenotype of the "visual snow" syndrome by worsening some of the additional visual symptoms and tinnitus. This might bias studies on "visual snow" by migraineurs offering study participation more likely than non-migraineurs due to a more severe clinical presentation. The independence of entoptic phenomena from comorbid migraine indicates "visual snow" is the main determinant. The hypermetabolic lingual gyrus confirms a brain

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dysfunction in patients with "visual snow." The metabolic pattern differs from interictal migraine with some similarities to migrainous photophobia. The findings support the view that "visual snow," migraine, and typical migraine aura are distinct syndromes with shared pathophysiological mechanisms that need to be addressed in order to develop rational treatment strategies for this disabling condition.

Key words: visual snow, migraine, aura, [18F]-2-fluoro-2-deoxy-D-glucose positron emission tomography

Abbreviations: OR odds ratio, VS visual snow, [18F]-FDG PET [18F]-2-fluoro-2-deoxy-D-glucose positron emission tomography

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Patients with "visual snow" (VS) describe a visual disturbance that consists of tiny dynamically flickering dots in the entire visual field resembling the "static" or "snow" of a badly tuned analogue television. The symptoms are continuous and can persist over years. Persistent visual disturbance is mentioned sporadically in the literature without larger systematic studies.[1-3] Patients are often diagnosed as having persistent migraine aura, malingering, or psychogenic disorder because objective measures for the condition are not available to date. A recent study of a substantial cohort of subjects with VS confirmed that the visual disturbance is often associated with migraine and migraine aura. However, not every patient with VS has a history of migraine. Further, VS starts only rarely with migraine aura, and the phenotypical description as well as the clinical course of VS by no means resembles typical migraine aura, which is in general homonymous, often presents with moving zigzag lines, and typically lasts less than 60 minutes. This suggests that VS is a unique condition different from migraine aura.[4-6] Importantly, VS should be seen as a syndrome since it is almost always associated with additional visual complaints including palinopsia, entoptic phenomena that arise from the optic apparatus itself (ie, floaters, blue field entoptic phenomenon, self-light of the eye and photopsia),[7] poor night vision (nyctalopia), and photophobia. A large proportion of VS patients has bilateral continuous tinnitus.[5]

To investigate the role of migraine and typical migraine aura mechanisms underlying VS, we sought to assess whether the presence of migraine or aura is associated with different phenotype of the *VS syndrome*. We prospectively recorded accompanying visual and auditory symptoms in a large cohort of

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patients with VS and correlated these symptoms with comorbid migraine and typical migraine aura. To assess potential pathophysiological correlates, we further studied brain metabolism in patients with the hypothesis that VS is associated with regional hypermetabolism distinct from previous findings in migraine.[8,9]

Clinical data of a subgroup of the study population have been previously presented in a report on the detailed phenotype[5] and in preliminary form.[10,11]

SUBJECTS AND METHODS

The study was approved by the Institutional Review Board (# 11-07270 and # 11-07431) and the radiation safety committee (58605-RU-04-URH) of the University of California, San Francisco. Patients were recruited via advertisements in social media with the support of a self-help group on VS (Eye on Vision Foundation; http://www.eyeonvision.org/). After being contacted by the patient, eligibility was assessed during telephone interviews.

Clinical Data.—*Telephone Interview*.—After being approached by the patient, verbal consent was obtained and subjects with self-suspected VS underwent a semi-structured telephone interview. The following items were covered during the interview:

1. Demographics (age, gender) and handedness.
2. Patients were asked to describe their current visual symptoms in their own words. Based on that information and additional open questions, a diagnosis of VS was made and associated visual symptoms were recorded as described recently.[10] In brief, VS was defined as dynamic, continuous, tiny dots in the entire visual field (similar to "TV static" or "TV snow") lasting longer than 3 months (criterion A).[5] Other symptoms were palinopsia ("afterimages" and "trailing" of moving objects), entopic phenomena (phenomena arising from the structure of the visual system itself including (1) excessive floaters in both eyes; (2) excessive blue field entoptic phenomenon, ie, uncountable little gray/white/black dots or rings shooting over the visual field in both eyes when looking at homogeneous bright surfaces, such as the blue sky; (3) self-light of the eye, ie, colored waves or clouds when closing the eyes in the dark; and (4) spontaneous photopsia, ie, bright flashes of light),[7] photophobia, and nyctalopia (impaired night vision). Due to its high prevalence in subjects with VS,[5] the presence or history of tinnitus was also covered during the interview despite being a non-visual symptom.
3. Headache history was assessed according to the International Classification of Headache Disorders – 2nd edition.[6] Migraine aura was only diagnosed when typical features were present, which are unilaterality (homonymous), development over 5 minutes, duration for less than 60 minutes, reversibility, zigzag lines, and scotoma.[4,6]

Data Analysis.—SPSS (v20, IBM Corp., Armonk, NY, USA) was used for the statistical analysis of the clinical data. Standard descriptive statistics were applied. If appropriate, data are presented as mean ± standard deviation. Nominal data were compared using chi-square or Fisher's exact test, ratio data using *t*-test. Statistical significance was defined as $P < .05$.

Functional Brain Imaging.—All subjects participating in the positron emission tomography (PET) study gave written informed consent. Inclusion criterion was VS with at least 2 additional visual symptoms as defined previously.[5] Control subjects did not have VS, associated visual symptoms, tinnitus, a history of frequent migraine attacks (more than 1 every 2 months), or of migraine aura. Exclusion criteria for both groups were ophthalmological pathology other than refraction anomalies, any lifetime history of intake of hallucinogenic drugs, and pregnancy in women. Each subject underwent a detailed personal interview with a focus on visual symptoms, migraine history including typical aura and general past medical history. On the scanning day, each subject had a fasting period of at least 6 hours prior to the acquisition of a high-resolution T1-weighted anatomical MR image (MPRAGE sequence) on a General Electric Signa HDxT 3.0 Tesla scanner (GE Healthcare, Fairfield, CT, USA). Afterwards, a [^{18}F]-2-fluoro-2-deoxy-D-glucose PET ([^{18}F]-FDG PET) scan was acquired using standard parameters, with injection of 10 mCi via an antecubital vein and 45 minutes distribution period in a dark room with eyes closed, on a

GE Discovery VCT PET/CT scanner (GE Healthcare) in three-dimensional (3D) mode with septa retracted. Images were reconstructed by 3D iterative reconstruction into 47 image planes (separation 3.27 mm) and into a 128 by 128 image matrix (pixel size: 2.1×2.1 mm^2). The structural magnetic resonance imaging (MRI) was coregistered to the PET using SPM8 (Wellcome Department of Imaging Neuroscience, http://www.fil.ion.ucl.ac.uk/spm). The coregistered MRI was automatically segmented into gray matter, white matter, and cerebrospinal fluid and normalized into standard stereotaxic space. The spatial normalization parameters from this step were applied to spatially normalize the PET image. Final voxel size was $2 \times 2 \times 2$ mm^3. PET images were then smoothed with a Gaussian Kernel of 12 mm full-width at half maximum. The group of VS patients was compared with controls using a 2-sample *t*-test with masking of non-brain tissue (whole brain explicit mask generated with WFU PickAtlas from Advanced Neuroscience Imaging Research Laboratory, Department of Radiology of Wake Forest University School of Medicine, http://fmri.wfubmc.edu/), and using proportional scaling. Due to the high prevalence of typical migraine aura in patients with VS,[11] the presence of migraine aura was used as a covariate of no interest. According to the clinical manifestation of VS, we suspected hypermetabolism in VS patients. We therefore assessed brain areas with *increased* metabolism in VS patients compared with controls in a voxel-wise fashion. In line with previous studies on migraine,[12,13] we considered voxels reaching a significance threshold of $P < .001$ uncorrected for multiple comparisons to be significant.

RESULTS

Clinical Data.—Of the 142 patients who contacted the Headache Center at the University of California, San Francisco, 120 subjects (mean age 31 ± 12 years; 62 female) met criterion A for "visual snow,"[5] ie, presence of dynamic, continuous, tiny dots in the entire visual field lasting longer than 3 months.

Additional Visual Symptoms.—Palinopsia with "afterimages" from stationary scenes was present in 84%, and with "trailing" in 58%. Excessive floaters were the most common entoptic phenomenon with a prevalence of 83%. Second most common was the blue field entoptic phenomenon (76%). Spontaneous photopsia and consistent self-light of the eye occurred in half of patients. About two thirds of patients had photophobia and nyctalopia. In addition to these visual symptoms, 64% of patients noted continuous bilateral and mainly high-pitched tinnitus (Table 1).

Table 1.—Additional Symptoms in Patients With "Visual Snow"

	All Visual Snow Patients N = 120	
Palinopsia ("afterimages")	101	84%
Palinopsia ("trailing")	69	58%
Floaters	99	83%
Blue field entoptic phenomenon	91	76%
Self-light of the eye	64	53%
Spontaneous photopsia	64	53%
Photophobia	86	72%
Nyctalopia	76	63%
Tinnitus	77	64%

Association of Additional Symptoms With Migraine and Typical Migraine Aura.—The presence of migraine was associated with an increased prevalence of the additional symptoms palinopsia (odds ratio [OR] 2.8 for "afterimages" and OR 2.6 for "trailing"), spontaneous photopsia (OR 2.9), photophobia (OR 3.2), nyctalopia (OR 2.7), and tinnitus (OR 2.9). Spontaneous photopsia was more prevalent in patients with typical migraine aura (OR 2.4, Table 2).

Functional Brain Imaging.—Seventeen patients (10 female, mean age ± standard deviation 31 ± 7 years) with VS and at least 2 additional visual symptoms were recruited for the imaging study. Seven had VS as long as they could remember. Mean age of onset in the remaining was 25 ± 8 years. Fourteen (82%) had a history of migraine. Five of those had migraine with typical aura, and 1 had typical migraine aura without history of migraine.[6] All 3 patients without history of migraine had a positive family history of migraine. Besides headache, past medical history included depression, Graves' disease, hypothyroidism, acne, and attention deficit hyperactivity syndrome, each present only in 1 subject. The current regular medication as well as the past medication

Table 2.—Correlations Between Additional Symptoms in Patients With "Visual Snow" and Comorbid Migraine and Typical Migraine Aura (Statistics: Chi-Square Test)

	Patients With "Visual Snow" N = 120							
	Migraine				Typical Migraine Aura			
	Yes n = 70	No n = 50	*P*	OR (95% CI)	Yes n = 37	No n = 83	*P*	OR (95% CI)
Palinopsia ("afterimages")	63	38	.04	2.8 (1.0; 7.8)	34	67	.12	—
Palinopsia ("trailing")	47	22	.01	2.6 (1.2; 5.5)	25	44	.14	—
Floaters	60	39	.27	—	30	69	.79	—
Blue field entoptic phenomenon	53	38	.97	—	28	63	.98	—
Self-light of the eye	38	26	.81	—	20	44	.92	—
Spontaneous photopsia	45	19	.004	2.9 (1.4; 6.2)	25	39	.04	2.4 (1.0; 5.3)
Photophobia	57	29	.005	3.2 (1.4; 7.2)	30	56	.13	—
Nyctalopia	51	25	.01	2.7 (1.2; 5.8)	26	50	.29	—
Tinnitus	52	25	.006	2.9 (1.3; 6.2)	27	50	.18	—

—, NA.

trials for VS are shown in Table 3. All subjects stated having normal ophthalmological exams except for some refraction anomalies. The 17 controls had the same age and gender distribution (10 female, 31 ± 7 years). Since history of migraine and typical migraine aura were exclusion criteria for controls, they differed significantly from VS patients in respect of history of migraine ($P < .001$, Fisher's exact test) and history of typical migraine aura ($P = .02$, Fisher's exact test).

The voxel-wise [^{18}F]-FDG PET group comparison evidenced hypermetabolism of the right lingual gyrus (Montreal Neurological Institute coordinates: 16-78-5; cluster size $k_E = 101$; $Z_E = 3.41$; $P < .001$) and a trend for the anterior lobe of the left cerebellum (Montreal Neurological Institute: -12-62-9; $k_E = 152$; $Z_E = 3.28$; $P = .001$) (Figure) in patients with VS when compared with healthy controls after adjusting for the presence of typical migraine aura.

DISCUSSION

"Visual snow" (VS) is a disabling disorder with patients complaining about TV-snow-like tiny flickering dots in the entire visual field. The symptoms can be continuous and might persist over years. In a recent study, almost all patients with VS had additional visual symptoms, such as palinopsia, entoptic phenomena (floaters, blue field entoptic phenomenon, and others), nyctalopia (impaired night vision), photophobia, and tinnitus suggesting that VS is likely a clinical syndrome.[5] In our study population, the majority of patients with VS had comorbid migraine (58%), and 31% had typical migraine aura. This high comorbidity, when compared with the general population,[14] has led to the assumption that VS might represent persistent migraine aura as often discussed in the initial case series,[1-3] although the clinical presentation is clearly different from typical migraine aura.[5]

Here, we sought to understand whether the VS syndrome manifests differently in patients with migraine or typical aura. For that, a cohort of VS patients was carefully phenotyped in respect to the clinical presentation and comorbidities. We found that VS patients, who also have migraine according to International Classification of Headache Disorders – 2nd edition[6] had a significantly higher likelihood of having palinopsia, photophobia, nyctalopia, and tinnitus. Of the entoptic phenomena, ie, visual perceptions arising from the optic apparatus itself,[7] only spontaneous photopsia was more prevalent in VS patients with migraine history, while floaters, blue

Table 3.—Current Regular Medication and Past Treatment Trials for "Visual Snow" in 17 VS Patients Who Took Part in the [18F]-FDG PET Study

	Current Medication	Medication for "Visual Snow"		
		Generic Name	Duration	Effect
1	—	—	—	—
2	—	Sertraline, fluoxetine	6 months	None
3	—	—	—	—
4	Dexlansoprazole, bupropion, zolpidem, topiramate, dicyclomine	—	—	None
5	Methimazole	Fluoxetine, verapamil, lamotrigine	—	None
	—	Sertraline	—	Worsening
6	—	Amitriptyline, propranolol	2 months	None
7	—	—	—	—
8	—	Naproxen	—	Improvement
	—	Sertraline, clonazepam	—	None
9	Throid (porcine), vitamin D, fexofenadine	—	—	None
10	—	—	—	—
11	—	—	—	—
12	—	—	—	—
13	Minocycline	—	—	None
14	—	—	—	—
15	—	—	—	—
16	—	—	—	—
17	—	—	—	—

—, no current medication and/or no medication tried for "visual snow" in the past.

field entoptic phenomenon, and self-light of the eye were equally distributed. Three major conclusions might be drawn from this: First, the presence of migraine might aggravate the manifestation of the VS syndrome by worsening some, but not all additional visual symptoms. Second, our study population was recruited via a self-help group, and it is possible that patients with a more severe clinical manifestation are more eager to participate in a research study. Therefore, a more severe manifestation of the VS syndrome in migraineurs indicates that the high prevalence of migraine in our VS study population might be subject to a selection bias suggesting that the relevance of migraine for VS pathophysiology might be overrated as well. In contrast, the presence of typical migraine aura, ie, the putative correlate of cortical spreading depression[15] that presents with a homonymous, centrifugally moving scintillating scotoma shaped in zigzag lines,[16,17] does not substantially alter the distribution of the additional visual symptoms in the VS syndrome. Typical migraine aura may thus not influence the VS phenotype suggesting that the high prevalence of aura is less subject to selection bias than migraine. Although VS is clearly not persistent migraine aura,[5] typical migraine aura might share some pathophysiological background with the VS syndrome. Third, the impressive entoptic phenomena floaters, blue field entoptic phenomenon, and self-light of the eye are present in VS patients independently of a history of migraine, suggesting that these symptoms are probably not mediated or facilitated by a migrainous mechanism. In contrast, they might depend solely on the presence of VS.

Some of the additional visual symptoms in patients with VS can also be found in migraineurs. This might, at least in part, explain how a migrainous, but not typical migraine aura, comorbidity might potentiate these symptoms in VS patients. For migraineurs without VS, the higher prevalence of palinopsia when compared with healthy controls seems to be of minor relevance since it affects only 14.2% of the group and occurs only episodically.[18]

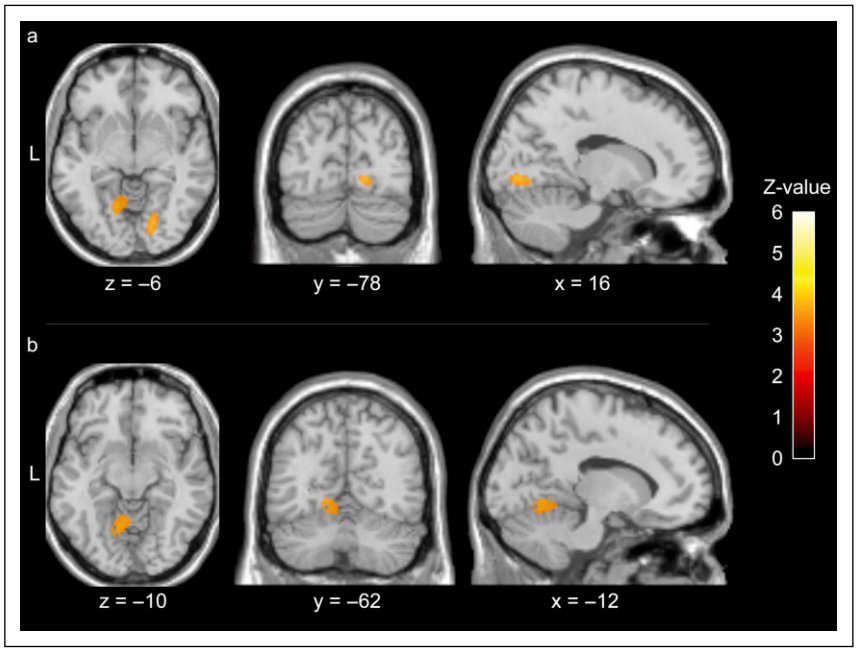

Figure.—When comparing the brain metabolism of patients with "visual snow" to healthy controls in [^{18}F]-FDG PET using a paired *t*-test in SPM8, the right lingual gyrus (in [a]; Montreal Neurological Institute 16-78-5; k_E = 101; Z_E = 3.41; *P* < .001) and the anterior lobe of the left cerebellum (in [b]; Montreal Neurological Institute -12-62-9; k_E = 152; Z_E = 3.28, *P* = .001) were metabolically more active in patients with "visual snow." The figure was thresholded at *P* ≤ .001.

However, this predisposition to palinopsia in migraineurs might perpetuate mechanisms of palinopsia in VS resulting in a higher prevalence and continuous presence.[5] For the key migraine symptom photophobia,[6] recent studies have suggested a pain-mediated increase in light sensitivity.[19] In VS, such mechanism is unlikely due to the low prevalence of chronic headache in patients with *continuous* VS and photophobia.[5] In contrast, photophobia as a symptom of the VS syndrome might be perpetuated by comorbid migraine in a non-pain-mediated manner. This is less clear for tinnitus, which is not a classical migrainous symptom[20] although migraine attack-associated episodes of tinnitus have been reported.[21] Tinnitus could be interpreted as noise within the acoustic system. The similarity to "TV-snow," ie, "TV-noise," has previously led to the interpretation that tinnitus might be the clinical correlate of the affection of the acoustic system by VS-like mechanisms.[5] In our study, tinnitus was also more prevalent in VS patients with comorbid migraine and thus behaved like the additional visual symptoms supporting that the VS syndrome might indeed include the non-visual symptom tinnitus.

In [^{18}F]-FDG PET, the right lingual gyrus and the anterior lobe of the left cerebellum were metabolically more active in patients with VS when compared with healthy controls. This first objective correlate of VS strongly suggests the VS syndrome is a neurological condition. This has important consequences for communication with patients, who have been frequently diagnosed as having a psychogenic disorder or as being malingerers. The relevance of the (trend) hypermetabolism of the left cerebellum is unclear. The cerebellum's key function for vision is extraocular motility.[22] Only little is known about its role in visual perception, but cerebellar disease has been associated with difficulties in depth perception[23] or with a phenomenon called upside-down vision.[24,25] When analyzed visually, this area seems to extend laterally and rostrally to the left lingual gyrus (Figure) possibly reflecting the relatively low spatial resolution of PET. Such bilateral hypermetabolism in the lingual gyrus might be a signature of hyperactivity of the visual system in VS. Interestingly, the same area showed hyperperfusion in [^{15}O]-water PET during high luminous stimulation in migraineurs[26] and during low light stimulation in spontaneous

migraine attacks indicating relevance for the migrainous phenomenon photophobia.[27] To put our finding into a broader neurobiological context, it has to be stated that the lingual gyrus is also involved in visual memory[28] and different higher order functions of vision, such as the perception of color,[29] the identification of facial expressions of emotions,[30] or grapheme-color synesthesia.[31] This broad involvement of the lingual gyrus in visual post-processing including photophobia during migraine attacks indicates that VS might also be a disorder of visual post-processing.

One limitation of the imaging part of the study is the higher prevalence of migraineurs in the VS group in comparison with the control group. This could potentially bias the results by showing an effect from migraine rather than from VS – or by "masking" VS correlates in PET by the presence of migraine in the VS group. To address this issue, future studies with pure VS patients without history of migraine or with migraineurs without VS as controls would be necessary. However, we believe that the hypermetabolism in our patients is VS related and not a migraine effect since not all subjects with VS had a history of migraine and, importantly, several recent studies were not able to show hypermetabolism in *interictal* migraineurs in comparison with controls despite including only migraineurs.[8,9,32] In addition, it is unlikely the metabolism data were biased by the higher number of patients with history of migraine aura in the VS group since only one third of VS patients had comorbid aura. Further, the analysis was adjusted for migraine aura and none of our subjects had experienced an episode of typical migraine aura during the distribution period of the tracer or during the scanning.

CONCLUSION

In a substantial cohort of patients with the "visual snow" (VS) syndrome, migraine is associated with an increased prevalence of the additional symptoms of palinopsia, photopsia, photophobia, nyctalopia, and tinnitus suggesting a more severe phenotype, although not with entoptic phenomena. VS patients with migraine might thus be more interested in participating in studies on VS than patients without migraine, creating a bias of migraine prevalence in such studies and an overestimation of the relevance of migraine for VS pathophysiology. In contrast to migraine, comorbidity of typical migraine aura did not alter the phenotype of the VS syndrome. The high prevalence of typical migraine aura in VS patients therefore is not associated with a worsening of the additional visual symptoms and thus not with an overestimation of aura prevalence in VS. This might indicate a pathophysiological overlap of VS and typical migraine aura despite the distinct clinical presentation. [^{18}F]-FDG PET revealed an objective correlate for VS symptoms. The unique pattern of hypermetabolism in the lingual gyrus in patients with VS has not been shown for *interictal* migraineurs alone. VS is thus a syndrome distinct from migraine, although the hyperperfusion of this area *during* migrainous photophobia indicates a potential pathophysiological overlap of both conditions and possibly reflects the perpetuation of the additional visual symptoms in VS patients by comorbid migraine. Understanding this overlap in more detail will be crucial to develop treatment strategies for this disabling neurological disorder in the future.

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'Visual snow' – a disorder distinct from persistent migraine aura

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Patients with 'visual snow' report continuous tiny dots in the entire visual field similar to the noise of an analogue television. As they frequently have migraine as a comorbidity with ophthalmological, neurological and radiological studies being normal, they are offered various diagnoses, including persistent migraine aura, post-hallucinogen flashback, or psychogenic disorder. Our aim was to study patients with 'visual snow' to characterize the phenotype. A three-step approach was followed: (i) a chart review of patients referred to us identified 22 patients with 'visual snow'. Fifteen had additional visual symptoms, and 20 patients had comorbid migraine, five with aura; (ii) to identify systematically additional visual symptoms, an internet survey ($n = 275$) of self-assessed 'visual snow' subjects done by Eye On Vision Foundation was analysed. In two random samples from 235 complete data sets, the same eight additional visual symptoms were present in $>33\%$ of patients: palinopsia (trailing and afterimages), entoptic phenomena (floaters, blue field entoptic phenomenon, spontaneous photopsia, self-light of the eye), photophobia, and nyctalopia (impaired night vision); and (iii) a prospective semi-structured telephone interview in a further 142 patients identified 78 (41 female) with confirmed 'visual snow' and normal ophthalmological exams. Of these, 72 had at least three of the additional visual symptoms from step (ii). One-quarter of patients had 'visual snow' as long as they could remember, whereas for the others the mean age of onset was 21 ± 9 years. Thirty-two patients had constant visual symptoms, whereas the remainder experienced either progressive or stepwise worsening. Headache was the most frequent symptom associated with the beginning or a worsening of the visual disturbance (36%), whereas migraine aura (seven patients) and consumption of illicit drugs (five, no hallucinogens) were rare. Migraine (59%), migraine with aura (27%), anxiety and depression were common comorbidities over time. Eight patients had first degree relatives with visual snow. Clinical investigations were not contributory. Only a few treatment trials have been successful in individual patients. Our data suggest that 'visual snow' is a unique visual disturbance clinically distinct from migraine aura that can be disabling for patients. Migraine is a common concomitant although standard migraine treatments are often unhelpful. 'Visual snow' should be considered a distinct disorder and systematic studies of its clinical features, biology and treatment responses need to be commenced to begin to understand what has been an almost completely ignored problem.

Keywords: visual snow; persistent migraine aura; flashback; migraine; positive persistent visual disturbance
Abbreviation: ICHD = International Classification of Headache Disorders

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Introduction

Patients with so-called 'visual snow' describe a persistent disturbance in the entire visual field resembling the 'static' or 'snow' of a badly-tuned analogue television. The symptoms are continuous and can persist over years. Although many primary care providers, ophthalmologists, neuro-ophthalmologists and neurologists have seen patients with such complaints, the problem remains undefined. Persistent visual disturbance is discussed infrequently in the literature (Haas, 1982; Liu *et al.*, 1995; Rothrock, 1997; Chen *et al.*, 2001; Jager *et al.*, 2005; Relja *et al.*, 2005; San-Juan and Zermeno, 2007; Wang *et al.*, 2008; Belvis *et al.*, 2010); some patients described have a disturbance more like migraine aura than visual snow, and others are not so clear. In these reports, patients frequently have comorbid migraine with or without aura leading to the assumption of visual snow being a migraine- or aura-related condition.

The exposure to hallucinogenic drugs, such as lysergic acid diethylamide (LSD), can result in post-hallucinogen perceptual disorder (PHPD) or 'flashbacks', which can last years (Abraham and Aldridge, 1993). As patients with visual snow also have continuous visual disturbances, they have been regarded by some as having post-hallucinogen perceptual disorder. Current explanations for visual snow seem inadequate, and current descriptions have not captured the detail of the clinical picture. Moreover, the presence of this disturbance in children and its remarkably stereotypic phenotype, which seems clearly distinct from migraine aura (Jager *et al.*, 2005), suggest the problem should be defined to allow its proper study.

The aim of our work was to characterize clinically patients with visual snow. We present criteria for the syndrome and discuss possible pathophysiological mechanisms. The description should enable studies leading to a better understanding of the disorder and treatment options for individuals affected by this disabling problem. The data have been presented in preliminary form to the 64th Meeting of the American Academy of Neurology (Schankin *et al.*, 2012*a*) and the 54th Meeting of the American Headache Society (Schankin *et al.*, 2012*b*).

Patients and methods

This is a three-step study starting with patients with visual snow who presented to us for diagnosis and management. In a second step, visual symptoms were retrospectively mapped by using data from an internet-based survey. Finally, prospective personal interviews were used to confirm the diagnosis and prevalence of these additional symptoms, to describe the clinical course and to assess the relevance of migraine, migraine aura, and drug use.

Retrospective chart review

We identified patients with visual snow by searching available outpatient clinic letters at the National Hospital for Neurology and Neurosurgery (NHNN, London, UK) as an audit of practice (P.J.G.) and the UCSF Headache Centre from 2001 to 2011. Keywords were either 'visual snow' or 'primary persistent visual disturbance' (Jager *et al.*, 2005). All patients had been seen by at least one of the authors (P.J.G.).

A standardized approach was followed. The diagnosis of visual snow was confirmed when the description in the notes corresponded to the most specific currently available literature [Patients 6–9 from Liu *et al.* (1995), Patient 1 from Jager *et al.* (2005), and Patients 1 and 2 from Wang *et al.* (2008)] requiring a visual disturbance of 'tiny dynamic or flickering dots in the entire visual field like an analogue television that has not been tuned properly' or similar. Demographics, age of onset, relation to headache, additional visual symptoms, and past investigations were collected only in cases with a clear diagnosis of visual snow.

Retrospective identification of additional visual symptoms

Study population

We next analysed data sets without personal identifiers provided by the self-help group for visual snow, Eye On Vision Foundation (http://www.eyeonvision.org/). Independently from ourselves, Eye On Vision had performed an internet-based survey between June and October 2010. The survey was announced on their website and patients with self-assessed visual snow could participate. The questions in the survey were defined by the Eye On Vision Foundation and were based on their experience with visual snow. The following items had been interrogated: age (categorized as 13–23, 24–34, 35–45, 46–56, 57–67, older than 68 years), age at onset and duration of visual snow (both in years), and gender. The survey asked for the presence of visual snow, which was not specifically defined. The additional visual symptoms were phrased in lay language and consisted of (i) moving objects leave 'trails'; (ii) prolonged after images; (iii) floaters (physical spots or strands in your vision); (iv) bright flashes occur briefly, then fade; (v) dark spots occur briefly, then fade; (vi) little cells that travel on a wiggly path; (vii) hard time seeing at night; (viii) waves or swirls during daylight hours; (ix) swirls, clouds or waves with eyes closed; (x) photophobia (light sensitivity); (xi) colour vision changes; (xii) vision seems to be 'dim'; and (xiii) astigmatism.

Data analysis

Only complete data sets with the presence of visual snow were analysed. To control for outliers and other inhomogeneities, a random 50% sample (Group A) was drawn to identify additional candidate symptoms. In a second step, these candidate symptoms were confirmed in the remaining 50% (Group B). To obtain a reasonable number of meaningful additional visual symptoms in patients with visual snow, we arbitrarily used a cut-off frequency of 33% in both groups. As the absolute age of the participants was not reflected in the age categories, the mean age of each category was chosen (i.e. 18, 29, 40, 51, 62, and 73 years) for the calculation of demographic parameters.

Prospective clinical characterization

Study population

The study was listed on social media sites for visual snow asking for subjects with self-assessed visual snow to contact us. No additional information was given in these announcements. Patients were included from November 2011 to March 2012. A semi-structured telephone interview was performed after obtaining verbal consent from the patient. After the interview, patients were asked to keep the content of the interview to themselves to avoid influencing potential future study

subjects. The study was approved by the Institutional Review Board of the University of California, San Francisco (# 11-07270).

Telephone interview

In addition to age in years and gender, the interview covered:

(i) Current visual symptoms in the patient's own words. No clues were given by the interviewers to reduce the risk of suggestion.
(ii) Based on that information, a checklist on visual symptoms was completed by the interviewer. If necessary, additional open questions were asked to enable a decision on the presence and absence of the 'additional candidate symptoms' derived from the retrospective survey. These were defined by translation into the most likely underlying medical term as shown in Supplementary Table 1. Some of the visual symptoms (floaters, blue field entoptic phenomenon, self-light of the eye) are noted under specific conditions by normal individuals. These were only counted as an additional symptom if the patient stated that they were either present during everyday conditions or when they started together with visual snow. Photophobia was defined as normal light being either too bright or painful. If present, patients should further state which visual symptom was responsible for nyctalopia (impaired night vision). Typical features of visual migraine aura: unilaterality (homonymous), development over 5 min, duration, reversibility, zigzag lines, and scotoma (Headache Classification Committee of The International Headache Society, 2004; Eriksen *et al.*, 2005), were probed for specifically.
(iii) Non-visual symptoms were noted.
(iv) Patients were asked about the beginning of their visual symptoms: age of onset of visual snow, continuous or episodic visual snow, progressive or stepwise worsening of all visual symptoms, worsening over how many years, duration of symptoms at current level.
(v) Patients who recalled the beginning of the visual snow or who had stepwise worsening were asked to describe further whether they had (a) headache attacks 3 days before or after; or (b) intake of illicit drugs [cannabis, ecstasy, cocaine, lysergic acid diethylamide (LSD), amphetamines, hallucinogenic mushrooms, and others] 7 days before the beginning/worsening of the visual symptoms. Headache was diagnosed according to the International Classification of Headache Disorders – 2nd edition (ICHD-II; Headache Classification Committee of The International Headache Society, 2004).
(vi) Headache history was assessed according to ICHD-II. Family history was noted.
(vii) Past medical history: as anxiety and depression were mentioned voluntarily by a substantial number of patients, all patients were contacted again and asked to complete Patient Health Questionnaire (PHQ)-8 to assess for depression (Kroenke *et al.*, 2009) and Generalized Anxiety Disorder (GAD-7; Lowe *et al.*, 2008) for anxiety. Current and past medication were noted, as well as a family history for visual snow.
(viii) We assessed the results of examination by a neurologist and ophthalmologist (dilated fundus exam, visual acuity, visual fields), electroretinogram, visual evoked potentials, MRI, electroencephalogram, and laboratory tests. No new tests were ordered solely for the study.
(ix) Patients were further asked to provide reports of their ophthalmology exams and to illustrate their visual symptoms. A selection is presented in Fig. 1 (with permission from the patients).

Data analysis

Only data sets of patients who met the following criteria were analysed to achieve a homogeneous study group: (i) spontaneous description (without clues) of visual snow as defined above for the retrospective chart review (Liu *et al.*, 1995; Jager *et al.*, 2005; Wang *et al.*, 2008), regardless of the colour of the dots reported; and (ii) absence of any ophthalmological pathology in fundoscopy and perimetry assessed by an ophthalmologist or neuro-ophthalmologist.

Statistics

SPSS (v20, IBM Corp.) was used for data analysis. Standard descriptive statistics were applied. If appropriate, data are presented as mean ± standard deviation (SD).

Results

Retrospective chart review

The letters of 38 patients were identified. Sixteen were excluded because of incomplete description of visual snow. The remaining 22 (mean age ± SD: 27 ± 9 years, range 13–45 years, 12 female) are reported.

Fifteen patients had visual symptoms in addition to visual snow with continuous photophobia (in eight, 36%; three had chronic migraine in addition) and palinopsia (eight, 36%, with four having trailing of moving objects in addition) being the most common (Table 1). Three patients had continuous tinnitus, and four concentration problems. Nineteen letters mentioned the duration of visual snow: one had visual snow as long as she could remember; in the remaining 18, mean age of onset was 23 ± 9 years. Only seven letters mentioned how visual snow started: three patients had headaches, one of these migraine with aura, and none had illicit drug use. The most common comorbidity was migraine (in 17; three migraine with aura, seven chronic migraine), and 17 patients had a positive family history of migraine. One patient noted some incomplete relief from propranolol (80 mg), another from lamotrigine (150 mg/day). Worsening of symptoms was mentioned by one patient each on topiramate and amitriptyline. All patients had a normal neurological exam. An ophthalmological exam was reported in 11 letters (all normal) and an MRI was done in 12 patients (normal in 11 and unspecific in one, Supplementary Table 2).

Retrospective identification of visual symptoms

Data sets from 275 subjects with self-assessed visual snow were randomly assigned to Group A ($n = 140$) and Group B ($n = 135$). In each group, 19 participants did not enter any symptom and one did not provide information on visual snow resulting in 120 patients to be analysed in Group A and 115 in Group B. Demographics are depicted in Supplementary Table 2.

The mean age was 26 years, age of onset was 17 years and mean duration of visual symptoms was 9 years. There were fewer females than males in both groups. In Group A, floaters were the most common additional symptom (73%), followed by

Figure 1 Illustrations done by three patients to demonstrate 'visual snow' (tiny dynamic flickering dots in the entire visual field) in the dark (**A**), during the day (**B**), floaters (**C**), palinopsia ('trailing') in (**D**), blue field entoptic phenomenon (**E**), and palinopsia (positive after images) in (**F**).

prolonged after images (63%), difficulties seeing at night (58%), little cells that travel on a wiggly path (57%), photophobia (54%), moving objects leave 'trails' (48%), bright flashes (44%), and swirls, clouds or waves with eyes closed (41%). In Group B, the same additional symptoms were present in more than one-third of participants.

Prospective clinical characterization

One hundred and forty-two patients contacted the UCSF Headache Centre. Twenty-two (15%) had visual symptoms that did not meet criteria for visual snow. Of the remaining 120 patients with visual snow, 26 had not been seen by a (neuro-)ophthalmologist and 16 had abnormal findings in fundoscopy or perimetry. The remaining 78 patients will be described here in more detail. Three patients had also taken part in the Eye on Vision survey.

Patient demographics and clinical course

The mean age of patients with visual snow was 30 ± 10 years, range 10–60 years. Interviews were carried out with subjects from the USA, Australia and 11 European countries. The female:male ratio was balanced. One-quarter of patients had visual snow as long as they could remember (Table 2). Age of onset in the remaining patients was in early 20s ('later onset'). Mean duration in these patients was 8 ± 10 years. The large majority of patients

Table 1 Demographics, comorbid migraine, additional visual symptoms and test results of patients seen at the NHNN and UCSF Headache Centre between 2001 and 2011

ID	Age (years)	Gender	Age of onset of visual snow	Comorbid migraine	Comorbid visual aura	Additional visual symptoms	Examinations		
							Neurological	Ophthalmological	MRI
1	21	M		+			[a]		
2	40	M	13			Bright flashes	+	+	+
3	37	M	33	+			+		
4	34	M	24	+	-		+		
5	31	M	31			Straight lines moving across the visual field, trailing, persistent after images, photophobia	+		
6	21	F	20	+			+	+	
7	20	F				Water running down a window, metamorphopsia, déjà vu	+		
8	31	M	30				+	+	+
9	20	M	18	+		Geometric and coloured images that distort vision	+	+	+
10	24	M	22	+		Excessive floaters	+		+
11	31	F	26	+	+	Persistent afterimages, photophobia	[b]		
12	21	F	17	+	-	Persistent afterimages, photophobia	+		
13	17	F	13	+	+		+	+	+
14	45	M	45	+	+	Flashing lights, photophobia	+	+	[c]
15	21	F	19	+	-		+		+
16	26	F	#	+		Trailing, persistent after images, excessive floaters, bright flashes, uncountable fast moving dots when looking at the blue sky, coloured clouds when closing eyes, photophobia	+	+	+
17	19	F	19	+		Photophobia	+		+
18	37	F	35	+		After images, trailing of moving objects	+		
19	20	F	19			Excessive floaters, coloured swirls with eyes closed	+	+	+
20	13	F	12	+	-	Bright flashes, twisting/moving of things, such as walls in the exam room, after images, photophobia	+	+	+
21	40	M	18	+	-	After images	+	+	+
22	25	F		+	-	Trailing, persistent afterimages, halos around light-sources, excessive floaters, fast moving tiny rings when looking at the blue sky, photophobia	+	+	

Symptoms present for as long as the patient can recall.
empty cells = no information available from clinical notes, + : present/normal, -: not present.
[a]Duane's syndrome.
[b]Mild postural and action tremor.
[c]Subcortical T_2 hyperintensities.

with later onset of visual snow had continuous symptoms from the beginning. Five patients had initial episodic visual snow. Continuous visual snow started in these patients 2 weeks to 15 years after the first episode. Less than half of patients had constant visual symptoms from the beginning (Table 2). The remaining patients had either progressive or stepwise worsening.

Additional visual symptoms

Some of the additional visual symptoms are illustrated in Fig. 1. Palinopsia manifesting with afterimages from stationary scenes was present in 86%, and with trailing in 60% (Table 3). Excessive floaters were the most frequent entoptic phenomenon (81%). Second most common was blue field entoptic phenomenon (79%). About two-thirds of patients had spontaneous photopsia, photophobia and nyctalopia. Consistent self-light of the eye occurred in half of patients. Nearly all patients complained of at least one additional symptom (76 of 78; 97%) and 72 (92%) had at least three additional visual symptoms.

Additional non-visual symptoms

The majority of patients complained about bilateral non-pulsatile tinnitus and concentration problems. Further, some patients felt lethargic and irritated (Table 3).

Events with the beginning or worsening of the visual disturbance

Sixty-four patients recalled the onset of their visual disturbance and/or a stepwise worsening. Twenty-three (36%) of these patients had a headache attack within 3 days before or after the

Table 2 Demographics, past medical history, family history, beginning of 'visual snow', and temporal development of the severity of all visual symptoms

	All patients with visual snow $n = 78$	
Age	30 ± 10	
Females (female:male)	41	1.1:1
History of headache	68	87%
Worsening with visual snow	29 of 68	37%
Chronic headache	17 of 68	22%
History of migraine	46	59%
History of typical migraine aura	21	27%
Only visual	18 of 21	86%
Visual and others	3 of 21	14%
Family history of headache	44	56%
Family history of headache in patients without history of headache	7 of 10	70%
History of anxiety	12 of 53	23%
History of depression	11 of 53	21%
Visual snow present since childhood[a]	19	24%
Later onset of visual snow[b]	59	76%
Start age (years)	21 ± 9	
Duration (years)	8 ± 10	
Continuous from beginning	54 of 59	92%
Initial episodic	5 of 59	8%
Constant from start	32	41%
Duration of constant symptoms (years)	14 ± 18	
Progressive worsening	33	42%
Duration of progressive worsening (years)	6 ± 8	
Now constant symptoms	16 of 33	48%
Duration of constant symptoms (years)	3 ± 3	
Stepwise worsening	10	13%
Now constant	10 of 10	100%
Duration of constant symptoms (years)	3 ± 2	
Both progressive and stepwise	3	4%

[a]Symptoms present as long as the patient can recall.
[b]Patient recalls period of life without visual snow.
About two-thirds of patients had visual snow starting later in life. A minority of these patients had initial episodes of visual snow before the beginning of the continuous visual snow. Anxiety (defined by a GAD-7 score ⩾ 10) and depression (PHQ-8 ⩾ 10) could not be assessed in all patients as indicated in the respective field.

worsening of the visual symptoms. Sixteen could be classified as migraine according to the ICHD-II criteria (Headache Classification Committee of The International Headache Society, 2004). Only seven patients in total had a typical visual aura, and five patients recalled consumption of cannabis (one used amphetamines in addition, no LSD or hallucinogenic mushrooms) before such beginning or worsening of the visual symptoms.

Experience with the consumption of illicit drugs

Cannabis has been tried at least once in 31 patients with visual snow (40%). In addition to the patients, who had a start of the visual snow after using cannabis, one experienced a temporary worsening of the visual snow while smoking. Ecstasy has been tried by eight patients with visual snow (10%). Cocaine produced a temporary worsening of the visual symptoms in one patient. Seven patients (9%) had experience with cocaine. LSD did not induce visual snow or any additional visual symptoms and was tried by three patients (4%). For recreational purposes, amphetamines were taken at least once by four patients (5%). None of our patients has tried hallucinogenic mushrooms.

Table 3 Additional visual and non-visual symptoms in patients with visual snow

	All patients with visual snow $n = 78$	
Palinopsia ('after images')	67	86%
Palinopsia ('trailing')	47	60%
Floaters	63	81%
Blue field entoptic phenomenon	62	79%
Spontaneous photopsia	49	63%
Self-light of the eye	41	53%
Photophobia	58	74%
Light is too bright	43	74%
Light is painful	15	26%
Nyctalopia	53	68%
Due to visual snow	25	47%
Due to palinopsia	3	6%
Due to halos	3	6%
Due to a combination	22	41%
Tinnitus	48	62%
Concentration problems	47	60%
Lethargy	43	55%
Irritability	29	37%

Past medical history and family history

Headache

Sixty-eight patients had a history of headache with 46 meeting the ICHD-II criteria for migraine (Table 2). Typical migraine aura was present in 21 (27%). A subjective worsening of the headache together with a worsening of the visual disturbance was noted by 29 and chronic headache was present in 17. Patients without personal headache history frequently stated a positive family history for headache.

Anxiety and depression

Moderate to severe anxiety defined as a GAD-7 score of ⩾10 was present in 12, and 11 had a PHQ-8 score of ⩾10 indicating moderate to severe depression.

Other past medical history

The main comorbidities mentioned by the patients were allergies, gastroesophageal reflux disease, vertigo and attention deficit disorder (all in <12%).

Family history of visual snow

Eight patients (10%) with visual snow had first degree family members with visual snow.

Previous investigations

Only patients with normal ophthalmological exams in terms of fundoscopy and perimetry were included in this study. Thirty-four patients (44% of 78) had normal uncorrected visual acuity, 34 were myopic and 10 were hyperopic. According to the patients, best corrected visual acuity was, in general, normal. The original ophthalmology reports could be obtained from 21 patients: 20 had normal best-corrected visual acuity and one patient had 20/25-1 bilateral. Fourteen patients had an electroretinogram (all normal). Fifty-four patients were seen by a neurologist (all had a normal exam) and 22 had visual evoked potentials (all normal). An electroencephalogram was abnormal in 2 of 29 (one had mild encephalopathy and one with history of epilepsy had epileptiform patterns). An MRI of the brain was done in 57 patients (four had non-specific white matter lesions; one patient had a pituitary microadenoma). Routine blood tests and medical exams (blood pressure, electrocardiogram) were normal or not contributory.

Effect of medication

Most patients have been treated empirically in the past by their primary care physician, a neurologist or an ophthalmologist. The main groups of medications include standard psychopharmaceuticals, pain medication, antiepileptics, and migraine prophylactics. No patient reported complete resolution of symptoms by treatment, and no medication has shown consistently to improve or worsen visual snow or its associated visual symptoms.

Discussion

Here we describe three substantial cohorts of patients with a persistent dynamic whole field visual disturbance that is stereotypic and, by clinical characterization, not at all like migraine aura. The syndrome has undoubtedly been seen in practice, certainly by ophthalmologists or neurologists, yet has not been hitherto formally characterized. The normal findings on routine ophthalmological and neurological tests have led to the condition being either dismissed as psychological, attributed to drug use or wrongly classified as migraine aura. The remarkable clinical congruence between each patient group, the minimal history of drug abuse, presence of symptoms in childhood and adolescence, minimal psychiatric co-morbidity and poor response to conventional treatments suggests the syndrome is real and unique. The disturbance has been called 'visual snow' by patients because of its remarkable similarity to the noise on analogue television, and we suggest naming the syndrome after this 'visual snow', or if one prefers a more classic approach 'chionous dysblepsia' named after the ancient Greek goddess of snow (Chione).

Retrospective chart review

Over one decade, we have personally seen almost 24 patients with the chief complaint visual snow as documented specifically in the clinical notes that we could access for details. Chronologically seen, the letters of the earlier patients only mentioned the main visual symptom. Over time, additional visual complaints were listed reflecting increased experience and the literature available (Liu *et al.*, 1995; Jager *et al.*, 2005; Wang *et al.*, 2008). After having seen a number of patients with identical descriptions from different origins, including children, our interest was aroused and with it, more detailed histories taken. Our main findings from this retrospective chart review were that patients with visual snow have (i) additional visual symptoms; (ii) often comorbid migraine; and (iii) typically normal ophthalmological exams.

Retrospective survey

The question of additional visual symptoms was approached by retrospectively analysing survey data provided by a self-help group on visual snow. A cut-off frequency of one-third was chosen to obtain a reasonable number of symptoms for future studies. More than one-third of patients complained about the same additional symptoms in both random groups (Groups A and B) suggesting a homogenous distribution of these visual symptoms.

Prospective study

All subjects in the prospective study underwent a detailed interview by experienced neurologists and headache specialists. A thorough history was taken to make sure that only patients with visual snow meeting the description of our chart review patients (spontaneous description of 'noise of an analogue television') were included in the final analysis. To avoid including ophthalmological disorders that might mimic visual snow, we excluded subjects who never had an exam by a (neuro-) ophthalmologist or who had pathological findings on fundoscopy or perimetry. Only a minority of patients were finally excluded because of pathological findings (16 of 94), and most of our patients had normal best-corrected visual acuity, consistent with Alissa *et al.* (2012), who have shown among nine patients with visual snow, that all had normal visual acuity, colour and rapid flicker sensitivity. The data indicate that visual snow is not a primary eye disease. However, three patients studied by Alissa *et al.* (2012) had absence of recovery of pupillary response following a coloured stimulus indicating prolonged retinal afferent signals, the first objective finding in visual snow.

Additional visual symptoms

The high prevalence of additional visual symptoms in our patients indicates that patients with visual snow have a unique 'syndrome' of visual disturbances. We propose that the additional visual symptoms can be grouped into: (i) palinopsia; (ii) entoptic phenomena; (iii) photophobia; and (iv) nyctalopia.

Palinopsia

Palinopsia is the persistence of a visual image following the removal of the exciting stimulus (Critchley, 1951). When such removal of the exciting stimulus occurs by movement relative to the retina, patients may experience the after image being behind the original ('trailing'). Palinopsia has to be distinguished from physiological retinal after images (Kinsbourne and Warrington, 1963). Palinopsia is associated with multiple conditions including consumption of illicit drugs (Abraham, 1983; Kawasaki and Purvin,

1996), with neurological diseases, such as focal neurological lesions (Critchley, 1951; Bender *et al.*, 1968), and migraine (Belcastro *et al.*, 2011). Pomeranz and Lessell (2000) described nine patients with palinopsia, of whom six did not have any pathology of the eye or the CNS. Notably, one patient had 'snow—like watching a television channel that isn't broadcasting' and another reported 'particles of snow floating around' suggesting that these patients also had visual snow. Therefore, the visual snow syndrome might represent an important aetiology for palinopsia in patients without cerebral pathology or drug use.

Entoptic phenomena

Entoptic phenomena have been recognized by physiologists and ophthalmologists for more than a century (von Helmholtz, 1896). Tyler (1978) summarizes them as 'phenomena arising from [any] structure of the visual system as a result of specific stimulation'. Entoptic phenomena thus can be perceived by healthy subjects, but according to our data, they occur 'during everyday conditions' in patients with visual snow indicating that such 'specific' stimulation is not necessary. For 'blue field entoptic phenomenon' (or Scheerer's phenomenon), the 'specific stimulation' is thought to be 'staring' at the sky or a bright snowfield through a blue glass (von Helmholtz, 1896) or through an entoptoscope resulting in up to 25 corpuscles seen with sudden acceleration in any direction by healthy individuals (Priestley and Foree, 1956). These corpuscles are thought to be leucocytes flowing within the macular retinal microvasculature (Sinclair *et al.*, 1989). The description of our patients 'little cells that travel on a wiggly path' corresponds well with such blue field entoptic phenomenon suggesting an identical mechanism although this was not formally tested using a blue field entoptoscope. The 'self-light of the eye' has been described as luminous clouds of orange or violet colour moving centrifugally or centripetally (Marshall, 1935), which suits well the phenomenon of 'swirls, clouds or waves with eyes closed' experienced by our patients. The cause of this perception is unknown, but it has been attributed to retinal circulation and intracerebral or intraocular pathologies (Marshall, 1935). Its prevalence and significance in the general population is unknown, but our patients seem to be frequently affected.

Photophobia

There is no completely standard medical definition of photophobia. Usually, patients avoid light as they either perceive it being too bright (abnormal sensitivity to light: photic photophobia or hypersensitivity) or painful (causing or worsening head pain or eye pain: photic allodynia). There is no evidence that photophobia is caused by typical ocular pathology (Garcia-Valenzuela *et al.*, 2003) in our patients. Vanagaite *et al.* (1997) have shown that healthy individuals can tolerate significantly higher luminance than migraineurs even outside a headache attack. Our patients with visual snow frequently had a history of headache and more than half of patients had a history of migraine although there was no influence of headache frequency on visual snow.

Nyctalopia

With lowering light intensity, the rod system is more and more involved in mesopic and scotopic vision (Stockman and Sharpe, 2006). In our patients, electroretinography, as one of the key diagnostic tests to assess cone and rod function (Petzold and Plant, 2006), and fundoscopy has been unremarkable. It is therefore unlikely to be a dysfunction of the photoreceptors that contributes to impaired night vision in visual snow.

Additional non-visual symptoms: tinnitus

The high prevalence of bilateral tinnitus indicates that other sensory systems might also be involved in patients with visual snow supporting that visual snow is a disorder of the brain and not the eyes. One could describe tinnitus as acoustic noise in this context. Whether tinnitus is part of the 'syndrome' of visual snow is currently unclear. The high prevalence in patients with visual snow (62%) in comparison with the general population, 7.9% have frequent tinnitus (Shargorodsky *et al.*, 2010), suggests that both disorders might share some pathophysiological mechanisms. Clinically, visual snow might be for the visual system what tinnitus, i.e. phantom auditory perception, is for the auditory system. Tinnitus is associated with changes in neuronal activity of central auditory structures, such as the primary auditory cortex (Arnold *et al.*, 1996) or with thalamocortical dysrhythmia (Llinas *et al.*, 1999). Similar to patients with visual snow, pharmacological treatment trials are often not able to suppress chronic tinnitus completely. The promising response of tinnitus sufferers to new approaches using neuromodulation (Vanneste and De Ridder, 2012*a*, *b*) thus might support the use of these techniques in patients with visual snow. Similarly, concentration problems, irritability or lethargy could be part of the biology of visual snow. Alternatively, these symptoms could be a consequence of the visual disturbance causing distraction, e.g. for visual tasks, or be migrainous as a coincidence. Whether there is an over-arching disorder of the brain in which sensory dysmodulation is the key, and to which each of migraine, visual snow and primary tinnitus belong, among other syndromes, remains a fascinating question.

The relevance of headache, migraine and migraine aura

In patients with visual snow, the prevalence of migraine and migraine with typical aura (Headache Classification Committee of The International Headache Society, 2004) is high in comparison with the general population (Lipton *et al.*, 2002). The lack of association with acute headache attacks or migraine aura episodes initially in visual snow suggests a link to interictal migraine pathophysiology. This is supported by psychophysical studies showing that migraineurs might experience some of the symptoms that are characteristic for visual snow. As an example, migraineurs have an elevated contrast threshold in the presence of high external luminance noise (Webster *et al.*, 2012), a lower threshold for interictal photophobia (Vanagaite *et al.*, 1997), a higher susceptibility for palinopsia (Belcastro *et al.*, 2011), and reduced visual contrast sensitivity (McKendrick and Sampson, 2009). Altered cortical excitability is discussed in migraine (Afra *et al.*, 1998; Mulleners *et al.*, 2001) and may be relevant in visual snow. None of the patients described the additional visual symptoms as being consistent with typical migraine aura, which is most likely an event analogous to cortical spreading depression (Hadjikhani *et al.*,

Table 4 Proposed criteria 'visual snow' syndrome

A	Visual snow: dynamic, continuous, tiny dots in the entire visual field lasting longer than 3 months.[a]
B	Presence of at least two additional visual symptoms of the four following categories:
	(i) Palinopsia. At least one of the following: afterimages (different from retinal after images)[b] or trailing of moving objects.
	(ii) Enhanced entoptic phenomena.[c] At least one of the following: excessive floaters in both eyes, excessive blue field entoptic phenomenon, self-light of the eye, or spontaneous photopsia.
	(iii) Photophobia
	(iv) Nyctalopia (impaired night vision)
C	Symptoms are not consistent with typical migraine visual aura.[d]
D	Symptoms are not better explained by another disorder.[e]

[a]Patients compare it to 'TV static' or 'TV snow'. The dots are usually black/grey on white background and grey/white on black background. Alternatives could be transparent dots, white flashing dots, or coloured dots.
[b]Palinopsia includes after images and trailing of moving objects. After images should be different from retinal after images, which occur only when staring at a high contrast image and are in complementary colour.
[c]Phenomena arising from the structure of the visual system itself and include: excessive floaters in both eyes, excessive blue field entoptic phenomenon (uncountable little grey/white/black dots or rings shooting over visual field in both eyes when looking at homogeneous bright surfaces, such as the blue sky), self-light of the eye (coloured waves or clouds when closing the eyes in the dark), or spontaneous photopsia (bright flashes of light).
[d]Typical migraine aura (IHS 1.2) as defined by the International Headache Society in the International Classification of Headache Disorders 2nd edition (Headache Classification Committee of The International Headache Society, 2004). Main features of typical migraine aura are: similarity to previous visual auras, unilaterality, movement, edges, positive and negative visual phenomena, zigzag lines (Eriksen *et al*., 2005).
[e]Normal ophthalmology tests (best corrected visual acuity, dilated fundus exam, visual field and electroretinogram), no intake of psychotropic drugs.

2001). In the literature of visual snow and persistent migraine aura, some patients were described as having flashing lights, zigzag lines (Rothrock, 1997; Jager *et al.*, 2005), scintillating scotoma (Relja *et al.*, 2005; San-Juan and Zermeno, 2007) occurring in one visual hemifield (Haas, 1982; Rothrock, 1997; Chen *et al.*, 2001; Jager *et al.*, 2005; Relja *et al.*, 2005; Wang *et al.*, 2008) or showing directed movement (Belvis *et al.*, 2010), which have developed with a typical migraine attack. These patients likely have migraine aura and have contributed to confusion over the syndrome.

Limitations

One limitation of this study is that all information was interview-based and thus exposed to the risk of suggestibility to patients by the interviewers. However, all questions were asked as openly as possible without any clues to reduce the likelihood of such errors. Similarly, the recruitment through the internet might result in patients coordinating answers with each other. This, however, seems to be highly unlikely, given the long time period covered by the chart review involving two headache clinics in two different countries and the high variability of our prospective study population (age range 10–60 years) coming from 13 different countries distributed over three continents. Given that the initial clinical patients were seen in the pre-social media era, and the same visual disturbance was reported in children, collusion seems a most unlikely explanation. Certainly, internet-based sampling attracts a younger more pro-active population, however, the clinical picture was so homogenous from all three cohorts, it seems likely that visual snow is a real entity.

Conclusion

From the data presented here, almost all patients with 'visual snow' have a variety of additional visual symptoms (palinopsia, enhanced entoptic phenomena, photophobia, and nyctalopia), which do not sound like typical migraine aura at all. Visual snow therefore represents a unique clinical syndrome. Our data acknowledge an overlap of migraine and visual snow but do not support the hypothesis that migraine attacks or individual episodes of migraine aura 'cause' visual snow. Our data do not support a view the visual snow syndrome is caused by anxiety, depression or the intake of illicit drugs, such as LSD. Remarkably, most patients with visual snow have normal best corrected visual acuity, perimetry and fundoscopy. Any association with visual loss or acute onset of visual symptoms similar to visual snow, especially floaters and photopsia, would therefore require appropriate assessment by a specialist before calling it 'visual snow'.

We would define the 'visual snow' syndrome by the presence of visual snow as the main criterion, with some additional visual criteria, and exclusion of migraine aura, and overlapping diseases, such as ophthalmological pathology or intake of psychotropic drugs (Table 4).

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Supplementary material

Supplementary material is available at *Brain* online.

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Visual Snow Questionnaire responses returned

A communication to all Visual Snow sufferers participating in the London Questionnaire Study on Visual Snow

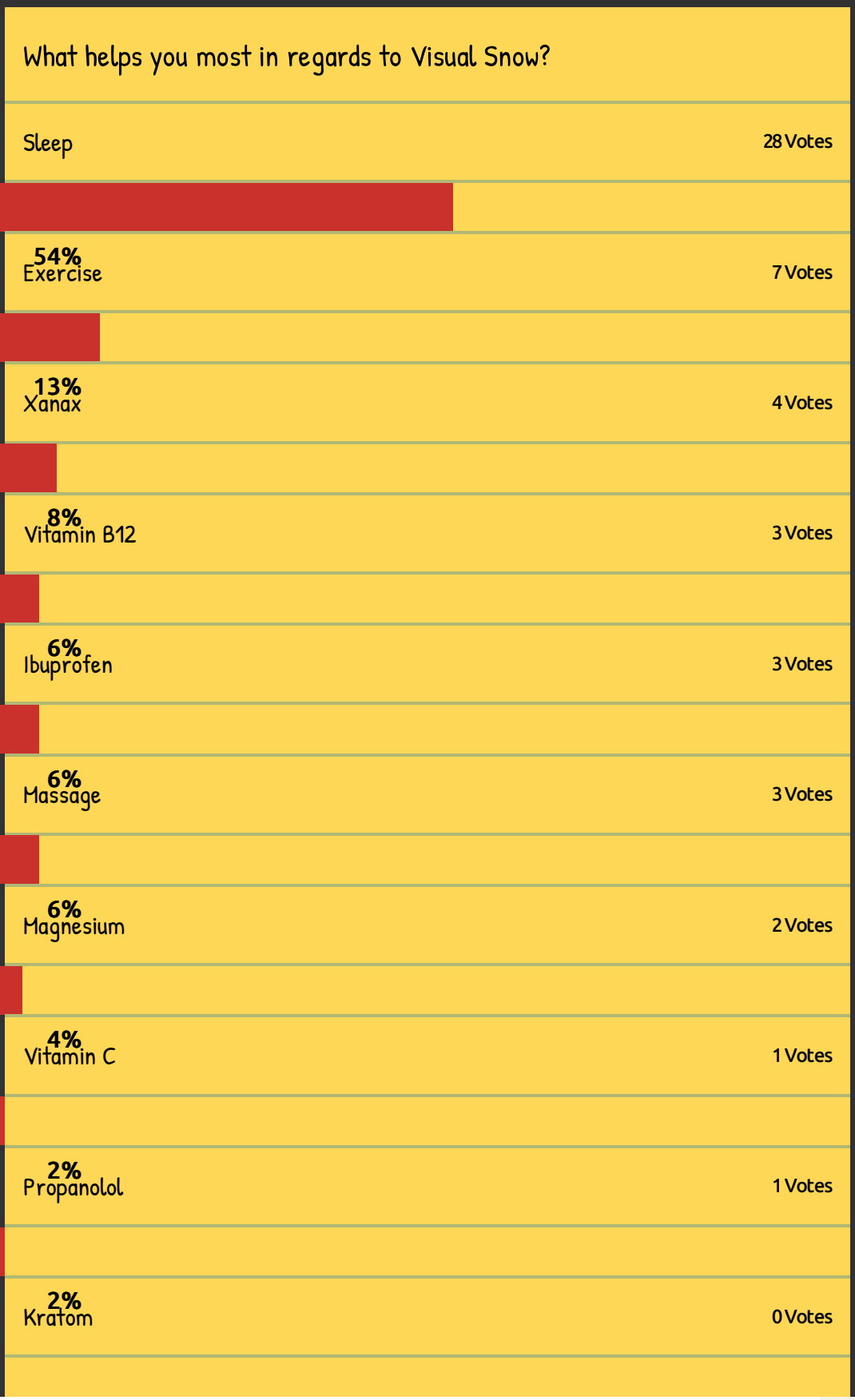
Thank you for your extraordinary interest in the London Questionnaire Study on Visual Snow! So far, we have been in contact with over 450 subjects, who expressed interest in participating in our research on this disabling condition.

We have emailed the documents for the study including two questionnaires to a large number of you. To date, however, only 67 have returned both documents. This is neither a representative sample of the 450 subjects nor is it sufficient to understand the condition Visual Snow in detail.

Direct participation from the Visual Snow community is extremely important for our goal to advance research and with it treatment of this problem. With this update, we would therefore like to invite all subjects to help us by returning their questionnaires as soon as possible. We believe that this study will gain significant important information on Visual Snow, but only if we are able to reach a substantial and meaningful number of participants.

Thank you again for your help and collaboration!

Professor Peter J Goadsby



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