Migraine biochemistry and visual snow

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Migraine prevalence in visual snow with prior illicit drug use (Hallucinogen Persisting Perception Disorder) versus without

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Abstract

Objective

To investigate migraine prevalence in persons with Hallucinogen Persisting Perception Disorder (HPPD) presenting as visual snow syndrome (VSS).

Methods

Persons with visual snow as persisting symptom after illicit drug use (HPPD) were recruited via a Dutch consulting clinic for recreational drug use. A structured interview on (visual) perceptual symptomatology, details of drugs use, medical and headache history was taken. As a control group, persons with visual snow who had never used illicit drugs prior to onset were included. The primary outcome was lifetime prevalence of migraine. Symptom severity was evaluated by the Visual Snow Handicap Inventory (VHI), a 25-item questionnaire.

Results

None of the 24 HPPD participants had migraine, whereas 20/37 (54.1%) of controls had migraine ($p < 0.001$). VHI scores did not differ significantly between the two groups; in both groups median score were 38 out of 100. In most HPPD cases (17/24; 70.9%), visual snow had started after intake of ecstasy; other psychedelic drugs reported included cannabis, psilocybin mushrooms, amphetamine, 4-FMP, 3-MMC, 2C-B, and nitrous oxide.

Conclusions

While none of the HPPD participants had migraine, over half of the visual snow controls without prior use of illicit drugs had migraine. This suggests that at least partly different pathophysiological factors play a role in both disorders. Users of ecstasy and other hallucinogens should be warned of the risk of visual snow. Further studies are needed to enhance understanding of the underlying neurobiology of HPPD and VSS to come to better management of these conditions.

Introduction

Patients with visual snow see countless, small dots in the entire visual field. These dots are continuously present, and patients often describe it as seeing "TV static".[1] Diagnosis is made after exclusion of secondary causes of pan-field visual disturbances, such as lesions in the visual pathway and retina. Most patients report additional visual symptoms such as: (i) palinopsia, (ii) enhanced entoptic phenomena, (iii) photophobia and (iv) nyctalopia. Therefore, visual snow *syndrome* (VSS) criteria have been proposed.[1,2] The symptoms can be very bothersome, and many patients suffer from comorbid depression and anxiety.[3] The pathophysiology of visual snow is not known, although there is some evidence that increased cortical excitability might play a role.[4–7]

Little is known about the epidemiology of visual snow with only one population-based study published, estimating prevalence at 1.4 - 3.3%.[8] First case series on visual snow patients suggest that migraine is an important comorbid condition as migraine prevalence is two times higher in patients with visual snow than in the general population (approximately 50% versus 25%).[1–3,9,10] Interestingly, most of these patients have migraine with visual aura, whereas migraine without aura is more common in the general population.[11] This indicates there may be a shared pathophysiology between visual snow and migraine with aura.

Remarkably, visual snow has also been reported as a persistent symptom after the intake of recreational drugs, especially hallucinogens such as ecstasy (XTC or MDMA referring to its active metabolite 3,4-methylenedioxymethamphetamine), lysergic acid diethylamide (LSD) and hallucinogenic mushrooms.[12–14] The DSM-V diagnosis 'Hallucinogen Persisting Perception Disorder' (HPPD) is often used to describe persistent visual complaints after hallucinogen use and "visual snow" is described as one of those symptoms.[15] A recent web-based study compared patients with VSS, who had never used illicit drugs, to patients with possible HPPD, i.e. visual snow patients who had used illicit drugs in the 12 months prior to visual snow onset.[2] Except for a later age of onset and male preponderance in the possible HPPD group no differences in clinical characteristics were found, suggesting that the clinical phenotypes overlap. Migraine was prevalent in both groups (72% in VSS and 57% in possible HPPD) suggesting that migraine may be an important shared trait and perhaps an important factor in developing visual snow. To further investigate this hypothesis, we studied a group of patients who presented with visual snow after illicit drug use at a consulting clinic for HPPD. A structured interview on (visual) perceptual symptoms, illicit drugs use, medical and headache history was taken. As controls, patients with visual snow (syndrome) who had never used illicit drugs prior to onset were included. The primary outcome was lifetime prevalence of migraine.

Methods

Persons with HPPD were recruited via a national consulting clinic specific for illicit/recreational drug use (Brijder, Alkmaar, the Netherlands). In the Netherlands persons can consult an addiction specialist (G.J.A.) for questions regarding the use of illicit drugs. The aim of this clinic is to educate persons about the harmful effects and avoid addiction and risk behavior. Persons with somatic or psychiatric complaints after illicit drug use can also consult this clinic. Since the foundation of the clinic in 2010 multiple patients were diagnosed with HPPD, including those reporting visual snow after illicit drug use. An informative email was sent to the patients with visual snow (identified after file review by treating physician G.J.A.) to inform that researchers from the Leiden University Medical Center (LUMC) were interested in interviewing persons with HPPD. To avoid selection bias the invite contained no information on migraine or headache. After informed consent, participants underwent a structured telephone interview on visual symptoms, details of illicit drugs use, medical history and headache history (by R.M.v.D.). Headache disorders were diagnosed according to ICHD-3 criteria.[16] Additionally, participants filled in a questionnaire on recreational drug use.

Cases were defined as HPPD if visual snow started within 12 months of intake of illicit drugs (similar to the web-based study).[2] Description of visual snow had to meet previously reported criteria (dynamic, continuous, tiny dots in the entire visual field).[1,2] Controls were patients with visual snow who had never used illicit drugs prior to onset. These were primarily recruited via the LUMC Neurology outpatient clinic and majority was also described in a previous retrospective study.[3] Controls had to meet previously published visual snow criteria[1,2] (supplement Table S1) but it was not required to meet VSS syndrome criteria since previous research showed that patients not meeting the additional symptom criterion (VS) were similar in other key clinical features with those having the full syndrome (VSS).[2] We therefore abbreviate this group as VS(S).

Patients with visual snow who had used illicit drugs >12 months before onset were not excluded from the study but included in a third group. Since most participants could not fully guarantee the time span was at least 12 months we refer to this group as "HPPD not excluded" (Table S1). General exclusion criteria were other neurological or ophthalmologic diseases that could explain pan-field visual disturbances, or signs of psychosis such as auditory hallucinations and delusions. Only participants ≥ 18 years old were included.

Impact of visual snow was evaluated using an electronic questionnaire called the Visual Snow Handicap Inventory (VHI). This questionnaire was developed by modifying the Tinnitus Handicap Inventory (THI), a 25-item questionnaire on the impact of tinnitus.[17] One question of the THI (#2) specifically focuses on auditory ability, and we therefore replaced

this question with a visual equivalent. The other 24 questions of the THI cover impact of symptoms on well-being and were only modified by replacing the word "tinnitus" with "visual snow". For the VHI and THI questionnaires see supplement Table S2 and S3. The total score ranges from 0 to 100 (even number only) with "0-16" considered "slight or no handicap", "18-36" considered "mild handicap", "38-56" considered "a moderate handicap", "58-76" considered "severe handicap" and "78-100" a "catastrophic handicap".

The primary outcome of this study was the lifetime-prevalence of migraine with or without aura (according to ICHD-III criteria[16]). Additionally, we studied one-year migraine prevalence (= at least one migraine attack in the 12 months prior to the interview). Participants also received a questionnaire on family history, including if their parents had migraine. SPSS Statistics Version 26.0 for Windows was used for statistical analysis (IBM Corp, Armonk, NY). The Mann-Whitney U test was used to compare numerical variables between the three groups. The Chi-Square test was used for categorical variables. P-values < 0.05 were considered significant. Post-hoc comparisons were carried out with the same tests, if the original comparison was significant.

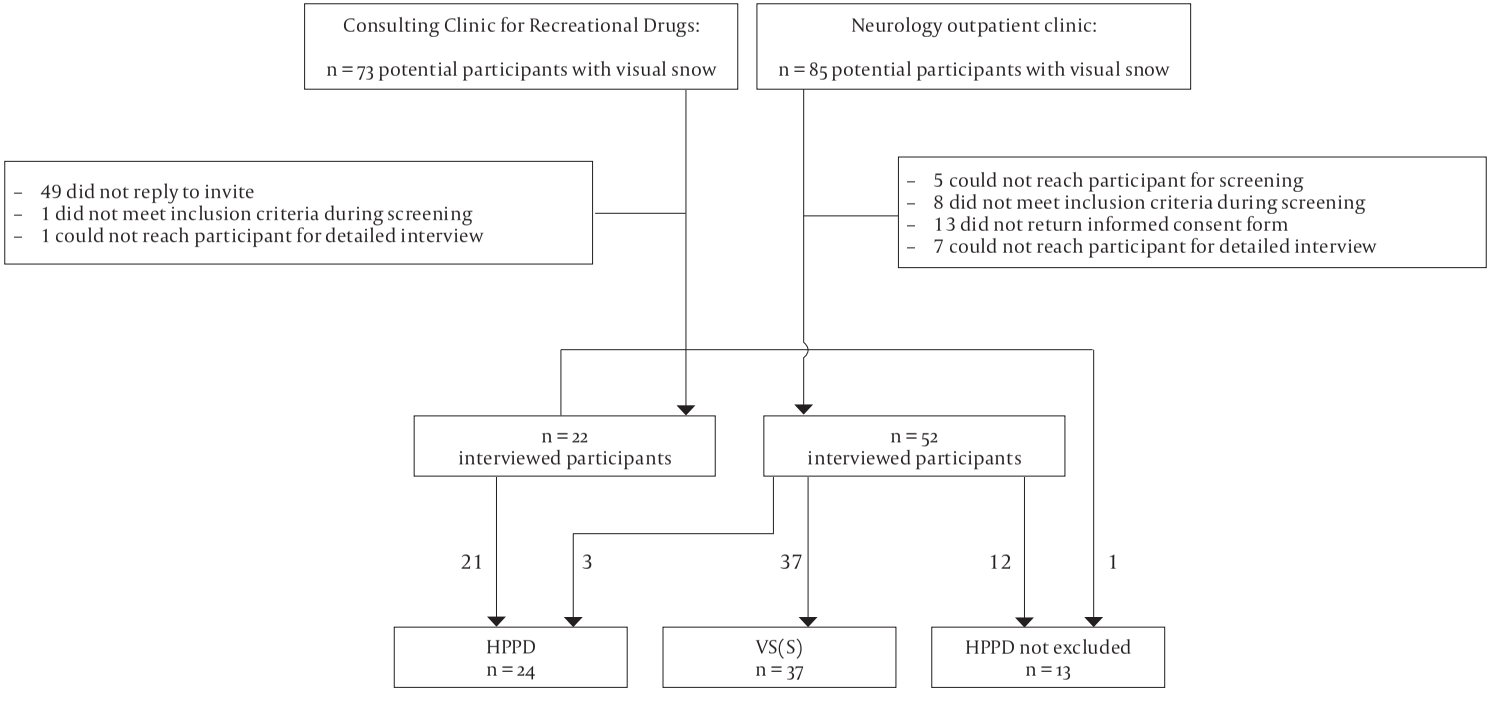
Standard protocol approvals, registrations, and patient consents
This study was approved by the ethical committee of the Leiden University Medical Centre. All participants provided written informed consent.

Data availability
Anonymized data can be obtained by request from any qualified investigator for purposes of replicating procedures and results.

Results

Clinical characteristics
In total, n= 24 HPPD patients were included and n= 37 controls with VS(S). A third group consisted of n= 13 patients in whom HPPD could not be excluded. Figure 1 illustrates the flow of participant inclusion. Descriptions of visual snow from potential participants with HPPD were highly similar to those from VS(S). Clinical and demographic characteristics of the three groups are summarized in Table 1. Participants with HPPD were younger and predominantly male (22/24). In all three groups, most patients met the additional criteria for visual snow syndrome based on the presence of two or more additional visual symptoms. Another frequently reported symptom in all three groups was seeing halos (extra layer of light around light sources or other objects). Descriptions of other symptoms can be found in the supplement (Table S4). Median VHI scores were 38, 38 and 26 respectively, with no significant differences between the groups (Table 1).

Figure 1. Flowchart of participant inclusion.



Legend: HPPD = Hallucinogen Persisting Perception Disorder, VS(S) = Visual Snow (Syndrome). See methods section for full study group definitions.

Type of illicit drugs and temporal relationship with onset of symptoms

Most HPPD participants (17/24; 70.9%) reported that visual snow had started after intake of ecstasy (XTC) pills. Three participants indicated they were informed on the MDMA concentration of the pill (80mg, 220mg and 225mg respectively) although they did not have an official test confirmation, a service available in the Netherlands with the aim of detecting serious toxic concentrations in an early stage and warn the public.[18] The remaining 14 cases did not know the MDMA concentration of the pills. Most cases had used illicit drugs on previous occasions. Three out of 17 XTC cases (17.6%) reported it was the first time they used XTC when visual snow developed. Of prior XTC users, two patients reported that they had temporary experienced visual snow before after using XTC, in one patient symptoms lasted almost 24 hours the first time and in the other patient visual snow lasted approximately one month the first time. In both patients visual snow relapsed during a next occasion of XTC use and did not disappear since.

Table 1. Clinical characteristics.

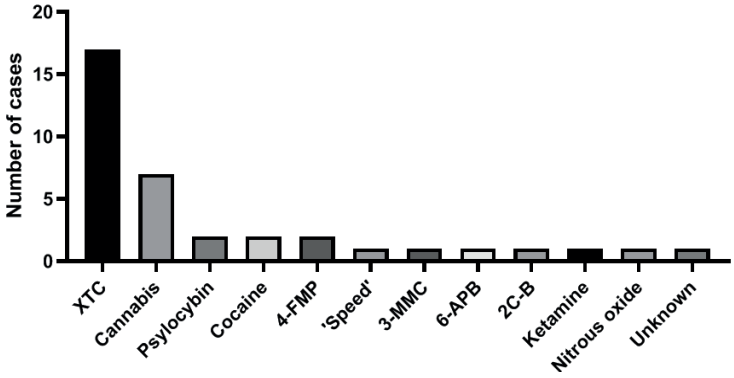
	HPPD N = 24	VS(S) N = 37	HPPD not excluded N = 13	Sign.
Age, years	25 (23-29) *	30 (26-39)	27 (24-31)	p = 0.031
Female	2/24 (8.3%) **	19/37 (51.4%)	6/13 (46.2%)	p = 0.002
Visual snow as long as patient can remember	0/24 (0.0%) *	13/37 (35.1%)	0/13 (0.0%) *	p < 0.001
Age of onset, years	22 (19-24)	23 (15-28) [b]	23 (20-26)	p = 0.225
Palinopsia	15/24 (62.5%)	26/37 (70.3%)	7/13 (53.8%)	p = 0.542
Entoptic phenomena [a]	15/24 (62.5%)	24/37 (64.9%)	6/13 (46.2%)	p = 0.483
Nyctalopia	9/24 (37.5%)	12/37 (32.4%)	5/13 (38.5%	p = 0.887
Photophobia	12/24 (50.0%)	25/37 (67.6%)	8/13 (61.5%)	p = 0.537
≥ 2 of the above additional symptoms	18/24 (75.0%)	30/37 (81.1%)	8/13 (61.5%)	p = 0.367
Visual snow handicap inventory (VHI) score	38 (28-53)	38 (22-58)	26 (16-40)	p = 0.452

Legend: HPPD = Hallucinogen Persisting Perception Disorder, VS(S) = Visual Snow (Syndrome). See methods section for full study group definitions. Numerical variables are reported as median with interquartile range. The Mann-Whitney U Test was used to compare numerical variables between the three groups, and the Chi-Square test for categorical variables. * $p < 0.05$ in post-hoc comparison with VS(S), ** $p < 0.05$ in post-hoc comparison with VS(S) and in post-hoc comparison with "HPPD not excluded". [a] Entopic phenomena: excessive floaters in both eyes, excessive blue field entoptic phenomenon, self-light of the eye, or spontaneous photopsia; see reference (1) and (2) for examples of these symptoms. [b] Calculated after excluding the n=13 patients who had visual snow as long as they can remember.

Cannabis was reported as trigger by 7/24 (29.2%) cases (Figure 2). Other mentioned drugs were psilocybin mushrooms, cocaine, 'speed' (amphetamine), '4-FMP' (4-fluoramphetamine), '3-MMC' (3-methylmethcathinone), '6-APB' (6-(2-aminopropyl) benzofuran), '2C-B' (22,5-dimethoxy-4-bromophenethylamine), ketamine and nitrous oxide ('laughing gas'). Eleven cases reported that they had used multiple drugs during the episode that was believed to have triggered the visual snow, primarily cannabis in combination with another drug.

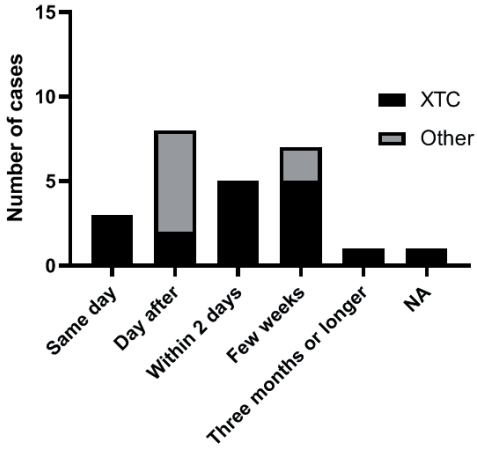
Time reported between intake of illicit drugs and onset of visual snow varied between "the same day" to "three months after intake" (Figure 3). The majority of XTC users, 10/17 (58.8%), reported an onset within two days. Only 5/24 (20.8%) participants reported experiencing visual hallucinations during the trip, of which two reported visual snow was one of these hallucinations.

Figure 2. Type of illicit drugs reported as trigger by HPPD patients.



Legend: XTC = ecstasy, cannabis = marihuana or weed, psilocybin = psilocybin mushrooms, 4-FMP = 4-fluoramphetamine, 'speed' = amphetamine, 3-MMC = 3-methylmethcathinone, 6-APB = 6-(2-aminopropyl)benzofuran, 2C-B = 22,5-dimethoxy-4-bromophenethylamine, nitrous oxide = 'laughing gas', unknown = one participant who used multiple illicit drugs at a party but not sure if it was XTC, ketamine, GHB (gamma-hydroxybutyric acid) or 'speed'. Eleven participants reported that they had used multiple drugs during the episode that was believed to have triggered the visual snow.

Figure 3. Time between intake of illicit drugs and onset of visual snow in HPPD participants.



Legend: Participants with HPPD were asked about the time between intake of illicit drugs and onset of their visual snow. Data are shown separate for ecstasy (black) and other drugs (grey). XTC = ecstasy. NA = not applicable: one patient reported that symptoms gradually developed during a period of extensive illicit drug use and that onset was not related to one specific episode of drug use.

Migraine prevalence

None of the HPPD cases had migraine versus 20/37 (54.1%) in the VS(S) group ($p < 0.001$; Table 2). Split by gender, 0/22 (0.0%) male HPPD patients had migraine compared to 4/18 (22.2%) male VS(S) patients ($p = 0.020$). While 16/19 (85.1%) females in the VS(S) group had migraine, we refrained from statistical testing as the HPPD group was composed of only 2 females. In the third "HPPD not excluded" group, 3/7 males (42.9%) and 3/6 females (50.0%) had migraine. When criteria for probable migraine were applied, only two additional cases were found, both in the VS(S) group. Analysis of one-year prevalence instead of lifetime prevalence showed similar results (Table 2).

Overall, most migraine patients had migraine with aura (Table 2). Eight patients had at least one attack per month, with a median frequency of 2.5 attacks/month (range 1-12). Age of onset ranged from 12-18 years. The number of individuals with a parent with migraine did not differ between the HPPD and VS(S) group (26.1% versus 30.6%). Tension-type headache was present in six HPPD cases, of which one fulfilled criteria for chronic tension-type headache with 30 headache days per month. No other primary or secondary headache disorders were found in HPPD patients.

Table 2. Migraine characteristics per study group.

	HPPD N = 24	VS(S) N = 37	HPPD not excluded N = 13	Sign.
Migraine, lifetime	0/24 (0.0%) **	20/37 (54.1%)	7/13 (53.8%)	p < 0.001
Males with migraine	0/22 (0.0%) **	4/18 (22.2%)	3/7 (42.9%)	p = 0.002
Females with migraine	0/2 (0.0%)	16/19 (84.2%)	3/6 (50.0%)	Not tested [a]
Migraine with aura	0/24 (0.0%) **	15/37 (40.5%)	7/13 (53.8%)	p < 0.001
Migraine without aura	0/24 (0.0%)	5/37 (13.5%)	0/13 (0.0%)	p = 0.068
Migraine, age of onset	NA	12 (12-15)	14 (14-18)	p = 0.283
Migraine, past 12 months	0/24 (0.0%) **	18/37 (48.6%)	5/13 (38.5%)	p < 0.001
Parent with migraine [b]	6/23 (26.1%)	11/36 (30.6%)	9/12 (75.0%) *	p = 0.010

Legend: Numerical variables are reported as median with interquartile range. The Mann-Whitney U Test was used for numerical variables, and the Chi-Square test for categorical variables. ** $p < 0.05$ in post-hoc comparison with VS(S) and in post-hoc comparison with "HPPD not excluded". * $p < 0.05$ in post-hoc comparison with HPPD and in post-hoc comparison with VS(S). NA = not applicable. [a] For females we refrained from statistical testing because of the limited number of female HPPD participants (n=2). [b] Missing data: three participants did not return the family history questionnaire (one in each group).

Discussion

We studied a group of patients with visual snow who report that the onset of visual snow was triggered by intake of illicit drugs (HPPD). Most patients had used ecstasy, of which almost 60% reported visual snow started within two days of intake. Migraine was absent

in all patients with HPPD and present in more than half (54.1%) of patients with visual snow who had never used illicit drugs prior to visual snow onset. This suggest migraine is not a shared factor between both groups.

The relationship between visual snow and HPPD has not been extensively investigated. In early descriptions of patients with HPPD[14], visual snow is listed as one of the possible symptoms but until recently the direct comparison between patients without a history of illicit drug use (VSS) and patients with visual snow after illicit drugs use (HPPD) has not been made. In a recent web-based study both groups were compared for the first time and their clinical characteristics did not differ (except for a later age of onset and male preponderance in the HPPD group).[2] This is in line with our observations. Patients from both groups gave similar descriptions of their visual snow, already at their different and independent recruitment sites. Furthermore, results on the additional visual symptoms and symptom severity (measured by the VHI) were similar. This supports the conclusions of the previous study that HPPD can manifest within the visual snow spectrum.

In contrast, our results on migraine prevalence are different. In the web-based survey 57% of HPPD patients reported to have migraine[2] whereas we observed no migraine in our HPPD patients. We believe these contrasting findings may result from different data collection methods. The previous web-based survey used one single non-specific question ("Have you ever been diagnosed with migraine, or have you had a headache of moderate or severe intensity in the past?")[2] whereas we used a structured interview by a physician, thereby reducing the chance of false positives. This is supported by the relatively high percentage of migraine in the VSS group (72%[2]) in the web-based survey compared to earlier studies (59%[1] and 47%[9]). The strong preponderance of males in our HPPD group likely also has influenced the low prevalence of migraine in our study, since migraine is more prevalent in women. However, we would still have expected several migraine cases among 22 males if migraine were to play an important role. As another possible explanation we hypothesize that migraine patients may avoid illicit drug use to avoid triggering a migraine attack, but there are no clear data on this topic.

The absence of migraine in HPPD suggests that, although the clinical phenotype may be like VSS, different initiation mechanisms may play a role. If there was an important interaction with migraine, i.e. the presence of migraine mechanisms is necessary to develop visual snow after drug use, we would have expected more migraine cases in our HPPD group. This observation, however, does not exclude that both disorders, HPPD and VSS, share a final common pathway in their pathophysiology. A final common pathway would certainly explain the identical symptomology.

To our knowledge there are no studies investigating pathophysiological correlates

in both VSS patients and HPPD patients. In the field of VSS progress in unraveling its pathophysiology is being made using positron emission tomography[4], visual behavioral testing[5], visual evoked potentials (VEP)[6,19] and (functional) magnetic resonance imaging,[7,20] but patients with illicit drug use prior to onset have been excluded in these studies. Similarly, in the field of HPPD, no patients with VSS have been included. Besides, the number of pathophysiological studies in HPPD patients is limited and primarily focused on users of LSD, the first group to report persistent visual complaints after illicit drug intake. It was hypothesized that LSD is neurotoxic for serotonergic ($5\text{-}HT_2$) inhibitory neurons and that this causes less inhibition leading to increased excitation ('disinhibition theory').[21,22] Indeed, in LSD users increased EEG coherence in the occipital region with reduced VEP latency was found.[21,22] More recent research has focused on MDMA. There is increasing evidence that MDMA is toxic for serotonergic neurons[23–25] leading to increased visual cortex activation demonstrated with transcranial magnetic stimulation fMRI and positron emission tomography [26–29] but attempts at replication show heterogenous results.[30] Interestingly, these MDMA studies were performed with persons without visual complaints, raising the question if activation would be stronger in persons with HPPD complaints. Of additional interest is the reversibility of the observed changes caused by MDMA, which still needs further investigation.[29] Our observation of the two cases with temporary visual snow after previous occasions of ecstasy use (i.e. before the visual snow became chronic after the more recent occasion of illicit drug use) suggest there could be an important preventive message for cases still experiencing temporary symptoms: refrain from further usage of illicit drugs. Finally, it should be noted that HPPD constitutes a wide clinical spectrum itself. Strictly speaking the DSM-V diagnosis of HPPD is "the reexperiencing, following cessation of use of a hallucinogen, of one or more of the perceptual symptoms that were experienced while intoxicated with the hallucinogen".[15] However, the diagnosis is now also commonly used for other perceptual symptoms that are not flashbacks to the drug intoxication, but continuous symptoms that started after the intoxication. "Type 2 HPPD" has been the proposed term for the latter.[12] Our patients and those from the previous web-based study[2] can be categorized in this category. Future research should elucidate if visual snow is the main symptom within this category or if there are other types of visual symptoms.

Our study has several limitations. The study may be prone to recall bias. HPPD cases could have incorrectly identified the illicit drugs as the trigger of their visual snow instead of another, yet unknown risk factor (i.e. stroboscope light in the discothèque), or perhaps there are no exogenous risk factors. However, we believe the large number of individuals describing a clear temporal relationship between illicit drug use and onset of visual snow, in our study and other studies[2,13], warrants attention to illicit drugs as a potential important risk factor for developing visual snow. Nonetheless, the risk of a non-causal relationship increases with a longer time window between drug use and onset of

symptoms. It may be argued that in future studies only persons with visual complaints <48 hours after drug use should be included. Another important limitation is the small sample size, especially of female cases, thereby limiting our conclusion on migraine prevalence to males. Also, HPPD cases were slightly younger and may still develop migraine later in life but we consider this unlikely since age of onset for migraine in the VS(S) controls was well below age of onset for visual snow in the HPPD group. Selection bias might have played a role as well. VS(S) patients were recruited via a Neurology outpatient clinic which is a tertiary headache center as well, increasing the a priori chance of comorbid migraine. However, the fact that other studies also observed a high prevalence of migraine in other recruitment settings[2,9] suggest that our observation is not biased. Besides, the patients were referred for continuous visual complaints and not because of headaches. Interestingly, there is some evidence that VSS is more severe when comorbid migraine is present.[31] Theoretically, it could be that our clinic only attracted the more severe cases and consequently observed more migraine. However, this bias would still not explain the absence of migraine in the HPPD group, which had similar severity (VHI) scores. Finally, we could not compare responders and non-responders of the consulting clinic of recreational drug use. Despite these limitations we still would have expected more migraine diagnoses in the HPPD group if migraine plays a key role in the pathophysiology. The major strength of this study is that we were able to study confirmed HPPD patients: patients had a clear temporal relationship with the illicit drug use and therefore presented at a drug consulting clinic experienced in HPPD diagnosis. Additionally, we used the golden standard for migraine diagnose, a structured interview. Lastly, in our experience the VHI was an easy tool to assess symptom severity and we believe this questionnaire could serve as outcome measure in future studies.

Given the popularity of recreational drug use, we believe future research should target visual snow as potential aftereffect of illicit drug use. Especially ecstasy use has increased in the past years. It is the second most used drug in the Netherlands after cannabis (2.8% of Dutch adults used ecstasy at least once in the past year).[32] This could explain why ecstasy and cannabis were reported as most common cause of HPPD. In contrast, LSD use is rare (0.2% of adults used LSD at least once in the past year). Perhaps even more worrisome, MDMA concentrations in ecstasy pills are rapidly increasing: in 2008 mean MDMA concentration per pill was 87mg, in 2013 this was 148 mg and in 2018 this rose to 171mg.[32] These trends could have unfavorable aftereffects. In one exploratory survey in nightlife participants (of which almost 50% indicated they had used ecstasy in the past year), visual snow was reported by 17% of the participants, suggesting visual snow is more common than earlier reports suggest.[33] Unfortunately, this survey contained no detailed information on whether symptoms were temporary or chronic. Additional population-based cohort studies are therefore necessary to better estimate the incidence of visual snow, and both illicit drug use and migraine should be studied as risk factors. Future

studies investigating potential pathophysiological mechanisms for visual snow should not only aim to replicate the earlier promising findings[4–7,20], but also include HPPD patients as a separate group.

In conclusion, in contrast to our hypothesis, none of the HPPD participants had migraine, whereas migraine was quite prevalent in visual snow controls without prior use of illicit drugs. Although data on migraine could be skewed by differences in sex between the two groups, we believe our observations suggest that migraine is not the common variable and that at least partly different pathophysiological factors may play a role. Furthermore, we believe users of ecstasy and other hallucinogens, should be aware of visual snow as a possible persistent aftereffect, and that this potential risk warrants further research.

References

1. Schankin, C. J., Maniyar, F. H., Digre, K. B. & Goadsby, P. J. 'Visual snow' - A disorder distinct from persistent migraine aura. *Brain* **137**, 1419–1428 (2014).
2. Puledda, F., Schankin, C. & Goadsby, P. J. Visual snow syndrome: A clinical and phenotypical description of 1,100 cases. *Neurology* **94**, e564–e574 (2020).
3. Van Dongen, R. M., Waaijer, L. C., Onderwater, G. L. J., Ferrari, M. D. & Terwindt, G. M. Treatment effects and comorbid diseases in 58 patients with visual snow. *Neurology* **93**, E398–E403 (2019).
4. Schankin, C. J. *et al.* Structural and functional footprint of visual snow syndrome. *Brain* **143**, 1106–1113 (2020).
5. McKendrick, A. M. *et al.* Behavioral measures of cortical hyperexcitability assessed in people who experience visual snow. *Neurology* **88**, 1243–1249 (2017).
6. Eren, O., Rauschel, V., Ruscheweyh, R., Straube, A. & Schankin, C. J. Evidence of dysfunction in the visual association cortex in visual snow syndrome. *Ann. Neurol.* **84**, 946–949 (2018).
7. Puledda, F. *et al.* Insular and occipital changes in visual snow syndrome: a BOLD fMRI and MRS study. *Ann. Clin. Transl. Neurol.* 1–11 (2020).
8. Kondziella, D., Olsen, M. H. & Dreier, J. P. Prevalence of visual snow syndrome in the UK. *Eur. J. Neurol.* (2020).
9. Lauschke, J. L., Plant, G. T. & Fraser, C. L. Visual snow: A thalamocortical dysrhythmia of the visual pathway? *J. Clin. Neurosci.* **28**, 123–127 (2016).
10. Viana, M., Puledda, F. & Goadsby, P. J. Visual snow syndrome: a comparison between an Italian and British population. *Eur. J. Neurol.* 2018–2020 (2020).
11. Launer, L. J., Terwindt, G. & Ferrari, M. The prevalence and characteristics of migraine in a population-based cohort: The GEM Study. *Neurology* **53**, 537–542 (1999).
12. Halpern, J. H., Lerner, A. G. & Passie, T. A review of hallucinogen persisting perception disorder (HPPD) and an exploratory study of subjects claiming symptoms of HPPD. *Curr. Top. Behav. Neurosci.* **36**, 333–360 (2018).
13. Litjens, R. P. W., Brunt, T. M., Alderliefste, G. J. & Westerink, R. H. S. Hallucinogen persisting perception disorder and the serotonergic system: A comprehensive review including new MDMA-related clinical cases. *Eur. Neuropsychopharmacol.* **24**, 1309–1323 (2014).
14. Martinotti, G. *et al.* Hallucinogen persisting perception disorder: Etiology, clinical features, and therapeutic perspectives. *Brain Sci.* **8**, (2018).
15. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders (5th ed.)*. (2013).
16. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. *Cephalalgia* **1**, 1–211 (2018).
17. Newman, C., Jacobson, G. & Spitzer, J. Development of the Tinnitus Handicap Inventory. *Arch Otolaryngol Head Neck Surg* **122**, 143–148 (1996).
18. Jellinek Prevention. 'Why-do-they-test-drugs-the-netherlands-and-how-does-it-work'. *Accessed 3 March 2020* Available at: https://www.jellinek.nl/vraag-antwoord/why-do-they-test-drugs-the-netherlands-and-how-does-it-work/.
19. Yildiz, F. G., Turkyilmaz, U. & Unal-Cevik, I. The Clinical Characteristics and Neurophysiological Assessments of the Occipital Cortex in Visual Snow Syndrome With or Without Migraine.

Headache **59**, 484–494 (2019).

20. Puledda, F. *et al.* Occipital cortex and cerebellum gray matter changes in visual snow syndrome. *Neurology* **95**, e1792–e1799 (2020).
21. Abraham, H. D. & Hopkins Duffy, F. EEG coherence in post-LSD visual hallucinations. *Psychiatry Res. - Neuroimaging* **107**, 151–163 (2001).
22. Abraham, H. D. & Duffy, F. H. Stable quantitative EEG difference in post-LSD visual disorder by split-half analysis: Evidence for disinhibition. *Psychiatry Res. - Neuroimaging* **67**, 173–187 (1996).
23. Simantov, R. & Tauber, M. The abused drug MDMA (Ecstasy) induces programmed death of human serotonergic cells. *FASEB J.* **11**, 141–146 (1997).
24. Erritzoe, D. *et al.* In Vivo Imaging of Cerebral Serotonin Transporter and Serotonin2A Receptor Binding in 3,4-Methylenedioxymethamphetamine (MDMA or "Ecstasy") and Hallucinogen Users. *Arch. Gen. Psychiatry* **68**, 562–576 (2011).
25. Kish, S. J. *et al.* Decreased cerebral cortical serotonin transporter binding in ecstasy users: A positron emission tomography/[11C]DASB and structural brain imaging study. *Brain* **133**, 1779–1797 (2010).
26. Oliveri, M. & Calvo, G. Increased Visual Cortical Excitability in ecstasy users: a TMS study. *J Neurol Neurosurg Psychiatry* **74**, 1136–1138 (2003).
27. Bauernfeind, A. L. *et al.* Human ecstasy use is associated with increased cortical excitability: An fMRI study. *Neuropsychopharmacology* **36**, 1127–1141 (2011).
28. Cowan, R. L. *et al.* MDMA use is associated with increased spatial BOLD fMRI visual cortex activation in human MDMA users. *Pharmacol. Biochem. Behav.* **84**, 219–228 (2006).
29. Urban, N. B. L. *et al.* Sustained recreational use of ecstasy is associated with altered pre and postsynaptic markers of serotonin transmission in neocortical areas: A PET study with 11 CDASB and 11 CMDL 100907. *Neuropsychopharmacology* **37**, 1465–1473 (2012).
30. Mueller, F. *et al.* Neuroimaging in moderate MDMA use: A systematic review. *Neurosci. Biobehav. Rev.* **62**, 21–34 (2016).
31. Schankin, C. J. *et al.* The relation between migraine, typical migraine aura and 'visual snow'. *Headache* **54**, 957–966 (2014).
32. Trimbos Institute. Drugs Information and Monitoring System (DIMS) Annual Report 2018.
33. Monshouwer, K., van der Pol, P., Drost, Y. & van Laar, M. The Comprehensive 2016 Nightlife Study. *Rep. Trimbos Inst. (Netherlands Inst. Ment. Heal. Addict.* 1–135 (2017).