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ORIGINAL ARTICLE

Migraine prevalence in visual snow with prior illicit drug use (hallucinogen persisting perception disorder) versus without

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Abstract

Background and purpose: This study was undertaken to investigate migraine prevalence in persons with hallucinogen persisting perception disorder (HPPD) presenting as visual snow syndrome (VSS).

Methods: Persons with visual snow as a 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, and 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 of 37 (54.1%) controls had migraine ($p < 0.001$). VHI scores did not differ significantly between the two groups; in both groups, the median score was 38 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-fluoroamphetamine, 3-methylmethcathinone, 4-Bromo-2,5-dimethoxypenethylamine, and nitrous oxide.

Conclusions: Whereas none of the HPPD participants had migraine, more than 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 these 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 enable better management of these conditions.

KEYWORDS
ecstasy, hallucinogen persisting perception disorder, illicit drugs, migraine, visual snow

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% vs. 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; also known as MDMA, referring to its active metabolite 3,4-methylenedioxymethamphetamine), lysergic acid diethylamide (LSD), and hallucinogenic mushrooms [12–14]. The Diagnostic and Statistical Manual of Mental Disorders, 5th edition (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, that is, visual snow patients who had used illicit drugs in the 12 months prior to visual snow onset [2]. Except for a later age at 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 drug use, and 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). 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 to avoid addiction and hazardous 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 persons have been diagnosed with HPPD, including those reporting visual snow after illicit drug use. An email was sent to the patients with visual snow (identified after file review by treating physician G.J.A.) to inform them that researchers from the Leiden University Medical Center (LUMC) were interested in interviewing persons with HPPD. To avoid selection bias, the invitation contained no information on migraine or headache. After informed consent, participants underwent a structured telephone interview on visual symptoms, details of illicit drug use, and medical history and headache history (by R.M.v.D.). Headache disorders were diagnosed according to International Classification of Headache Disorders 3rd edition (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; the majority were also described in a previous retrospective study [3]. Controls had to meet previously published visual snow criteria [1,2] (Table S1), but it was not required to meet VSS criteria, because previous research showed that patients not meeting the additional symptom criterion (VS) were similar in other key clinical features to those having the full syndrome (VSS) [2]. We therefore abbreviate this group as VS(S).

Patients with visual snow who had used illicit drugs but not in the 12 months prior to visual snow onset, were not excluded from the study but included in a third group. Because 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 or older 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 on 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 Tables S2 and S3. The total score ranges from 0 to 100 (even numbers only) with "0–16" considered "slight or no handicap," "18–36" considered "mild handicap," "38–56" considered "moderate handicap," "58–76" considered "severe handicap," and "78–100" considered "catastrophic handicap."

The primary outcome of this study was the lifetime prevalence of migraine with or without aura (according to ICHD-3 criteria [16]). Additionally, we studied 1-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 whether their parents had migraine. SPSS Statistics version 26.0 for Windows was used for statistical analysis (IBM). The Mann–Whitney *U* test was used to compare numerical variables between the three groups. The chi-squared test was used for categorical variables. Probability values of less than 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 LUMC. All participants provided written informed consent.

RESULTS

Clinical characteristics

In total, *n* = 24 HPPD patients were included, as were *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 VSS 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).

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 XTC pills. Three participants indicated they were informed on the MDMA concentration of the pill (80, 220, and 225 mg, respectively), although they did not have an official test confirmation, a service available in the Netherlands with the aim of detecting serious toxic concentrations at an early stage and warning 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 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 temporarily experienced visual snow before after using XTC; in one patient symptoms lasted almost 24 h the first time, and in the other patient visual snow lasted approximately 1 month the first time. In both patients, visual snow relapsed during a next occasion of XTC use and had not disappeared since.

Cannabis was reported as a trigger by seven of 24 (29.2%) cases (Figure 2). Other mentioned drugs were psilocybin mushrooms, cocaine, "speed" (amphetamine), "4-FMP" (4-fluoroamphetamine), "3-MMC" (3-methylmethcathinone), "6-APB" (6-(2-aminopropyl) benzofuran), "2C-B" (2,5-dimethoxy-4-bromophenethylamine), ketamine, and "laughing gas" (nitrous oxide). 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 “3 months after intake”

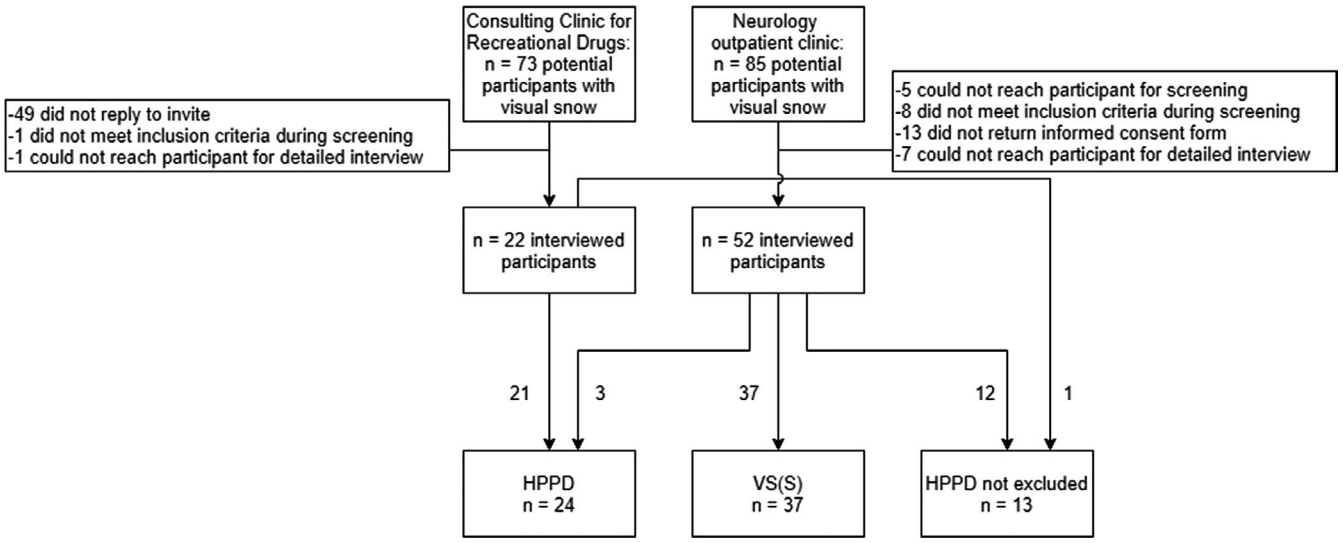

FIGURE 1 Flowchart of participant inclusion. HPPD, hallucinogen persisting perception disorder, VS(S), visual snow (syndrome). See Methods section for full study group definitions

TABLE 1 Clinical characteristics

Characteristic	HPPD, *n* = 24	VS(S), *n* = 37	HPPD not excluded, *n* = 13	*p*
Age, years	25 (23–29)*	30 (26–39)	27 (24–31)	0.031
Female	2/24 (8.3%)**	19/37 (51.4%)	6/13 (46.2%)	0.002
Visual snow as long as patient can remember	0/24 (0.0%)*	13/37 (35.1%)	0/13 (0.0%)*	<0.001
Age at onset, years	22 (19–24)	23 (15–28)[a]	23 (20–26)	0.225
Additional symptoms				
Palinopsia	15/24 (62.5%)	26/37 (70.3%)	7/13 (53.8%)	0.542
Entoptic phenomena[b]	15/24 (62.5%)	24/37 (64.9%)	6/13 (46.2%)	0.483
Nyctalopia	9/24 (37.5%)	12/37 (32.4%)	5/13 (38.5%)	0.887
Photophobia	12/24 (50.0%)	25/37 (67.6%)	8/13 (61.5%)	0.537
≥2 of the above	18/24 (75.0%)	30/37 (81.1%)	8/13 (61.5%)	0.367
Halos	12/24 (50.0%)	20/37 (54.5%)	7/13 (53.8%)	0.119
VHI score	38 (28–53)	38 (22–58)	26 (16–40)	0.452

Note: 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-squared test was used for categorical variables.

Abbreviations: HPPD, hallucinogen persisting perception disorder; VHI, Visual Snow Handicap Inventory; VS(S), visual snow (syndrome).

[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.

*$p < 0.05$ 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".

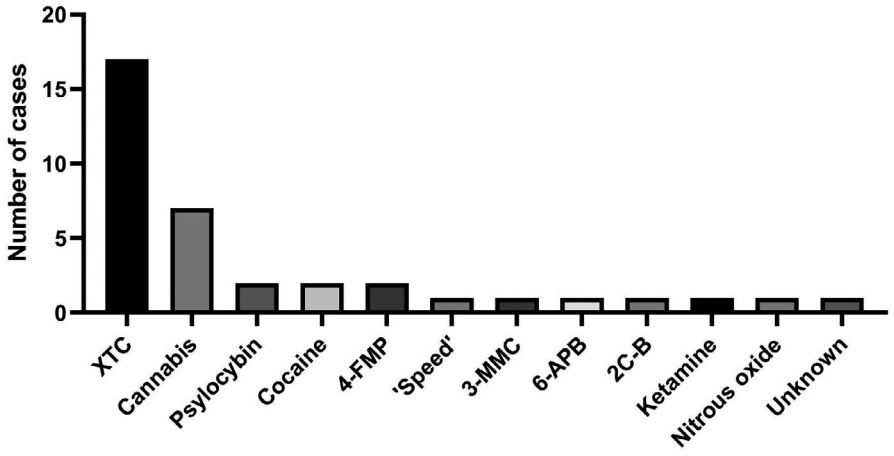

FIGURE 2 Type of illicit drugs reported as trigger by HPPD patients. APB = 6-(2-aminopropyl)benzofuran; 4-FMP = 4-fluoramphetamine, 'speed' = amphetamine, 3-MMC =3-methylmethcathinone, 2C-B = 4-Bromo-2,5-dimethoxypenethylamine; XTC = ecstasy, cannabis = marihuana or weed, psilocybin = psilocybin mushrooms; 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). The majority of XTC users, 10 of 17 (58.8%), reported an onset within 2 days. Only five of 24 (20.8%) participants reported experiencing visual hallucinations during the trip, of whom two reported that visual snow was one of these hallucinations.

Migraine prevalence

None of the HPPD cases had migraine versus 20 of 37 (54.1%) in the VS(S) group ($p < 0.001$; Table 2). Split by gender, 0 of 22 (0.0%) male HPPD patients had migraine compared to four of 18 (22.2%) male VS(S) patients ($p = 0.020$). Although 16 of 19 (85.1%) females in the VS(S) group had migraine, we refrained from statistical testing, as the HPPD group was composed of only two females. In the third group, "HPPD not excluded," three of seven males (42.9%) and three of six 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 1-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 at onset ranged from 12 to 18 years. The number of individuals with a parent with migraine did not differ between the HPPD and VS(S) groups (26.1% vs. 30.6%).

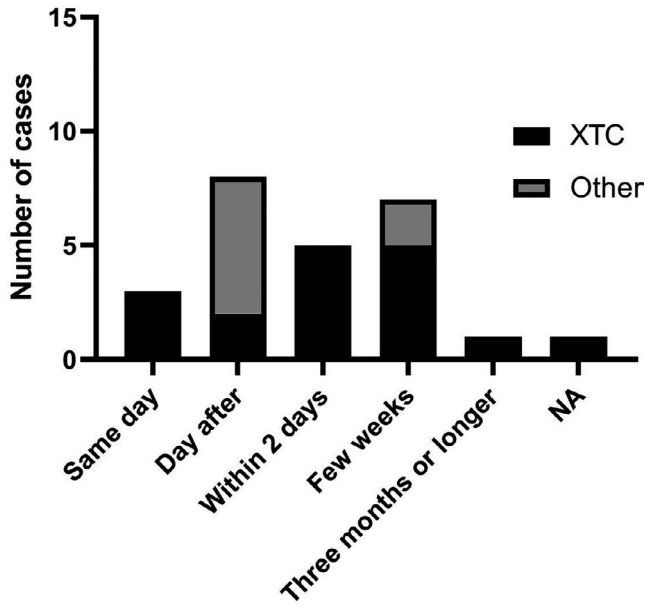

FIGURE 3 Time between intake of illicit drugs and onset of visual snow in hallucinogen persisting perception disorder (HPPD) participants. Participants with HPPD were asked about the time between intake of illicit drugs and onset of their visual snow. Data are shown separately for ecstasy (XTC; black) and other drugs (gray). 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)

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.

DISCUSSION

We studied a group of patients with visual snow who reported that the onset of visual snow was triggered by intake of illicit drugs (HPPD). Most patients had used XTC, of whom almost 60% reported visual snow started within 2 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 suggests that migraine is not a shared factor between the groups.

The relationship between visual snow and HPPD has not been extensively investigated. In early descriptions of patients with HPPD [14], visual snow was 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 drug use (HPPD) has not been made. In a recent web-based study, the groups were compared for the first time, and their clinical characteristics did not differ (except for a later age at 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 were reported to have

TABLE 2 Migraine characteristics per study group

Characteristic	HPPD, *n* = 24	VS(S), *n* = 37	HPPD not excluded, *n* = 13	*p*
Migraine, lifetime	0/24 (0.0%)*	20/37 (54.1%)	7/13 (53.8%)	0.001
Males with migraine	0/22 (0.0%)*	4/18 (22.2%)	3/7 (42.9%)	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%)	<0.001
Migraine without aura	0/24 (0.0%)	5/37 (13.5%)	0/13 (0.0%)	0.068
Migraine, age at onset, years	NA	12 (12–15)	14 (14–18)	0.283
Migraine, past 12 months	0/24 (0.0%)*	18/37 (48.6%)	5/13 (38.5%)	<0.001
Parent with migraine[b]	6/23 (26.1%)	11/36 (30.6%)	9/12 (75.0%)**	0.010

Note: Numerical variables are reported as median with interquartile range. The Mann–Whitney *U* test was used for numerical variables, and the chi-squared test was used for categorical variables.

Abbreviations: HPPD, hallucinogen persisting perception disorder; NA, not applicable; VS(S), visual snow (syndrome).

[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).

*$p < 0.05$ in post-hoc comparison with HPPD and 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".

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 a single nonspecific 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, as 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 (VEPs) [6,19], and (functional) magnetic resonance imaging (MRI) [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. In addition, 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 inhibitory neurons and that this causes less inhibition, leading to increased excitation (disinhibition theory) [21,22]. In LSD users, increased electroencephalographic 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 functional MRI 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 of whether 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 XTC 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 whether visual snow is the main symptom within this category or whether 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 (e.g., stroboscope light in discothèques), 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 noncausal 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 less than 48 h 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, because age at onset for migraine in the VS(S) controls was well below age at 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 that is a tertiary headache center as well, increasing the a priori chance of comorbid migraine. However, that other studies also observed a high prevalence of migraine in other recruitment settings [2,9] suggests that our observation is not biased. In addition, 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 nonresponders 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' symptoms had a clear temporal relationship with illicit drug use, and therefore they presented at a drug consulting clinic experienced in HPPD diagnosis.

Additionally, we used the gold 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 an outcome measure in future studies.

Given the popularity of recreational drug use, we believe future research should target visual snow as a potential aftereffect of illicit drug use. Especially XTC 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 XTC at least once in the past year) [32]. This could explain why XTC and cannabis were reported as the most common causes 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 XTC pills are rapidly increasing; in 2008 mean MDMA concentration per pill was 87 mg, in 2013 this was 148 mg, and in 2018 this rose to 171 mg [32]. These trends could have unfavorable aftereffects. In one exploratory survey in nightlife participants (of whom almost 50% indicated they had used XTC 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 XTC and other hallucinogens should be aware of visual snow as a possible persistent aftereffect, and that this potential risk warrants further research.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Robin M. van Dongen: Conceptualization (lead), data curation (lead), formal analysis (lead), investigation (lead), methodology (lead), project administration (lead), resources (equal), software (equal), visualization (lead), writing–original draft (lead), writing–review & editing (equal). **Gerard J. Alderliefste:** Conceptualization (equal), resources (supporting), writing–review & editing (equal). **Gerrit L. J. Onderwater:** Writing–review & editing (equal). **Michel D. Ferrari:** Funding acquisition (equal), supervision (equal), writing–review & editing (equal). **Gisela M. Terwindt:** Funding acquisition (equal), investigation (equal), supervision (equal), writing–review & editing (equal).

DATA AVAILABILITY STATEMENT

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

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

Table S1-S4

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