A Review of Hallucinogen Persisting Perception Disorder (HPPD) and an Exploratory Study of Subjects Claiming Symptoms of HPPD

John H. Halpern, Arturo G. Lerner and Torsten Passie

Abstract Hallucinogen persisting perception disorder (HPPD) is rarely encountered in clinical settings. It is described as a re-experiencing of some perceptual distortions induced while intoxicated and suggested to subsequently cause functional impairment or anxiety. Two forms exist: Type 1, which are brief "flashbacks," and Type 2 claimed to be chronic, waxing, and waning over months to years. A review of HPPD is presented. In addition, data from a comprehensive survey of 20 subjects reporting Type-2 HPPD-like symptoms are presented and evaluated. Dissociative Symptoms are consistently associated with HPPD. Results of the survey suggest that HPPD is in most cases due to a subtle over-activation of predominantly neural visual pathways that worsens anxiety after ingestion of arousal-altering drugs, including non-hallucinogenic substances. Individual or family histories of anxiety and pre-drug use complaints of tinnitus, eye floaters, and concentration problems may predict vulnerability for HPPD. Future research should take a broader outlook as many perceptual symptoms reported were not first experienced while intoxicated and are partially associated with pre-existing psychiatric comorbidity.

Keywords Hallucinogen Persisting Perceptual Disorder (HPPD) · Drug-induced flashback · Flashback · LSD · Hallucinogens · Posttraumatic Stress Disorder (PTSD) · Dissociation

J.H. Halpern (✉) · T. Passie
Laboratory for Integrative Psychiatry, Division of Alcohol and Drug Abuse,
McLean Hospital, 115 Mill Street, Oaks Building, Belmont, MA 02478-1064, USA
e-mail: john_halpern@gmail.com

J.H. Halpern · T. Passie
Department of Psychiatry, Harvard Medical School, Boston, MA, USA

A.G. Lerner
Lev Hasharon Mental Health Center, Pardesya, Israel

A.G. Lerner
Sackler Medical School, Tel Aviv University, Tel Aviv, Israel

T. Passie
Senckenberg Institute for History and Ethics in Medicine, Goethe-University
Frankfurt/Main, Frankfurt, Germany

Contents

1 Introduction

The use of hallucinogens in uncontrolled settings is widespread. In the USA, 19 % of adults by age 50 are estimated to have tried a hallucinogen (Johnston et al. 2013). Most such drug experiences occur without medically significant sequelae, but there have long been reports of subsequent perceptual effects in some users (Ellis 1898; Mayer-Gross 1931; Fischer 1971, 1976; Naditch 1974; Holsten 1976; Matefy et al. 1978).

1.1 Definitions of Hallucinogen Persisting Perceptual Disorder (HPPD)

The first formal description of "a repetition of the acute phase of the experience days or even weeks after the initial doses" emerged from a study of LSD-assisted psychotherapy (Sandison and Whitelaw 1957). Around 1970, the term "flashback" began to appear in the literature; as in Heaton and Victor (1976): "A flashback is the transient recurrence of psychedelic drug symptoms after the pharmacologic effects of such drugs have worn off and a period of relative normalcy has occurred." The ICD-10 (World Health Organization 1992) lists "F16.283 hallucinogen dependence with hallucinogen persisting perception disorder (HPPD) (flashbacks)" as temporary, short-lived re-experiences of aspects of the initial drug intoxication. Clinically meaningful impairment and/or suffering are required for its diagnosis. The DSM-V (American Psychiatric Association 2013) lists "HPPD (Flashbacks)" as a typically temporary re-experience of aspects of the drug intoxication. It also includes a subform involving long-term visual disturbances (Textbox 1). Identification of this form of HPPD is based on work by one psychiatrist researching this specific domain (Abraham 1982, 1983; Abraham and Aldridge 1993). Systematic and group

studies exist for the brief temporary "flashback" type and some case studies for the chronic subtype; only a few studies have examined flashbacks in groups of users (Halpern and Pope 2003).

Textbox 1

DSM-V criteria for HPPD
(A) 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 (e.g., geometric hallucinations, false perceptions of movement in the peripheral visual fields, flashes of color, intensified colors, trails of images of moving objects, positive afterimages, halos around objects, macropsia, and micropsia)
(B) The symptoms in Criterion A cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
(C) The symptoms are not due to a general medical condition (e.g., anatomical lesions and infections of the brain, and visual epilepsies) and are not better accounted for by another mental disorder (e.g., delirium, dementia, and Schizophrenia) or hypnopompic hallucinations

To meet DSM-V criteria, hallucinogen use must precede the syndrome. The word "re-experiencing" in criterion A indicates that the symptom should resemble that of an actual hallucinogen-induced experience.

The requirement for "distress or impairment" in criterion B suggests that perceptual phenomena should be outside the range of normal experience. For example, seeing bright spots in front of one's eyes upon entering a dark room should not qualify.

Criterion C requires that alternative etiologies for perceptual changes be considered before diagnosing HPPD. DSM-V cites visual seizure, migraine, delirium, dementia, schizophrenia, hypnopompic hallucination, post-traumatic stress disorder (PTSD), and depersonalization and derealization associated with significant anxiety and depression as specific disorders to rule out. Finally, one must exclude other hallucinogen-induced disorders recognized by DSM-V, such as hallucinogen-induced psychotic, mood, or anxiety disorders.

1.2 Two Entities of HPPD

These definitions and other work (Hermle et al. 2008; Holland and Passie 2011) may warrant distinguishing two types of HPPD. We offer these tentatively to help define the findings of this article in terms of the literature. We note that Abraham's definition of HPPD with continuous visual perception disorders is still a subject of debate due to the absence of replication studies and methodological concerns (Halpern and Pope 2003; Studerus et al. 2011; Holland and Passie 2011).

1. *Type 1 HPPD* (consistent with the ICD-10 definition) consists of brief re-experiences of alterations in perception, mood, and/or consciousness, as previously experienced during a hallucinogenic intoxication. Brevity, infrequency, and intermittency of symptoms are signified in the concept of a "flashback" (ICD-10). "Flashbacks are sudden and unexpected re-experiences of aspects of a psychedelic drug trip that happened weeks, months, or even years before" (Matefy et al. 1979). Type 1 HPPD symptoms may be pleasurable and even controllable (Hasse and Waldmann 1971; Holsten 1976). They appear days to months after the hallucinogen-induced experience, sometimes without apparent cause. The subject is usually aware of the unreality of the experience. Often symptoms are visual increases in perceived color intensity, dimensionality, or vibrancy; illusory changes; and/or movement of a perceived object. The perception of time may be altered. Strong emotion felt during the drug experience may recur and in some cases ego boundaries can become diffuse. A significant element of the definition of HPPD in the ICD-10 is: "Flashbacks may be distinguished from psychotic disorders partly by their episodic nature, frequently of very short duration (seconds or minutes), and by their duplication (sometimes exact) of previous drug-related experiences." Relevant reviews concluded that "they are usually self-limited and diminish in duration, intensity and frequency with time…" (Strassman 1984; see also Horowitz 1969; Siegel and Jarvik 1975; Holland and Passie 2011).
2. *Type 2 HPPD* (consistent with Abraham (1983) and part of the definition in the DSM-V) entails constant or near-constant visual effects. These can include the following:

    1. Palinopsia: the persistent perception of an object removed from view;
    2. halos: a brightening glow or colored shining/shimmering surrounding objects;
    3. trails or akinetopsia: a series of discrete positive afterimages following in the wake of moving objects; and
    4. visual snow: a TV static-like graininess superimposed upon the visual field.

Symptoms may occur alone or in combination. Sound and other perceptions are unaffected. In most cases, visual phenomena are reported to be uncontrollable and disturbing, though some individuals regard them as enriching (Baggott et al. 2011). Claimed constant visual phenomena are often accompanied by mild-to-moderate depersonalization, derealization, anxiety, or depression (Holland and Passie 2011). These psychopathological states are claimed to trigger the occurrence and intensity of visual phenomena (Abraham 1982, 1983; Abraham and Duffy 1996, 2001) depending on the waxing and waning nature of current affect.

Interestingly, Type 2 HPPD was never clearly reported during the 1960s when millions of Americans took LSD on a regular basis with less knowledge about hallucinogens and more resultant complications. HPPD was not described in the comprehensive retrospective surveys of LSD use in psychotherapy in approximately 10,000 patients during the 1950–1960s (Cohen 1960; Malleson 1971; Passie 1997).

1.3 Prevalence

Data do not permit us to estimate, even crudely, HPPD's prevalence according to DSM-V or ICD-10 criteria. Although millions of doses of hallucinogens were consumed by millions of individuals since the 1960s (SAMHSA 2011), few large HPPD case series were reported. Horowitz (1969), Cohen (1960, 1977) estimate the incidence of Type 1 HPPD in a population of regular hallucinogen users in the 1960–1970s as 1:20. Type 2 HPPD, if it exists as a reliable and distinct entity, appears to be very rare (Hermle et al. 2008, 2015; Holland and Passie 2011). Grinspoon and Bakalar (1997) estimate that Type 2 HPPD occurs in 1 of 50,000 hallucinogen users. Baggott et al. (2011) collected data online in a Web-based questionnaire from 2455 individuals reporting visual experiences while drug-free that resembled a past hallucinogen intoxication. Most of these experiences were simple, non-disturbing "flashbacks," while 4.2 % found these visual phenomena significant enough to at least contemplate seeking treatment.

1.4 Reviews of Data and Theories on HPPD

Comprehensive reviews of the literature (Halpern and Pope 2003; Holland and Passie 2011) show that HPPD definitions vary broadly in the scientific literature. The disorder's clinical relevance and etiologies remain unclear. Causation may be linked to a complex set of triggers alone or in combination (see Fig. 1).

The known neurochemical activity of hallucinogens is poorly correlated with their physiological and cognitive effects (Brimblecombe and Pinder 1975; Nichols 2004; Passie and Halpern 2014). We have virtually no data on the processes occurring during the latency between drug effect and flashback or on what predisposing vulnerabilities may result in the two types of HPPD. HPPD may also easily be confused or misdiagnosed for some other ophthalmological, neurological, or psychopathological phenomena (see Materials and Methods below for a list). Several studies show HPPD-like experiences (intense memories, depersonalization, derealization, and over-intensification of perceptional phenomena) occur quite often in normal, healthy populations (Parish 1894; Shor 1960; Dixon 1963; Kokoszka 1992–1993). Even Abraham (1984) acknowledges that several non-LSD exposed individuals in his study on visual phenomenology of the LSD flashback (1983) described visual disturbances similar to those reporting LSD flashbacks (although with much less intensity and number of symptoms).

Holland and Passie's (2011) evaluation of proposed etiological models found that in every case, individuals reporting flashbacks experienced some elements relating to the original experience—level of arousal, music playing, environmental cues, ingesting the same kind of drug, time of day, and so forth. Therefore, different etiologies may apply to each specific case. But for every case, the formative causes of such associations may vary—sensitization effects, trauma and reaction patterns, state-dependent memory, psychophysical vulnerabilities, and more (Fig. 1).

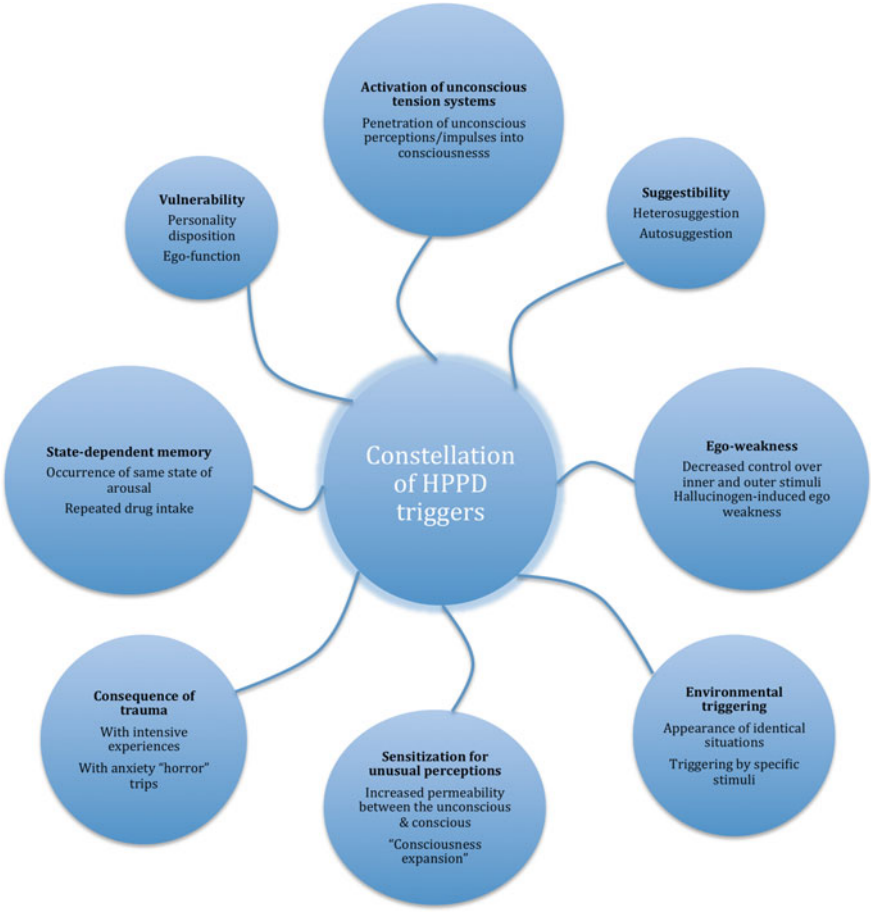


Fig. 1 Factors and triggers for the occurrence of HPPD phenomena (based on Holland and Passie 2011). According to the model of Holland and Passie (2011), a different pattern of factors (alone and/or in combination as well as their specific quantitative influences) contributes to the occurrence of HPPD in every instance

1.5 Risk Factors Associated with HPPD?

There are no recognized risk factors for HPPD (Halpern and Pope 2003). Some report a relationship between flashbacks and number of drug exposures (McGlothlin and Arnold 1971; Abraham 1983), but others have not (Horowitz 1969; Stanton and Bardoni 1972; Matefy et al. 1978). Abraham (1982, 1983) speculates there might be a very rare psychophysical vulnerability to a supposed toxic effect of LSD in Type 2 HPPD. In Type 1 HPPD, some older studies suggest pre-existing personality features (Naditch and Fenwick 1977), suggestibility

(Heaton and Victor 1976), or pre-existing psychopathology (Abraham and Duffy 1996) as possible contributing factors.

1.6 Treatment Options

No controlled treatment studies exist. Treatment of Type 1 HPPD is obviously brief; only very rarely will Type 1 HPPD lead to clinically relevant pathology. For those claiming Type 2 HPPD, improvements have been reported with sunglasses (Abraham 1983) and psychotherapy (Abraham et al. 1996). With Type 2 HPPD, antipsychotic drugs worsened some symptoms (Abraham and Mamen 1996; Morehead 1997, Lerner et al. 2002; Goldman et al. 2007). SSRIs worsened 4 cases documented by Markel et al. (1994), but other clinicians report improvements (Young 1997; Aldurra and Crayton 2001). Anti-seizure drugs and clonidine were also used with some success (Alarcon et al. 1982; Lerner et al. 2000). It is not easy to determine how best to treat HPPD given this literature. The widely variable, partially contradictory findings may require us to speculate on placebo effects, idiosyncratic neurochemistry, and spontaneous recovery, or perhaps more simply, an inadequately defined HPPD.

2 Materials and Methods

We conducted a study with a questionnaire specifically developed to identify prevalence and characteristics of self-reported altered perception experiences in hallucinogen users and to find relationships with drug use. Despite the obvious limitations of self-report questionnaires, a more carefully and thoroughly designed Web application seemed appropriate for delineating types of visual phenomena, triggering drug experiences, pre-existing medical conditions, general drug using habits, personality features, and more.

We sought individuals reporting persisting disorders of perception that started or worsened after a "triggering event," usually a drug intake, but other causes were explicitly not excluded. In this way, those who experienced problems prior to drug use, or even without a history of drug use, as well as those with a hallucinogen-related onset could complete the survey. Participants first gave informed consent as approved by the Institutional Review Board of McLean Hospital, assuring confidentiality. Survey software was LimeSurvey (v1.1; www.limesurvey.org) and was hosted on hospital servers for completion by adults aged 18 or older with access to the Internet. Recruitment occurred by word of mouth, postings about the survey at Web sites devoted either to the HPPD community or to those interested in the effects of hallucinogens, or from informing self-identified HPPD patients who had sought out the authors about the condition in response to the authors' prior publications on this condition. No compensation was provided for participation.

Subjects were asked about date of birth, marital status, level of education attained, employment, and family mental health and drug abuse. Then, a differential-diagnosis

list was presented with yes/no buttons for disorders that might account for HPPD-type symptoms: HPPD, "visual snow," brain lesion, brain infection/meningitis, seizure disorder in general, temporal lobe epilepsy, persistent migraine aura, schizophrenia or other psychotic disorder, bipolar disorder, PTSD, borderline personality disorder, conversion disorder, hypochondriasis, dissociative disorder (including Dissociative Identity Disorder), delirium, dementia, corneal or retinal disorder or damage to the eye in general, optic neuritis, multiple sclerosis, Charles Bonnet Syndrome, or Lyme disease.

The survey asked participants to rank the severity of disturbance across senses (vision, hearing, smelling, balance, touch, taste, and pain). Subjects were required to detail which drug, substances, or other triggering events they associate with their subsequent disorder. They were asked to quantify dose, frequency of use, drugs used in combination, prior drug use, drug use since HPPD-like symptoms commenced, and to list and rank which substances may worsen or improve the condition from an extensive list of drugs and drug categories. Subjects had to select a defined time interval from time of triggering event to time of development of HPPD-like symptoms. Subjects were asked about the presence of anxiety or panic before, during, and after the triggering event, including whether prior experiences with the same offending drug included anxiety or panic. Subjects listed the number of doctors, if any, they sought for treatment of their perception disorder. They were asked whether their condition made them contemplate or attempt suicide. They also had access to textboxes to write freely about their situations.

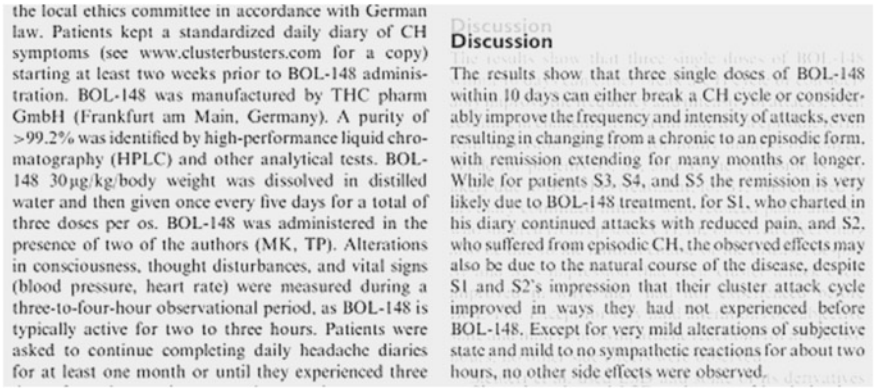
Based on clinical experience, subjects were asked about 21 forms of visual disturbance and 4 other symptoms (problematic concentration, communication, auditory hallucination, and tinnitus). For each statement, the participant had to declare whether or not the symptom presented occurred before the triggering drug event, during the worst episode of perception distortions, and in the last 30 days. For each of these three time points, subjects were asked to rank from 0 to 100 the severity of the symptom presented, the time duration and frequency the symptom would occur, and how much the particular symptom reminds them of what they experienced during the HPPD-triggering drug event.

Participants completed the 28-question Dissociative Experiences Scale (DES), a reliable, validated self-report measure quantifying the frequency of dissociative experiences (Bernstein-Carlson and Putnam 1986; Carlson and Putnam 1993). There are also three subscales evaluating forms of dissociation: amnestic (memory losses), absorption and imaginative involvement (preoccupations that distract from

Fig. 2 Photograph 1. Negative afterimage

present occurrences), and depersonalization and derealization (detachments from sense of self and/or mental function; sensations of unreality). Higher scores correlate with increased clinical severity of dissociation. Depending on population, normative scores range from 4 to just below 20. Scores greater than 20 are suggestive of PTSD or a dissociative disorder. Scores of 45 or more suggest severe conditions such as Dissociative Identity Disorder.

Finally, four photographs (see Figs. 2, 3, 4 and 5) and one short animation (http://www.youtube.com/watch?v=y63juPiMHu4) were presented, and subjects were asked to quantify how well they represented aspects of their symptoms.


the local ethics committee in accordance with German law. Patients kept a standardized daily diary of CH symptoms (see www.clusterbusters.com for a copy) starting at least two weeks prior to BOL-148 administration. BOL-148 was manufactured by THC pharm GmbH (Frankfurt am Main, Germany). A purity of >99.2% was identified by high-performance liquid chromatography (HPLC) and other analytical tests. BOL-148 30µg/kg/body weight was dissolved in distilled water and then given once every five days for a total of three doses per os. BOL-148 was administered in the presence of two of the authors (MK, TP). Alterations in consciousness, thought disturbances, and vital signs (blood pressure, heart rate) were measured during a three-to-four-hour observational period, as BOL-148 is typically active for two to three hours. Patients were asked to continue completing daily headache diaries for at least one month or until they experienced three

Discussion

Discussion

The results show that three single doses of BOL-148 within 10 days can either break a CH cycle or considerably improve the frequency and intensity of attacks, even resulting in changing from a chronic to an episodic form, with remission extending for many months or longer. While for patients S3, S4, and S5 the remission is very likely due to BOL-148 treatment, for S1, who charted in his diary continued attacks with reduced pain, and S2, who suffered from episodic CH, the observed effects may also be due to the natural course of the disease, despite S1 and S2's impression that their cluster attack cycle improved in ways they had not experienced before BOL-148. Except for very mild alterations of subjective state and mild to no sympathetic reactions for about two hours, no other side effects were observed.

Fig. 3 Photograph 2. Ghosted text in right column (portion of photograph 1)

Fig. 4 Photograph 3. Positive afterimage

Fig. 5 Photograph 4. Repeating pattern only in snow (portion of photograph 3)

The photographs included a negative afterimage of a flower in a different color, a page of text with a ghosted second text over it, a positive afterimage, and a repeating geometric pattern superimposed upon a winter scene. The animation was a single photograph with a repeating loop of flickering grain to simulate "visual snow."

3 Results

Though subjects could save their answers and resume later (3 did), only 23 subjects completed the survey out of 67 who started it. The survey took 2 h to complete on average. Of the 23, two were healthy normals. One individual noted persisting perception problems after head trauma and temporal lobe epilepsy. These 3 individuals were excluded from further evaluation for not reporting Type 1 or Type 2 HPPD-like symptoms. One (Subject 5) reported "visual snow" since age 5 with no drug use but is included in the dataset because of HPPD-like symptoms.

Nineteen subjects (15M/4F) reported persisting perceptual disturbances triggered or worsened by past drug use. Sixteen were evaluated by physicians because of their disorder. Six were (co-)diagnosed with HPPD (all of the Type 2 variety), 3 persistent migraine aura, 2 psychotic disorders, 1 PTSD and 3 other anxiety disorders, 2 depression, 2 hypochondriasis (one of whom claims related eye injury and PTSD), and 3 dissociative disorders (one also having a history of psychosis). Family psychiatric histories included 6 reporting depression and/or anxiety in a primary relative.

In terms of demographics, mean age was 25.8 years (median 24.5, 18–40 range). Three were married and 17 single (2 cohabiting). Educational levels included 1 grade school graduate, 1 some high school, 3 high school graduates, 2 technical/vocational graduates and 1 who had started but not finished, 5 with some college, 6 college graduates, 1 with some graduate education, and 1 completed a master's degree. All participants self-identified as white. Prior-year income was 3 unemployed or on disability, 5 earning less than $10,000, 4 less than $25,000, 4 less than $50,000, 3 less than $75,000, and 1 more than $250,000.

In the survey, 17 complained of active symptoms consistent with Type 2 HPPD. When asked about perception disturbance symptoms (see Table 4), all 20 subjects noted they experienced some abnormality in the prior 30 days including all 20 reporting nighttime visual snow. All 20 report a chronic condition with 4 having symptoms of 1–6 months, 1 for less than 1 year, 4 for 1–2 years, and 11 for years longer. All 20 selected vision as their most significantly altered sense.

Other than Subject 5, all believe a drug triggered their perception disorder or markedly worsened visual symptoms associated with persisting migraine with aura (subjects 3 and 14). Seven subjects report symptoms starting after a single drug exposure. LSD was most commonly identified (12 of 19) and then psilocybin (4 of 19) (see Table 1). Four reported other substances: Subject 2, MDMA with alcohol; Subject 3, marijuana; Subject 13, 2C-I (2,5-dimethoxy-4-iodophenethylamine); and Subject 11, amphetamines, opiates, and an SSRI. Subjects 2, 3, and 13 had never tried LSD or psilocybin prior to their triggering experience. Subject 11 extensively used hallucinogens years before his disorder started (see Table 2), which occurred on his first day on the SSRI antidepressant citalopram, intensifying over the two weeks he continued to take it. Overall, subjects described an extensive range of drug and alcohol use histories. Twelve individuals' reports met criteria for a drug use disorder for one or more substances (see Table 2) prior to the start of persisting perception problems and 8 did after such problems started (Table 3). Subjects reported decreasing hallucinogen use after the start of their persisting perception disorder (with, e.g., 7 individuals admitting to use of LSD prior to the disorder and only one subject reporting subsequent LSD use).

Twelve claimed perception disturbances began during or within 24 h of the triggering drug experience (Table 1). Seven described disturbances starting one week to months after the experience (the rest of the individuals, as listed in Table 1, had symptoms start within 1 week or 1 month or longer). Five of the 7 felt they had no explanation for their condition other than this past drug exposure, yet only 4 of these 7 found perceptual disturbances reminiscent of the drug intoxication. In fact, only 8 of 19 subjects agreed to any degree that their symptoms are "exactly like" their triggering drug experience (see Table 4). However, all 19 recalled anxiety and/or panic reactions while on the drug. Of the 14 who described the intensity of their anxiety, 1 selected "mild," 1 "moderate," 5 "marked," and 7 "extreme." Three admit to psychiatric hospitalization because of their perception disorder.

Table 4 presents the 25 statements of symptoms (see also Textbox 2 for a typical HPPD history). Subject 5, with persisting migraine aura and complaints of visual snow, reported no history with hallucinogens or other drugs of abuse, yet she

Table 1 Drug use reported as contributing to triggering a persisting perception disorder

When did the altered perceptions start?	Subject #	Alcohol	Tobacco	MJ	Synthetic MJ	LSD	Psilocybin	2C	MDMA	Amphe-tamines	Opiates	Sedative-hypnotics	SSRI	Other
Within 3 months	1		Y				Y							
Within 24 h	2	Y							Y					
Almost immediately	3			Y										
Almost immediately[b]	4		Y	Y		Y	Y							
Started age 5. Never any drug use[a]	5													
Almost immediately	6					Y								
Almost immediately	7			Y		Y								
Almost immediately	8					Y								
Within 3 months[b]	9		Y	Y		Y			Y			Y	Y	
Almost immediately	10					Y								
Almost immediately	11									Y	Y		Y	
Within a month	12					Y[c]		Y[c]						

(continued)

Table 1 (continued)

When did the altered perceptions start?	Subject #	Alcohol	Tobacco	MJ	Synthetic MJ	LSD	Psilocybin	2C	MDMA	Amphe-tamines	Opiates	Sedative-hypnotics	SSRI	Other
Within 24 h	13							Y						
Within 24 h	14	Y	Y	Y		Y								
Within a month	15						Y		Y					
Almost immediately	16		Y	Y		Y								
Within a month	17	Y	Y	Y		Y		Y	Y					
A week after	18	Y	Y	Y	Y		Y		Y					LSA & Bromo-dragonfly
A week after	19	Y				Y								
Almost immediately	20	Y					Y							amoxicillin

Each subject who consumed one or more of the following drugs considered them to contribute or somehow be related to resultant disorders of perception. For some, there was a brief period of heavy polydrug use over a short time-span, for others they distinctly refer to a single drug event. Drugs that no one responded as having taken are not listed. We asked specifically about use of alcohol, tobacco, cannabis, synthetic cannabinoid analogs, 2-C series hallucinogens, DMT, mescaline, MDMA, 5-MeO-DIPT, alpha-methyltryptamine, Salvia divinorum, ketamine, PCP, dextromethorphan, cocaine, stimulant/amphetamines, inhalants, sedative-hypnotic/anxiolytics, traditional antipsychotics, atypical antipsychotics, SSRIs, TCAs, SNRIs, opiate antagonists, anticonvulsants, and Other. Subjects 3 and 14 have persisting migraine aura which pre-dated their drug use and found drug use worsened their visual symptoms. Shaded rows signify that the subject reported their perception disorder commenced after only a single drug exposure/event

Y = yes, drug consumed/contributed to disorder

[a]History of psychotic disorder

[b]Subject 5 with persisting migraine aura and no drug use associated with perception disturbances

[c]Subject is unsure if this was the drug consumed

Table 2 Drug use reported before persisting perception disorder started

Subject #	Drug																		
	Alcohol	Tobacco	MJ	Synthetic MJ	LSD	Psilocybin	2C	Mescaline	MDMA	S. divinorum	Ketamine	PCP	Cocaine	Amphetamines	Opiates	Inhalants	Sed/ Hypnotics	SSRI	SNRI
1	Y	Y	Y											Y					
2	Y		Y						Y				Y						
3	Y	Y	Y						Y				Y	Y	Y		Y		
4	Y	Y	Y																
5																			
6	Y	Y	Y																
7																			
8	Y	Y	Y														Y		
9		Y	Y			Y			Y				Y			Y			
10			Y																Y
11	Y	Y	Y		Y	Y		Y	Y		Y		Y	Y	Y				
12	Y				Y		Y[a]												
13							Y		Y					Y				Y	
14	Y	Y			Y				Y				Y						
15	Y		Y	Y	Y	Y	Y	Y	Y	Y				Y					
16	Y	Y	Y	Y	Y				Y	Y	Y		Y	Y		Y			
17	Y	Y	Y	Y	Y	Y			Y	Y									Y
18	Y	Y	Y																
19	Y		Y		Y							Y				Y			
20	Y																		

The following drugs were consumed BEFORE persisting perception problems started (or worsened for subjects 3 and 14) and such use is separate from association with the drug-triggering event ("Y" = yes, drug consumed; blank = drug not consumed). Any evidence of drug abuse or dependence results in a "**Y**" that is bolded. We asked specifically about use of alcohol, tobacco, cannabis ("MJ"), synthetic cannabinoid analogs ("synthetic MJ"), 2-C series hallucinogens, DMT, mescaline, MDMA, 5-MeO-DIPT, alpha-methyltryptamine, Salvia divinorum, ketamine, PCP, dextromethorphan, cocaine, stimulant/amphetamines, inhalants, sedative-hypnotic/anxiolytics, traditional antipsychotics, atypical antipsychotics, SSRIs, TCAs, SNRIs, opiate antagonists, anticonvulsants, and Other. Drugs that no one responded as having taken are not listed.

[a]Subject is unsure if this was the drug consumed.

Table 3 Drug use reported after persisting perception disorder started

Subject #	Drug																				
	Alcohol	Tobacco	MJ	Synthetic MJ	LSD	Psilocybin	2C	MDMA	S. divinorum	Ketamine	Cocaine	Amphetamines	Opiates	Inhalants	Sed/ Hypnotics	Atypical antipsychotics	SSRI	SNRI	Opioid antagonist	Anticonvulsant	Other
1	Y	Y	Y																		
2	Y							Y							Y						
3								Y					Y		Y						
4	Y	Y	Y																		
5	Y	Y													Y	Y	Y				
6	Y																				
7																					
8	Y	Y	Y																		
9	Y	Y	Y					Y						Y							
10															Y	Y	Y				
11	Y		Y										Y								
12																					
13		Y					Y	Y				Y									Mephedrone
14	Y	Y	Y									Y					Y				
15	Y		Y	Y					Y						Y	Y			Y		
16	Y	Y	Y	Y				Y		Y				Y	Y					Y	Mephedrone
17	Y	Y	Y	Y																	
18	Y	Y	Y			Y		Y				Y	Y		Y	Y	Y	Y			
19	Y		Y		Y						Y			Y	Y		Y				
20	Y														Y			Y			

The following drugs were consumed AFTER persisting perception problems started (or worsened for subjects 3 and 14) and such use is separate from association with the drug-triggering event ("Y" = yes, drug consumed; blank = drug not consumed). Any evidence of drug abuse or dependence results in a "**Y**" that is bolded. We asked specifically about use of alcohol, tobacco, cannabis ("MJ"), synthetic cannabinoid analogs ("synthetic MJ"), 2-C series hallucinogens, DMT, mescaline, MDMA, 5-MeO-DIPT, alpha-methyltryptamine, Salvia divinorum, ketamine, PCP, dextromethorphan, cocaine, stimulant/amphetamines, inhalants, sedative-hypnotic/anxiolytics, traditional antipsychotics, atypical antipsychotics, SSRIs, TCAs, SNRIs, opiate antagonists, anticonvulsants, and Other. Drugs that no one responded as having taken are not listed.

Table 4 Queried symptoms of persisting perception disorder

Symptom	# of subjects (max = 19) reporting symptom prior to drug use that triggered persisting perception disorder	Mean severity of symptom (0–100)	# of subjects (max = 20) reporting symptom during worst persisting perception episode	Mean severity of symptom (0–100)	# of subjects (max = 20) reporting symptom over the prior 30 days	Mean severity of symptom (0–100)	% of subjects who find symptom a little or more reminiscent of what was experienced during the drug intoxication(s) attributed to triggering persisting perception disorder (%)
Difficulty with color identification	1+	32	11++	43.5	9++	38.7	72.7
Seeing "halos" or "auras" around objects/people	2	14.5	18++*	69.8	18++*	58.7	88.2
Stationary objects appear to sway or move	1	27	15++*	68.5	15++*	48.6	100
See objects or faces when pressure placed to closed eyes	3+	7.3	11++*	56	10++*	39.6	80
Colored objects change in brightness	1	5	12++	58.3	12++	36.6	75
Macropsia	0	–	6	40.2	4	14.5	100
Micropsia	0	–	4*	35.3	2	17.5	100
Afterimage in other color	7++	4.7	18++*	67.2	18++*	52.1	88.2

(continued)

Table 4 (continued)

Symptom	# of subjects (max = 19) reporting symptom prior to drug use that triggered persisting perception disorder	Mean severity of symptom (0–100)	# of subjects (max = 20) reporting symptom during worst persisting perception episode	Mean severity of symptom (0–100)	# of subjects (max = 20) reporting symptom over the prior 30 days	Mean severity of symptom (0–100)	% of subjects who find symptom a little or more reminiscent of what was experienced during the drug intoxication(s) attributed to triggering persisting perception disorder (%)
Afterimage in same color	3++	4	15++*	71	15++*	59	85.7
Trailing image to moving object	3+	9.3	17++*	61.9	17++*	46.5	93.8
Seeing faces/objects in wood, clouds, trees	4++	11.3	7	54.4	6	32.6	71.4
"TV Static" (visual snow) projected over vision in DAYTIME	5+	16.8	19++*	69.4	19++*	62.4	66.7
"TV Static" (visual snow) projected over vision in NIGHTTIME	8	10.8	20++*	77.2	20++*	60.9	78.9
"Floaters" in field of vision	13++	23.5	18++*	69.6	18++*	59.3	70.6

(continued)

Table 4 (continued)

Symptom	# of subjects (max = 19) reporting symptom prior to drug use that triggered persisting perception disorder	Mean severity of symptom (0–100)	# of subjects (max = 20) reporting symptom during worst persisting perception episode	Mean severity of symptom (0–100)	# of subjects (max = 20) reporting symptom over the prior 30 days	Mean severity of symptom (0–100)	% of subjects who find symptom a little or more reminiscent of what was experienced during the drug intoxication(s) attributed to triggering persisting perception disorder (%)
Ghosted afterimage of text being read	1	20	16++*	76.4	15++	67.6	66.7
"Flash" of bright light appearing without explanation	2	2.5	11 + *	66.8	12 + *	50.7	72.7
Geometric patterns in field of vision whether eyes open or closed	2	12.5	13++*	56	12++*	40.8	100
Difficulty communicating thoughts	9+	8.8	18++*	63	18++*	43.2	88.2
Perceiving room as moving	1	1	16++*	49.4	13++*	38.8	93.3
Auditory hallucinations ("voices")	0	–	7++*	29.3	4++	16.8	66.7
Feel pressure in the head	4	6.5	16++*	58	15++*	34	13

(continued)

Table 4 (continued)

Symptom	# of subjects (max = 19) reporting symptom prior to drug use that triggered persisting perception disorder	Mean severity of symptom (0–100)	# of subjects (max = 20) reporting symptom during worst persisting perception episode	Mean severity of symptom (0–100)	# of subjects (max = 20) reporting symptom over the prior 30 days	Mean severity of symptom (0–100)	% of subjects who find symptom a little or more reminiscent of what was experienced during the drug intoxication(s) attributed to triggering persisting perception disorder (%)
Difficulty to light accommodation	6+	6.7	19++*	63	19++*	50.6	77.8
Trouble with concentration	14+	23	19++*	75.4	18++*	59.7	83.3
Faces appear distorted	0	–	11++*	41.2	7++	30.1	100
Tinnitus (ringing in ears)	12++	7.4	19++*	49.4	19++*	32	86.7

"+"/"++" = the # of subjects includes either one subject ("+") with a history of psychotic disorder or both subjects ("++") with that history, "*" = the # of subjects includes Subject 5 with persisting migraine aura and no drug use associated with perception disturbances; "+" and "*" is to show how symptoms broadly overlap between those with a history of psychosis, the individual with no drug use, and those reporting HPPD symptoms post-drug use

reports symptoms similar to those who claim an association between their drug use and perceptual disorders.

Textbox 2

Typical history of type 2 HPPD (subject 1)

The long story short is I ate 2.5 g of strong shrooms. My family has a history of anxiety and depression, which I was not really aware of at the time. The trip itself started amazingly then took a turn for the worse when I got a stomachache. I bad tripped for a couple hours, but I told myself it would end at some point and mainly relegated myself to a chair and just chilled with my eyes closed. It was a bad setting with many people coming in and out of my residence, and this definitely made the vibe worse. Eventually, I felt better, and the trip was cool again…all ended well. Several months later, I started having trouble sleeping due to extremely bright closed-eye blotchy shapes that oozed around whenever I tried to sleep. Also at this time, I started having severe panic attacks that brought me to the hospital several times (only to be told that I was fine). The next 8 months was hell. I was convinced I was slowly going crazy, and that I would have to be committed. Then I found out about HPPD and have worked to beat it. At this point, I am happy. I have occasional anxiety, but my symptoms of depression and depersonalization have gone down drastically. In turn, my visual symptoms are less as well, although I still notice them every day (they don't bother me as much now). I have a ringing in my ears a lot of the time though, which is very bothersome. I have the sensation that I'm hearing sounds sometimes, but I usually chalk it up to being anxious and hypersensitive to my environment. Many times, I have found the source of the sound that I suspected to be not real (i.e. a beeping watch under some clothes, etc.) I find the fear of going crazy/hearing voices/seeing things that aren't there the permeating factor in many people with HPPD I've talked to, also including myself. Even though I've never actually heard or seen anything not real (besides HPPD visual phenomena which I don't consider "seeing" but rather "perceiving"), I have a worry that I soon will. I have largely gotten over this worry

To diagnose HPPD, symptoms must meet the DSM-V Criterion A: "The re-experiencing, following cessation of use of a hallucinogen, of one or more of the perceptual symptoms that were experienced while intoxicated with the hallucinogen." Of the 19 subjects associating their symptoms with drug use, only 5 symptoms were agreed by all who had that symptom that it felt somewhat or more like a re-experiencing of the triggering drug experience: "macropsia," "micropsia," "stationary objects appear to sway or move," "seeing geometric patterns in their field of vision whether eyes are open or closed," and "faces appear distorted." But all 20 subjects claim many of the 25 symptoms presented, including ones not part of their drug experience.

Some symptoms were experienced by most participants *prior* to the triggering event (of the 19 drug users): 12, mild tinnitus; 13, "floaters"; 14, trouble with concentration (Table 4). Symptoms experienced by at least 75 % of the 19 subjects *after* their disorder commenced were as follows: 15, head pressure; 15, ghosted afterimage of text being read; 15, stationary objects appear to sway or move; 15, afterimage seen in the same color, or, 18, in a different color; 17, trails; 18, halos or auras; 18, floaters; 18, difficulty communicating; 19, difficulty with light

accommodation; 19, difficulty concentrating; 19, tinnitus; 19, daytime visual snow; 19, nighttime visual snow. Symptoms were always much more severe after the triggering drug event.

Of the 20 subjects, 6 had total Dissociative Experiences Scale scores over 20 with 2 greater than 45. Two scored above 20 (38.75 and 40) on the amnestic dissociation subscale, 9 scored at or greater than 20 (with 2 greater than 45) on the absorption and imaginative involvement subscale, and 8 scored greater than 20 (with 3 greater than 45) on the depersonalization and derealization subscale. Three subjects, as mentioned, were already aware of possible dissociative disorders and one additional subject self-identified as having problems with dissociation. Higher dissociative scores have been found in healthy individuals reporting perceptual anomalies (Wolfradt 1999).

Survey participants were asked to list substances that worsened (Table 5) or improved (Table 6) their symptoms. Cannabis was most commonly cited as worsening, whereas sedative-hypnotics ranked first for amelioration. Alcohol was second on both lists. SSRIs, atypical antipsychotics, and tobacco were also on both.

Responses to the 5 visual simulators are summarized in Table 7. Only the small photograph animation of daytime visual snow was chosen by all 20 participants as reflecting one element of their persisting perception disturbance and also had the highest score (0 to 10) on accuracy (7.9). Photographs 1 and 3 (Figs. 2 and 4) presented different afterimages with nearly as high a score on accuracy as the visual snow animation but 15–20 % of subjects stated they do not get those symptoms. Photograph 2 (Fig. 3) of ghosted text was identified as experienced by 95 % of subjects but had a much lower score on accuracy (5.6).

Table 5 Subjects that attribute worsening persisting perception problems to a specific drug or drug class

Drug	# of subjects (%)
Cannabis	12 (60 %)
Alcohol	6 (30 %)
MDMA	4 (20 %)
SSRIs	4 (20 %)
Stimulants	3 (15 %)
Atypical antipsychotics	3 (15 %)
Tobacco	2 (10 %)

Table 6 Subjects that attribute improved persisting perception problems to a specific drug or drug class

Drug	# of subjects (%)
Sedative-hypnotics	9 (45 %)
Alcohol	8 (40 %)
Opioids	2 (10 %)
Opioid antagonists	2 (10 %)
SSRIs	2 (10 %)
Atypical antipsychotics	2 (10 %)
Tobacco	2 (10 %)

Table 7 Photograph simulators. 0–10 score on how accurate it reflects an element of the perception disturbance

		# of Subjects (N = 20) who do not experience this as a symptom	Score 0–10 (avg.)
Photo 1	Negative afterimage	4	7.8
Photo 2	Ghosted text	1	5.6
Photo 3	Positive afterimage	3	7.3
Photo 4	Geometric pattern	7	3.9
Movie	Visual snow	0	7.9

10 = 100 % accurate and 0 = not accurate at all

4 Discussion

Only 23 of 67 subjects completed the survey between September 2010 and March 2012. Likely the time involved for survey completion kept a majority of survey initiators from finishing. It is impossible to know whether symptom severity interacted with completion rates. If there is a larger pool of individuals with HPPD-type symptoms, it is those who seek out medical and mental health attention whom we still need to be most aware of. The brief, time-limited effects described in Type 1 may be of such subclinical significance that none with this form elected to participate.

The DSM-V states that HPPD requires that the disturbances subsequent to hallucinogen use should be reminiscent of what was experienced during intoxication. Although all subjects reported primarily visual symptoms, by far not every disorder of vision detailed was also reminiscent of the triggering intoxication. One possibility is that hallucinogen use triggered subsequent disordered processing of vision beyond the alterations originally encountered. Another possibility is that those with Type 2 HPPD have a pre-existing set of subclinical symptoms that can be aggravated by various experiences, particularly by hallucinogens. Acute intoxication and later awareness of abnormal, "overactive" vision may alarm those with a pre-existing propensity for anxiety and may trigger states of more or less depersonalization in individuals with an appropriate predisposition.

If Type 2 "HPPD" symptoms are not only repetitions of a drug experience and/or existed prior to drug intoxication in milder intensity, this suggests that HPPD goes beyond hallucinogen use. The DSM-V criterion of re-experiencing focuses on drug exposure, but the constellation of symptoms is apparently more complex. One possibility is that hallucinogen use may generate symptoms not experienced during intoxication. The subjects might also be inaccurately recalling their histories, but it is also a possibility that some symptoms occurred well before drug use and that additional symptoms occur after, regardless of the drug experience. Our data suggest that there is a primary disorder of "overactive vision" prior to hallucinogen intake. Moreover, 7 of 19 subjects report their symptoms did not start "almost immediately" or "within 24 h" from exposure to the drug(s) they attribute to

triggering their condition (Table 1): that a chronic disorder only in some starts weeks to months later, long after the drug has been excreted from the body, and that symptoms go beyond what the drug experience itself induced instead suggests a more subtle condition that remains poorly defined and understood, especially in respect to its causation.

Abraham (1982, 1983) postulated that a specific "LSD toxicity" that destroys some neurons of the visual system might be involved in HPPD. But many different substances, including non-hallucinogens, such as nefazodone (Kraus 1996; Horton and Trobe 1999), trazodone (Hughes and Lessell 1990), mirtazepine (Ihde-Scholl and Jefferson 2001), and others, can induce Type 2 HPPD-equivalent symptoms. One comprehensive review about HPPD concluded there is no consistent relationship between specific substances and the induction of HPPD: The range goes from alcohol and benzodiazepines to hallucinogens, cannabis, amphetamines, and inhalants (Holland and Passie 2011). Therefore, no single neuroreceptor system appears to be associated with the pathophysiology of Type 1 and Type 2 HPPD. It is evident from neuroimaging studies that the different drugs induce distinct alterations of brain activity, implying that different patterns of brain activity can lead to the same more or less lasting perceptual changes.

Even with a limited number of subjects, our data provide some tentative insight into who might be at risk for Type 2 HPPD. Those with individual or family histories of anxiety, who have pre-drug use complaints of tinnitus, visual floaters, and concentration problems, may be most susceptible for later development of persisting perception disorder (of Type 2 HPPD), particularly after LSD and or psilocybin. Our data also indicate that non-hallucinogenic substances can trigger HPPD symptoms.

Prominent anxiety during the drug intoxication, benzodiazepine anxiolysis appearing most helpful in reducing HPPD symptoms, and Dissociative Experiences Scale results (30 % reporting clinically significant pathology) together suggest that HPPD may be an anxiety disorder not unlike PTSD, where the triggering drug experience is the traumatic event. Indeed, in PTSD, DSM-V (Textbox 1) refers in Criterion B to an individual having intrusive recollections of the trauma, including the possibility of "Acting or feeling as if the traumatic event were recurring (includes a sense of reliving the experience, illusions, hallucinations, and dissociative flashback episodes, including those that occur upon awakening or when intoxicated)." With HPPD (Type 2 especially), the symptoms may wax and wane depending on environment and emotional state but symptoms may be described as durably present to some degree. As such, Type 2 HPPD might best be considered a disorder of "overactive vision," which, after worsening or the individual being more aware/concerned about the condition, renders clinically meaningful symptoms of anxiety.

In our subjects, claimed HPPD phenomena included symptoms that cannot be described as a "re-experiencing" of hallucinogen intoxication and Subject 5's HPPD-like symptoms, though indistinguishable from other subjects' descriptions, manifested despite declaring no history of any drug exposure whatsoever. As noted earlier, Type 1 and Type 2 HPPD have been reported after intoxication with alcohol, amphetamines, tobacco, and other substances. Subject 11's HPPD symptoms commenced years after last hallucinogen use but immediately after starting

citalopram. Such delays in timing and the wide variety of triggering drugs do suggest a syndrome that is subclinical for most and which is aggravated perhaps most by hallucinogen exposure. As such, causation for HPPD has been linked to hallucinogens, but our findings combined with the reports of others, instead *suggest a kind of pre-existing neurological disorder or vulnerability of perception processing primarily in the visual domain that worsens with anxiety*. History of pre-morbid (to drug exposure) anxiety, family history of anxiety, and co-morbid dissociative phenomena (especially depersonalization and derealization) together suggest that the misprocessing of visual perception when drug-free takes on clinical significance for individuals who also meet criteria for an anxiety disorder (Passie et al. 2013). That so many substances are listed as worsening as well as ameliorating symptoms of HPPD (Tables 5 and 6) also suggests that this condition either may have more than one pathophysiological route to its expression and/or that indeed anxiety pushes individuals to latch on to whatever each discovers as useful for themselves.

4.1 Limitations of the Study

As with some other studies (Baggott et al. 2011), our findings are limited by a study design based on Internet survey of individuals not directly examined and without control and who may not be representative of the actual disorder. Yet, reports did show remarkable overlap across subjects, whether or not with an associated history of psychosis, dissociation, or even lifelong visual snow without any drug use. Moreover, the perceptual changes noted can briefly be experienced by most people without the disorder (simple examples of visual illusions we are all susceptible to can be explored at http://faculty.washington.edu/chudler/flash/nill.html). This may explain why, for example, 84.2 % of subjects experienced ghosted text as an afterimage in their worst HPPD-type event, but 95 % agreed that they experience the ghosted text displayed in our visual simulator (with a low score of 5.6 out of a possible 10 for how accurate it is for what they experience as HPPD-like). An additional limitation to the study of HPPD may indeed be that how we define the disorder is in need of revision.

4.2 Suggestions for Future Studies

In addition to careful screening for Type 1 versus Type 2 HPPD, future research would benefit from comparisons with healthy subjects or non-hallucinogen using patients with anxiety and depressive disorders. If possible, valid operationalized diagnostic procedures should be employed, including excluding other psychiatric, neurologic, ophthalmologic, and other medically relevant pre-existing conditions. It is especially important to exclude patients with a history of psychosis, which were

sometimes consciously included (Abraham 1982), and dissociative disorders. Screening should include clinical evaluation for dissociative phenomena and disorders, pre-morbid visual disturbances, anxiety disorders, depression and dysthymia, psychotic disorders, and hypochondria.

Many endogenous and environmental etiologies have been created for HPPD, and they may account for the symptoms in a specific individual constellation in every single case, as proposed in the model of Holland and Passie (2011) (Fig. 1). A focus of future studies might be the validity of the Type 2 HPPD as initially proposed by Abraham (1982, 1983). More detailed examination of "HPPD" subjects is needed, especially of accompanying neurological and psychiatric disorders. One finding of our study is that anxiety and dissociation appear to be tightly connected to HPPD and may represent a significant vulnerability toward it, or even a partial model of its mechanisms.

Researchers as well as scientific journals have to be very careful about publishing case studies or case series because usually the descriptions in these are typically too crude for a scientific evaluation and may lead to inappropriate classification of psychological disturbances—usually without evaluating for further psychiatric/medical diagnoses. A scientific caveat is that such publications (together with a publication bias, preferring danger-related case stories about hallucinogens) may end up more as a science artifact than fact.

In conclusion, our results support the need for more rigorous research that goes beyond crude current definitions and case studies/series. It appears especially necessary to take into account the possibility that a subtle (pre-existing) over-activation of neural pathways for visual perception may be worsened and/or becomes a trigger for anxiety after the ingestion of an arousal-altering psychoactive drug. HPPD symptoms also appear to have a significant association with psychological trauma and dissociation. As revealed in our data, many perceptual symptoms are not consistent with the DSM-V Criterion A of HPPD that they are re-experiences of what transpired while hallucinogen intoxicated.

Acknowledgments The authors thank Vicka Corey, Ph.D. for numerous helpful comments and suggestions to an earlier draft of the manuscript.

Conflict of interest: The authors declare that there is no conflict of interest.

Funding: Supported in part by an unrestricted grant by the HPPD Foundation (www.hppdfoundation.org).

References

Abraham HD (1982) A chronic impairment of colour vision in users of LSD. Brit J Psychiatry 140:518–520

Abraham HD (1983) Visual phenomenology of the LSD flashback. Arch Gen Psychiatry 40:884–889

Abraham HD (1984) LSD flashbacks (In reply). Arch Gen Psychiatry 41:632–633

Abraham HD, Aldridge A (1993) Adverse consequences of LSD. Addiction 88:327–334
Abraham HD, Duffy FH (1996) Stable qEEG differences in post-LSD visual disorder by split half analysis: evidence for disinhibition. Psychiatry Res 67:173–187
Abraham HD, Duffy FH (2001) EEG coherence in post-LSD visual hallucinations. Psychiatry Res 107:151–163
Abraham HD, Mamen A (1996) LSD-like panic from risperidone in post-LSD visual disorder. J Clin Psychopharmacol 16:238–241
Abraham HD, Aldridge AM, Gogia P (1996) The psychopharmacology of hallucinogens. Neuropsychopharmacology 14:286–298
Alarcon RD, Dickinson WA, Dohn HH (1982) Flashback phenomena, clinical and diagnostic dilemmas. J Nerv Ment Dis 170:217–223
Aldurra G, Crayton JW (2001) Improvement of hallucinogen persisting perception disorder by treatment with a combination of fluoxetine and olanzapine: case report. J Clin Psychopharmacol 21:343–344
American Psychiatric Association (2013) Diagnostic and statistical manual of mental diseases (DSM-V), 5th edn. American Psychiatric Association Press, Washington, DC
Baggott MJ, Coyle JR, Erowid E, Erowid F, Robertson LC (2011) Abnormal visual experiences in individuals with histories of hallucinogen use, a web-based questionnaire. Drug Alcohol Depend 114:61–67
Bernstein-Carlson EB, Putnam FW (1986) Development, reliability, and validity of a dissociation scale. J Nerv Ment Dis 174:727–735
Brimblecombe RW, Pinder R (1975) Hallucinogenic agents. Wright-Scientechnica, Bristol
Carlson EB, Putnam FW (1993) An update on the dissociative experiences scale. Dissociation 6:16–27
Cohen S (1960) LSD, side effects and complications. J Nerv Ment Dis 130:30–40
Cohen S (1977) Flashbacks. Drug Abuse Alcohol Newslett 6:1–4
Dixon JC (1963) Depersonalization phenomena in a sample of college students. Br J Psychiatry 109:371–375
Ellis H (1898) Mescal: a new artificial paradise. Contemp Rev 73: 130–141 (reprinted in The Smithsonian Institution Annual Report 1898, 537–548)
Fischer R (1971) The "flashback": arousal-statebound recall of experience. J Psychedelic Drugs 3:31–39
Fischer R (1976) On the remembrance of things present: the state-bound and stage-bound nature of consciousness. Man-Environ Syst 6:131–136
Goldman S, Galarneau D, Friedman R (2007) New onset LSD flashback syndrome triggered by the initiation of SSRIs. Ochsner J 7:37–39
Grinspoon L, Bakalar J (1997) Psychedelics reconsidered, 3rd edn. The Lindesmith Center, New York
Halpern JH, Jr Pope HG (2003) Hallucinogen persisting perception disorder, what do we know after 50 years? Drug Alcohol Depen 69:109–119
Hasse HE, Waldmann H (1971) "Flashback", Spontane psychotische Episoden als Folgeerscheinung des Phantasticagebrauchs Jugendlicher. Arch Psychiat Nervenkr 214: 399–439
Heaton RK, Victor RG (1976) Personality characteristics associated with psychedelic flashbacks in natural and experimental settings. J Abnorm Psychol 85:83–90
Hermle L, Kovar KA, Hewer W, Ruchsow M (2008) Halluzinogen-induzierte psychische Störungen. Fortschr Neurol Psychiatr 76:334–342
Hermle L, Ruchsow M, Täschner KL (2015) Halluzinogen-induzierte Persistierende Wahrnehmungsstörung (HPPD) und Flashback-Phänomene-Differenzialdiagnose und Erklärungsmodelle. Fortschr Neurol Psychiatr 83:506–515
Holland D, Passie T (2011) Flashback-Phaenomene als Nachwirkung von Halluzinogeneinnahme VWB-Verlag, Berlin
Holsten F (1976) Flashbacks, clinical and social significance 1.5–4 years after the first admission. Tidsskr f d norske Lægefor 96:876–878

Horowitz MJ (1969) Flashbacks: recurrent intrusive images after the use of LSD. Am J Psychiatry 126:565–569
Horton JC, Trobe JD (1999) Akinetopsia from nefazodone toxicity. Am J Ophthalmol 128:530–531
Hughes MS, Lessell S (1990) Trazodone-induced palinopsia. Arch Ophthalmol 108:399–400
Ihde-Scholl T, Jefferson JW (2001) Mitrazapine-associated palinopsia. J Clin Psychiatry 62:373
Johnston LD, O'Malley PM, Bachman JG, Schulenberg JE (2013) Monitoring the future national survey results on drug use, 1975–2012. In: Volume II: college students and adults ages 19–50. Institute for Social Research, The University of Michigan, Ann Arbor
Kokoszka A (1992–1993) Occurrence of altered states of consciousness among students, profoundly and superficially altered states in wakefulness. Imagin Cogn Pers 12:231–247
Kokoszka H (1993) Flashbacks and schizophrenia. Irish J Psychol Med 10:37–39
Kraus RP (1996) Visual "trails" with nefazodone treatment. Am J Psychiatry 153:365–366
Lerner AG, Gelkopf M, Oyffe I, Finkel B, Katz S, Sigal M, Weizman A (2000) LSD-induced hallucinogen persisting perception disorder treatment with clonidine, an open pilot study. Int Clin Psychopharmacol 15:35–37
Lerner AG, Shufman E, Kodesh A, Kretzmer G, Sigal M (2002) LSD-induced Hallucinogen Persisting perception disorder with depressive features treated with reboxetine, case report. Is J Psychiatry Relat Sci 39:100–103
Malleson N (1971) Acute adverse reactions to LSD in clinical and experimental use in the United Kingdom. Brit J Psychiatry 118:229–230
Markel H, Lee A, Holmes RD, Domino EF (1994) LSD flashback syndrome exacerbated by selective serotonin reuptake inhibitor antidepressants in adolescents. L Ped 125:817–819
Matefy RE, Hayes C, Hirsch J (1978) Psychedelic drug flashbacks, subjective reports and biographical data. Addict Behav 3:165–178
Matefy RE, Hayes C, Hirsch J (1979) Psychedelic drug flashbacks, attentional deficits? J Abnorm Psychol 88:212–225
Mayer-Gross W (1931) Über Synästhesien im Meskalinrausch. In: Anschütz G (Ed) Farbe-Ton-Forschungen Bd. III, pp 266–277. Hamburg Psychologisch-ästhetische Forschungsgesellschaft, Hamburg
McGlothlin H, Arnold D (1971) LSD revisited: a ten-year follow-up of medical LSD use. Arch Gen Psychiatry 24:35–49
Morehead DB (1997) Exacerbation of hallucinogen-persisting perception disorder with risperidone. J Clin Psychopharmacol 17:327–328
Naditch MP (1974) Acute adverse reactions to psychoactive drugs, drug usage, and psychopathology. J Psychoactive Drugs 22:305–311
Naditch MP, Fenwick S (1977) LSD flashbacks and ego functioning. J Abnormal Psychol 86:352–359
Nichols DE (2004) Hallucinogens. Pharmacol Ther 101:131–181
Parish E (1894) Über die Trugwahrnehmungen mit besonderer Berücksichtigung der internationalen Enquete über Wachhalluzinationen bei Gesunden. Schr Ges psychol Forsch 7 (8):1–154
Passie T (1997) Psycholytic and psychedelic therapy Research: A complete international bibliography. Laurentius Publishers, Hannover
Passie T, Halpern JH (2014) The pharmacology of hallucinogens (Chapter 14). In: Ries RK, Fiellin DA (eds) Principles of addiction medicine, 5th edn. Lippincott Williams & Wilkins, NY
Passie T, Schneider U, Borsutzky M, Breyer R, Emrich HM, Bandelow B, Schmid-Ott G (2013) Impaired perceptual processing and conceptual cognition in patients with anxiety disorders: a pilot study with the binocular depth inversion paradigm. Psychol Health Med 18:363–374
Sandison RA, Whitelaw JD (1957) Further studies in the therapeutic value of lysergic acid diethylamide in mental illness. J Ment Sci 103:332–342
Shor RE (1960) The frequency of naturally occurring "hypnotic-like" experiences in the normal college population. Int J Clin Exp Hypn 8:151–156

Siegel RK, Jarvik ME (1975) Drug-induced hallucinations in animals and man. In: Siegel RK, West LJ (eds) Hallucinations: behavior, experience, and theory. Wiley, New York, pp 81–162

Stanton MD, Bardoni A (1972) Drug flashbacks, reported frequency in a military population. Am J Psychiatry 129:751–755

Strassman RJ (1984) Adverse reactions to psychedelic drugs, a review of the literature. J Nerv Ment Dis 172:577–595

Studerus E, Kometer M, Hasler F, Vollenweider FX (2011) Acute, subacute and long-term subjective effects of psilocybin in healthy humans: a pooled analysis of experimental studies. J Psychopharmacol 25:1434–1452

Substance Abuse and Mental Health Services Administration (SAMHSA) (2011) Results from the 2010 national survey on drug use and health: summary of national findings. Substance Abuse and Mental Health Services Administration, Rockville

Wolfradt U, Oubaid V, Straube ER, Bischoff N, Mischo J (1999) Thinking styles, schizotypal traits and anomalous experiences. Pers Indiv Differ 27:821–830

World Health Organization (1992) The ICD-10 classification of mental and behavioural disorders. World Health Organization, Geneva

Young CR (1997) Sertraline treatment of hallucinogen persisting perception disorder. J Clin Psychiatry 58:85