Received: 31 March 2021 | Accepted: 19 August 2021

DOI: 10.1111/head.14213

HEADACHE CURRENTS

Visual snow syndrome, the spectrum of perceptual disorders, and migraine as a common risk factor: A narrative review

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Funding information
CJS was funded by the Baasch-Medicus Foundation.

Abstract

Objective: The aim of this narrative review is to explore the relationship between visual snow syndrome (VSS), migraine, and a group of other perceptual disorders.

Background: VSS is characterized by visual snow and additional visual and nonvisual disturbances. The clinical picture suggests a hypersensitivity to internal and external stimuli. Imaging and electrophysiological findings indicate a hyperexcitability of the primary and secondary visual areas of the brain possibly due to an impairment of inhibitory feedback mechanisms. Migraine is the most frequent comorbidity. Epidemiological and clinical studies indicate that other perceptual disorders, such as tinnitus, fibromyalgia, and dizziness, are associated with VSS. Clinical overlaps and parallels in pathophysiology might exist in relation to migraine.

Methods: We performed a PubMed and Google Scholar search with the following terms: visual snow syndrome, entoptic phenomenon, fibromyalgia, tinnitus, migraine, dizziness, persistent postural-perceptual dizziness (PPPD), comorbidities, symptoms, pathophysiology, thalamus, thalamocortical dysrhythmia, and salience network.

Results: VSS, fibromyalgia, tinnitus, and PPPD share evidence of a central disturbance in the processing of different stimuli (visual, somatosensory/pain, acoustic, and vestibular) that might lead to hypersensitivity. Imaging and electrophysiological findings hint toward network disorders involving the sensory networks and other large-scale networks involved in the management of attention and emotional processing. There are clinical and epidemiological overlaps between these disorders. Similarly, migraine exhibits a multisensory hypersensitivity even in the interictal state with fluctuation during the migraine cycle. All the described perceptual disorders are associated with migraine suggesting that having migraine, that is, a disorder of sensory processing, is a common link.

Conclusion: VSS, PPPD, fibromyalgia, and chronic tinnitus might lie on a spectrum of perceptual disorders with similar pathophysiological mechanisms and the common risk factor migraine. Understanding the underlying network disturbances might give insights into how to improve these currently very difficult to treat conditions.

Abbreviations: BOLD, blood-oxygen-level-dependent; DTI, diffusion tensor imaging; FDG-PET, [^{18}F]-2-fluoro-2-deoxy-D-glucose positron emission tomography; fMRI, functional magnetic resonance imaging; H-MR-spectroscopy, proton magnetic resonance spectroscopy; PET, positron emission tomography; PPPD, persistent postural-perceptual dizziness; SPECT, single photon emission computed tomography; VBM, voxel-based morphometry; VSS, visual snow syndrome.

KEYWORDS
fibromyalgia, migraine, persistent postural-perceptual dizziness, sensory processing, tinnitus, visual snow syndrome

INTRODUCTION

Visual snow syndrome (VSS) has recently been described as a disorder distinct from migraine and migraine aura, although migraine is its most prevalent comorbidity.[1] Both migraine and VSS are associated with other perceptual disorders such as dizziness (i.e., persistent postural-perceptual dizziness [PPPD]), fibromyalgia, and chronic tinnitus.[2–7] These conditions have in common that there is clinical evidence suggesting hypersensitivity to certain external and/or internal stimuli. This review aims to explore the common underlying mechanisms and the relation between the disorders.

METHODS

We performed a narrative literature review using Google Scholar and PubMed, searching for articles in English using the following keywords: visual snow syndrome, entoptic phenomenon, fibromyalgia, tinnitus, migraine, dizziness, PPPD, comorbidities, symptoms, pathophysiology, thalamus, thalamocortical dysrhythmia, and salience network. We found articles covering a multitude of topics and extracted information relevant to this review. Abstracts were screened to evaluate whether they gave clinical, pathophysiological, or radiological information on the topic of this review. Furthermore, we examined the literature lists of relevant reviews to identify additional relevant articles.

RESULTS

Visual snow syndrome

Up to 2.2% of the population could be affected by VSS.[8] In a study by Puledda et al. with 1100 patients, it was shown that the symptoms seem to be on a spectrum so that their prevalence might actually be higher than expected in the population.[9]

Typically, patients describe visual disturbances with the key symptom visual snow, a continuous static in the entire visual field, palinopsia (trailing and afterimages), enhanced entoptic phenomena, photophobia, and nyctalopia (impaired night vision).[1,10,11] Up to 40% of patients with VSS report to have had symptoms their whole life.[9] Patients who have later onset or stepwise worsening report correlations with headache.[1,7] In most cases, however, there is no identifiable cause. Usually, the visual disturbances are persistent.[7,9]

The prevalence of migraine in patients with visual snow was reported in up to 72%.[9] Comorbid migraine seems to aggravate the clinical presentation of VSS.[12] Treatment of migraine, however, does not seem to improve VSS.[1]

Additionally, there is an association with other "perceptual disorders," such as tinnitus in 52%[13] to 75%,[9] fibromyalgia in up to 7.1%, dizziness in up to 13.3%,[7] and psychiatric comorbidities, especially depression and anxiety.[7]

In most cases, neuro-ophthalmologic and radiological findings are normal.[7,14]

The clinical presentation indicates a hypersensitivity to internal and external visual stimuli. For example, entoptic phenomena are produced by structures of the eye and are a normal phenomenon.[15] In VSS, however, these entoptic phenomena are "enhanced" and experienced excessively.[1,16]

There is evidence suggesting failure of inhibitory processes. Palinopsia, for example, is an abnormal persistence of visual memory.[17,18] In this respect, the visual threshold in discrimination tasks was higher in patients with VSS as a sign of lacking inhibitory control.[19,20] The same abnormality was reported in patients with migraine in the interictal state.[21–23] Additionally, visually evoked potentials demonstrate prolonged P145-response pointing toward disturbed processing in the secondary visual areas[24] and a hyperactivation (lack of inhibition during the double pulse adaptation paradigm) in the primary visual cortex.[25]

Such involvement of secondary visual areas was also demonstrated in an FDG-PET study that found hypermetabolism in the right lingual gyrus,[26] which corresponded to a significant increase in lactate concentrations in H-MR-spectroscopy in this same cortical area indicating reduced metabolic reserves.[27]

In functional magnetic resonance imaging (fMRI), the so-called blood-oxygen-level-dependent (BOLD) signal is measured, that is, the diamagnetic properties of the oxygenated hemoglobin in the blood vessels as an indirect measure for the metabolic activity of a brain area.[28,29] Such functional MRI data demonstrated a widespread hyperconnectivity of the primary (V1) and secondary visual cortices within and beyond the visual system. Furthermore, there seem to be disturbances in the salience network and the dorsal and ventral attention network, as well as in the visual precortical pathways such as visual cortico-striatal loop and the thalamocortical projections.[30] The latter take part in visual learning and the selection of relevant visual information.[30–32]

The functional abnormalities could be reflected by structural changes such as an increase in gray matter volume in the primary and secondary visual cortices (including the right lingual-fusiform gyrus junction and the left primary and secondary visual cortices).[26,33]

Migraine

Migraine affects about 15% of the population.[34] Having migraine is characterized by a predisposition to recurrent headache attacks

of the migrainous phenotype.[35] Migraine can be seen as a sensory gating disorder with a cycling devolution.[36] This can be measured in the form of sensory thresholds, which reach their minimal turning point in the ictal phase.[37] However, even in the interictal state, hypersensitivity to multimodal stimuli persists.[37,38] The pathogenesis is probably a multifactorial process with a significant genetic component.[39–41]

An MRI study by Karsan et al. demonstrated hyperperfusion of the hypothalamus, anterior cingulate cortex, midbrain, and limbic areas before the onset of nitroglycerine-triggered migraine attacks.[42] In studies by Schulte et al. with consecutive fMRI scans over 30 days, hypothalamic activity as a response to trigeminal nociceptive stimulation and the pain-related hypothalamic functional connectivity to the spinal trigeminal nuclei were increased during the preictal phase.[43,44] An early hypothalamic involvement in the premonitory phase and during the headache phase was also shown in PET-studies.[45,46] The hypothalamus as a driving force of the migraine cycle would also explain the periodicity of the disease manifestation and the triggering through internal homeostatic and external deviations.[43,47,48]

Anatomically, the hypothalamus is closely linked to the thalamus,[49] sympathetic and parasympathetic brainstem nuclei,[50] and the trigeminovascular system.[51] The thalamus is a central relay station[52–54] projecting to widespread areas of the cortex including sensory areas.[55–57] Some groups have highlighted the role of the trigeminovascular system and its connections to the parasympathetic efferents leading to peripheral nociceptor activation[58,59] or the cortex, since the cortical spreading depression correlates with headache onset and aura.[60] In MRI studies, there were structural gray and white matter volume alterations (VBM and DTI) in widespread cortical areas including sensory areas, the prefrontal cortex, the cerebellum, the brainstem, the insula, and the anterior cingulate cortex.[61–66] Functional studies of the interictal state revealed alterations in several functional networks including the default mode network,[67] the dorsal attention network, the salience network,[68] and the visual cortex.[69]

Fibromyalgia

Fibromyalgia is regarded as the classical centralized pain syndrome in the sense of a sensory-processing disorder.[70,71] About 5% of the population are affected.[70,72]

Fibromyalgia is per definition a chronic and persistent disease. The main symptoms are widespread pain in several parts of the body, typically characterized as "musculoskeletal," and additional cognitive symptoms, often described as "brain fog".[73,74]

Similar to migraine, patients affected by fibromyalgia have a general hypersensitivity to painful stimuli. An fMRI study by Gracely et al. showed that less than half the stimulus intensity is needed to evoke a BOLD response in brain areas previously shown to be involved in pain processing in patients with fibromyalgia compared with healthy controls, suggesting central augmentation of the peripheral stimuli, turning neutral signals into "unpleasant" ones.[75]

This phenomenon might extend to the other senses as well like auditory perception[76] and smell.[77,78] Beyond that, migraine, tinnitus, and dizziness are common comorbidities in fibromyalgia.[79–81]

Similar to patients with VSS, tinnitus, and PPPD, patients with fibromyalgia report triggers such as stress, trauma, or environmental changes associated with the onset of the syndrome and flares.[82–84] The widespread pain symptoms with the additional cognitive symptoms indicate a central pathology involving an excessive activation of the pain system and/or an impaired antinociceptive system.[85,86] In this respect, repetitive mechanical stimulation leads to excessive temporal summation for fibromyalgia patients at lower stimulus intensities and frequencies, as well as more pronounced painful aftersensations compared with healthy controls suggesting a lack of pain inhibition.[87,88]

In patients with fibromyalgia, Wagner et al. demonstrated a specific and significantly more expansive BOLD response to painful stimuli in brain areas implicated in pain processing including the bilateral insula, the secondary somatosensory cortex, and the thalamus.[89] Other workgroups found in addition increased activity in the prefrontal cortex, the cerebellum, and the primary somatosensory cortex.[90–93] There was reduced connectivity between the somatosensory cortex and increased connectivity between the somatosensory cortex and the bilateral anterior insula.[94] Structural imaging showed total gray matter volume decrease in fibromyalgia in one study[95] and widespread regional decreases in the cingulate, insular and medial frontal and prefrontal cortices, parahippocampal gyri, thalamus, and pons.[90,96–98]

Tinnitus

Tinnitus is an acoustic misperception occurring in the absence of an external acoustical source.[99] It is often associated with hyperacusis[100] and has severe impact on quality of life.[101] Tinnitus has a high prevalence in the general population, between 11.9% and 30.3%.[102] It is clearly more prevalent in patients affected by VSS,[1] fibromyalgia,[81] and migraine.[6] Patients with complete resections of the auditory nerve can still have persistent tinnitus. This points toward a central component.[103] However, hearing loss is a trigger for the development of tinnitus[104–106] potentially via sensory deafferentation and development of a lack of inhibitory input resulting in cortical hyperexcitability.[107,108] Functional MRI studies of patients with tinnitus showed an increase in sound-evoked BOLD signal in the inferior colliculus, auditory midbrain, thalamus, and primary auditory cortex.[109–111] A ^{15}O-H_2O positron emission tomography study indicated a decrease in regional blood flow over the auditory cortex after the application of lidocaine correlating with tinnitus loudness.[112]

The conscious perception and distress of tinnitus seems to be influenced by the connectivity patterns detected using fMRI resting state in the anterior cingulate cortex and left precuneus, the posterior cingulate cortex, and right medial prefrontal cortex.[113] The limbic and auditory systems interact at the thalamic level and modulate the perception of auditory signals.[114]

Persistent postural-perceptual dizziness

PPPD, formerly called phobic postural vertigo, space-motion discomfort, visual vertigo, or chronic subjective dizziness, is a perceptual disorder, which makes up to 15%–20% of patients presenting in neuro-otologic centers.[115,116] In the population, symptoms probably lie on a spectrum.[117]

Patients typically describe diffuse dizziness, waxing, and waning over longer periods (hours), aggravated by upright posture and moving stimuli. The disorder is typically triggered by an acute or episodic vertigo condition, for example benign paroxysmal positional vertigo. Per definition, it is a chronic disorder lasting more than 3 months.[116] There is a link between central-type vertigo in migraine[118] and an increased prevalence of migraine in patients fulfilling the criteria of PPPD.[119] Individuals with increased PPPD symptoms also show increased sensitivity across a range of sensory modalities including touch, taste, smell, and audition.[119,120] PPPD probably results from an overreliance on visual and postural stimuli and reduced input from the central vestibular system.[116]

A seed-based fMRI study demonstrated an increased functional connectivity between the thalamus, occipital, and cerebellar areas, as well as between the associative visual cortex and the middle frontal gyrus and precuneus.[121] Reduced BOLD response to sound-evoked vestibular stimulation was shown in the multisensory vestibular cortical regions in the insula and increased visual cortical activity correlating with symptom severity.[122] Similarly, a SPECT study demonstrated insular and frontal hypoperfusion and cerebellar hyperperfusion.[123] In MRI, gray matter volume decreases in the temporal cortex (V5, perisylvian vestibular cortex), cingulate cortex, hippocampus, prefrontal cortex, insula, caudate nucleus, and cerebellum were demonstrated[124,125] including the regions of the multisensory vestibular network.[126]

Depression, anxiety, "brain fog," and sleep

All the above-described perceptual disorders are associated with mood disorders, especially anxiety and depression.[7,127–130] Additionally sleep disturbances in the sense of insomnia, abnormal sleep architecture, and sleep fragmentation are well known in fibromyalgia[131,132] but have also been reported in patients with tinnitus[133] and migraine.[134] We found no literature on this topic concerning VSS and PPPD.

Cognitive symptoms such as declines in memory and mental alertness, the so-called "brain fog," are reported in about 50% of patients with fibromyalgia[135,136] and are frequent in VSS as well.[1,7]

SUMMARY AND DISCUSSION

There are many overlaps between VSS, fibromyalgia, tinnitus, and PPPD. Patients affected by these disorders exhibit a hypersensitivity to external and internal stimuli in the sense of perceptional disorders. Reduced sensory thresholds often exceed the predominantly affected sensory modality. Fittingly, these distinct disorders are frequently associated with one another.

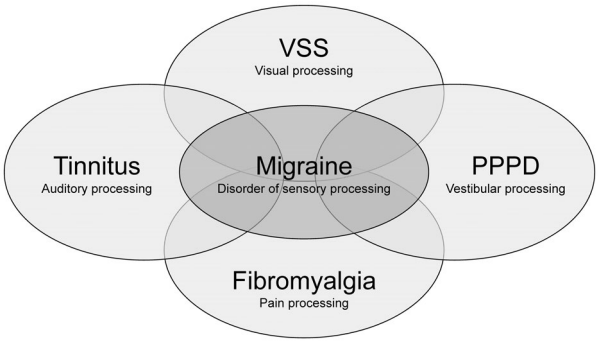

FIGURE 1 Migraine is comorbid with several chronic and difficult to treat disorders of sensory processing, such as visual snow syndrome (VSS), chronic tinnitus, persistent postural-perceptual dizziness (PPPD), and fibromyalgia. Having migraine involves recurrent headache attacks of migrainous phenotype, as well as interictal difficulties during multimodal sensory processing. Migraine might be a common link to processing disorders of more specific modalities, such as the visual (i.e., VSS), vestibular (PPPD), auditory (tinnitus), and pain system (fibromyalgia). This might also partly explain the clinical overlap of these disorders and why they are often related to each other.

The defining symptoms of VSS, tinnitus, PPPD, and fibromyalgia, that is, visual or acoustic noise, vertigo, and somatosensory discomfort, might be more prevalent within the general population than expected. These disorders might therefore be regarded as extremes of a spectrum between normal and pathologic with the diagnostic criteria representing a cutoff. The suspected underlying pathophysiology might be network disorders involving a disbalance between inhibitory and excitatory connections resulting in a hyperactive or disinhibited state of primary and/or secondary perceptual brain areas. Networks involved in the management of attention (salience network) and the regulation of emotions (limbic system) might be affected as well.

Migraine is a sensory gating disorder with a periodic course probably driven by hypothalamic fluctuations as a reaction to homeostatic and external changes. Importantly, patients exhibit decreased sensory thresholds in all sensory domains even interictally.

Our hypothesis is, therefore, that migraine constitutes a risk factor for the development of the other persistent perceptual disorders. In other words, having migraine might be the common link between the difficult to treat perceptual disorders presented in Figure 1.

This is supported by the clinical presentation of patients described in detail above and by the neuroanatomical correlates. The anterior cingulate gyrus and the insula, both of which are components of the salience network,[137] seem to be affected in all the mentioned perceptual disorders. There is evidence that this network is also relevant in the pathophysiology of depression and anxiety.[138,139] The salience network is involved in the direction of attention and the switch between other large-scale brain networks such as the default mode network, which is usually active during the resting state, and the central execute network, which is

active during tasks.[140] It seems to play a crucial role in the evaluation and prioritization of stimuli and perceptual decision-making.[141] Therefore, an impairment of these functions might modulate symptom perception and might even explain the link with the psychiatric symptoms.

The thalamus is a central component of all sensory networks.[142–145] It receives input from afferent sensory pathways and projects to widespread primary and secondary sensory areas of the cortex. The thalamus is part of feedback mechanisms (loops) implicated in the "filtering" and partly "suppression" of sensory input.[32,146] The above-described imaging findings indicate an involvement of the thalamus in all the perception disorders discussed in this paper. The concept of a "thalamocortical dysrhythmia" has been discussed as the neuronal correlate of VSS,[147] fibromyalgia,[148] tinnitus,[149] and several other neurologic and psychiatric disorders. This term has been used because of the detection of abnormal electroencephalographic oscillatory patterns, that is, reduced alpha and increased theta power over certain cortical areas of the brain, which might indicate a disturbance in thalamocortical interactions.[150]

This review focuses on disorders chosen based on striking similarities and clinical associations but does not claim to be exhaustive. Other perceptual symptoms might be present in the affected patients and would support our concept of an underlying, common network disorder. Whether the link between perceptual disorders is a common predisposition, such as having migraine, or a genetic link remains to be investigated.

CONCLUSION

VSS, PPPD, fibromyalgia, and chronic tinnitus might lie on a spectrum of perceptual disorders. Understanding the similarities in these network disorders and the role of migraine as a possible risk factor might move forward the quest for successful treatment of these often debilitating and difficult to treat disorders.

CONFLICT OF INTEREST

AK: No conflicts. CJS: CJS received scientific support, travel support, and/or honoraria from Novartis, Eli Lilly, TEVA Pharmaceuticals, Lundbeck, Allergan, Almirall, Amgen, MindMed, and Grünenthal. He received research grants from the German Migraine and Headache Society, Eye on Vision Foundation, and Baasch-Medicus Foundation.

ACKNOWLEDGMENTS

Open Access Funding provided by Universitat Bern.

AUTHOR CONTRIBUTIONS

Study concept and design: Antonia Klein, Christoph J. Schankin. *Acquisition of data*: Antonia Klein, Christoph J. Schankin. *Analysis and interpretation of data*: Antonia Klein, Christoph J. Schankin. *Drafting of the manuscript*: Antonia Klein, Christoph J. Schankin. *Revising it for intellectual content*: Antonia Klein, Christoph J. Schankin. *Final approval of the completed manuscript*: Antonia Klein, Christoph J. Schankin.

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How to cite this article: Klein A, Schankin CJ. Visual snow syndrome, the spectrum of perceptual disorders, and migraine as a common risk factor: A narrative review. *Headache*. 2021;61:1306–1313. https://doi.org/10.1111/head.14213