MONASH University

CHARACTERISING OCULAR MOTOR CONTROL AND PSYCHIATRIC SEQUELAE IN VISUAL SNOW SYNDROME

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Abstract

Visual snow syndrome (VSS) is a poorly understood visual processing disorder which presents with a range of additional sensory and psychiatric symptoms alongside core visual disturbances. With little understanding of the pathophysiological underpinnings of the disorder, and no known objective markers, the diagnosis of VSS is one of exclusion. Individuals with VSS often report significant distress and daily impairment associated with the disorder, but the few available treatment options are largely ineffective. Identifying objective markers of dysfunction in VSS will aid in developing effective treatment strategies for these individuals, and help elucidate the pathological changes underlying the condition.

Decades of research has demonstrated that ocular motor assessment provides an objective measure of brain function. The neural networks subserving eye movement control share an obligatory anatomical and functional relationship with the visual l processing network. Dysfunction affecting the visual system, as is presumed to underly VSS, was expected to manifest as changes in ocular motor characteristics. Therefore, the first aim of this thesis was to investigate the utility of OM measures in assessing visual processing dysfunction in VSS.

Here, results revealed consistent differences in ocular motor performance between individuals with VSS and neurologically healthy controls (Chapter 3 and Chapter 4). Specifically, VSS was associated with the speeded generation of an eye movement towards a visual target, and difficulty inhibiting an unwanted eye movement triggered by a suddenly appearing visual target or an internal shift of attention. These ocular motor characteristics were not influenced by psychiatric comorbidities in those with VSS (Chapter 6).

The second aim of this thesis was to characterise the psychiatric sequalae associated with VSS, and ascertain their relationship to the more salient sensory changes. Little is known about the prevalence or severity of common psychiatric symptoms in VSS. Clarifying these

questions is important in the context of effective clinical management. Where little can be done at present to ameliorate patients' sensory dysfunctions, managing psychiatric comorbidities offers an alternative treatment approach to improve patient quality of life.

Here, individuals with VSS reported relatively high levels of depression, stress, anxiety, sleep problems, fatigue, and inattentive and hyperactive/impulsive symptoms, and frequent experiences of depersonalization and derealization (Chapter 5 and Chapter 7). Notably, the presence of psychiatric symptoms was linked to poorer quality of life and more negative ratings of visual snow severity.

Overall, these results support the utility of ocular motor assessment in VSS, both in providing an objective behavioural marker of dysfunction, and in characterising deficits in visual and attentional processes. The ocular motor changes identified are consistent with current theories proposing hyperexcitability of sensory cortices in VSS, and altered functioning of thalamocortical and/or salience networks. Further, these mechanisms may also contribute to psychiatric vulnerability in VSS.

With further refinement, ocular motor assessment would allow objective monitoring of symptom severity in VSS. However, until effective treatments for VSS sensory dysfunctions are identified, screening for psychiatric symptoms in these individuals and implementing appropriate therapeutic strategies may significantly improve their quality of life and capacity to tolerate their disturbing sensory symptoms.

General declaration

I hereby declare that this thesis is an original work of my research and contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes four original papers published in peer reviewed journals and one manuscript under consideration (revisions submitted). The core theme of the thesis is characterising ocular motor control and psychiatric sequalae in visual snow syndrome. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the student, working within the Central Clinical School under the supervision of Associate Professor Joanne Fielding, Doctor Meaghan Clough, and Professor Owen White.

The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.

In the case of chapters three to seven, my contribution to the work involved the following:

Thesis chapter	Publication title	Publication status	Nature and % of student contribution	Co-author names & contributions
3	Ocular motor measures of visual processing changes in visual snow syndrome	Published in Neurology	70% - data collection, data analysis and interpretation, conceptualisation and preparation of the manuscript	Meaghan Clough –design, data interpretation, manusript drafting Allison M. Mckendrick – manuscript drafting

Thesis chapter	Publication title	Publication status	Nature and % of student contribution	Co-author names & contributions
				Paige Foletta – data collection, manuscript drafting Owen B White – concept, recruitment, manuscript drafting Joanne Fielding – concept, design, data interpretation, manuscript drafting
4	Eye movement characteristics provide an objective measure of visual processing changes in patients with visual snow syndrome	Published in Scientific Reports	70% - data collection, data analysis and interpretation, conceptualisation and preparation of the manuscript	Meaghan Clough –design, data interpretation, manusript drafting Allison M. Mckendrick – manuscript drafting Paige Foletta – data collection, manuscript drafting Owen B White – concept, recruitment, manuscript drafting Joanne Fielding – concept, design, data interpretation, manuscript drafting
5	The Psychiatric Symptomology of Visual Snow Syndrome	Published in Frontiers in Neurology	80% - concept, recruitment, data collection, data analysis and interpretation, conceptualisation and preparation of the manusript	Meaghan Clough – concept, data interpretation, manuscript drafting Paige Foletta- concept, design, data collection Owen B. White – concept, recruitment, manuscript drafting Joanne Fielding – concept, data interpretation, manuscript drafting

Thesis chapter	Publication title	Publication status	Nature and % of student contribution	Co-author names & contributions
6	Eye movement characteristics are not significantly influenced by psychiatric comorbidities in people with visual snow syndrome	Published in Journal of the Neurological Sciences	75% - concept, data collection, data analysis and interpretation, conceptualisation and preparation of the manuscript	Meaghan Clough – concept, design, data interpretation, manuscript drafting Allison M. Mckendrick – manuscript drafting Owen B. White – recruitment, manuscript drafting Joanne Fielding – concept, design, data interpretation, manuscript drafting
7	The prevalence and impact of inattentive and hyperactive/impulsive symptoms in people with Visual Snow Syndrome	Under consideration with Psychiatry and Clinical Neurosciences (Revisions submitted)	85% - concept, design, recruitment, data collection, data analysis and interpretation, conceptualisation and preparation of the manuscript	Meaghan Clough – data analysis and interpretation, manuscript drafting Allison M. Mckendrick – manuscript drafting Owen B. White – recruitment, manuscript drafting Joanne Fielding – data interpretation, manucript drafting

I have renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

Student signature: **Date:**

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the student's and co-authors' contributions to this work.

Main supervisor signature: **Date:**

Publications during enrolment

Publications presented in this thesis

Solly, E. J., Clough, M., McKendrick, A. M., Foletta, P., White, O. B., & Fielding, J. (2020). Ocular motor measures of visual processing changes in visual snow syndrome. *Neurology*. https://doi.org/10.1212/WNL.0000000000010372

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Solly, E. J., Clough, M., Foletta, P., White, O. B., & Fielding, J. (2021). The Psychiatric Symptomology of Visual Snow Syndrome. *Front Neurol*, *12*, 703006. https://doi.org/10.3389/fneur.2021.703006

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Other publications

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Strik, M., Clough, M., Solly, E. J., Glarin, R., White, O. B., Kolbe, S. C., & Fielding, J. (2022). Microstructure in patients with visual snow syndrome: an ultra-high field morphological and quantitative MRI study. *Brain communications*, *4*(4). https://doi.org/10.1093/braincomms/fcac164

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Abbreviations

ACC – Anterior cingulate cortex

AUDIT – Alcohol Use Disorders Identification Test

ADD - Attention Deficit Disorder

ADHD – Attention Deficit Hyperactivity Disorder

AS – Antisaccade

ASRS – Adult ADHD Self-report Scale

BFEP – Blue field entoptic phenomena

BOLD – Blood oxygenation level dependent

CBT – Cognitive behavioural therapy

CDS – Cambridge Depersonalization Scale

DASS – Depression Anxiety Stress Scale

dlPFC – Dorsolateral prefrontal cortex

DUDIT – Drug Use Disorders Identification Test

FEF – Frontal eye fields

fMRI – functional magnetic resonance imaging

FSS – Fatigue Severity Scale

HPPD – Hallucinogen Persisting Perception Disorder

LGN – Lateral geniculate nucleus

MEG – Magnetoencephalography

MRI – Magnetic resonance imaging

NART – National Adult Reading Test

OM – Ocular motor

PFC – Prefrontal cortex

PSQI – Pittsburgh Sleep Quality Index

PS – Prosaccade

QOL – Quality of life

SC – Superior colliculus

SD – Standard deviation

SEF – Supplementary eye fields

SF-36 – Short Form 36 Health Survey version 2

TC – Thalamocortical

TCD – Thalamocortical dysrythmia

TRN – Thalamic reticular nucleus

VS – Visual snow

VSS – Visual Snow Syndrome

Chapter One: Literature Review

Introduction

Individuals who experience visual snow (VS) describe perceiving tiny, continuous flickering dots throughout their visual field, similar to the 'snow or static' seen on an old television screen when out of tune (Bou Ghannam & Pelak, 2017). The first published account of VS is attributed to Liu et al. (1995), who discussed the cases of ten migraine patients reporting persistent positive visual phenomena. Patient accounts of the visual phenomena were remarkably similar, describing the perception of diffuse particles throughout their vision variously explained as 'grainy vision', 'a million dots', 'tv static', 'snow', and 'rain-like'.

Ophthalmological and neurological examinations of these patients failed to return results that could account for their unusual symptoms, which were not reduced or alleviated by standard migraine medications. The sparse articles published on VS in the following decade, mostly continuing to classify VS as a migraine variant, reported a similar lack of ocular or neurological abnormalities using clinical tests (W. T. Chen et al., 2011; Evans & Aurora, 2012; Jäger, Giffin, & Goadsby, 2004; Raghavan, Remler, Rozman, & Pelli, 2010; Simpson, Goadsby, & Prabhakar, 2013; Wang, Fuh, Chen, & Wang, 2008).

Due to the lack of recognition and understanding of VS, patients seeking treatment were often diagnosed as suffering a persistent variant of migraine aura (W. T. Chen et al., 2011; Jäger et al., 2004; Liu et al., 1995), and told their symptoms were psychogenic in origin, or assumed to be malingering (Schankin & Goadsby, 2015; Schankin, Maniyar, Digre, & Goadsby, 2014; White, Clough, McKendrick, & Fielding, 2018).

It was not until 2014 that Visual Snow Syndrome (VSS) was proposed, and a set of diagnostic criteria were formed (Schankin, Maniyar, Digre, et al., 2014). There is now far more public and clinical awareness of visual snow, however individuals with VSS still often

face difficulty in finding health professionals familiar with condition. Even when a diagnosis is obtained, treatment options are few in number and typically ineffective (Francesca Puledda, Nicolas Vandenbussche, et al., 2021; van Dongen, Waaijer, Onderwater, Ferrari, & Terwindt, 2019).

Notably, VSS is often accompanied by a constellation of additional sensory and psychiatric disturbances not captured by the diagnostic criteria (Fraser, 2022). The prevalence and severity of co-occurring psychiatric symptoms, which include mood and anxiety disorders, fatigue, and concentration difficulties, have not been systematically investigated, and their association with the core visual disturbances of VSS is unknown.

VSS is a complex and poorly understood disorder. With no known objective markers of dysfunction, the diagnosis is necessarily one of exclusion, and any assessment of severity is based on solely on patient self-reports of symptoms. The identification of objective markers of VSS presence or severity could aid in diagnosis and the investigation of potential treatment strategies. An improved understanding of co-occurring psychiatric symptoms could also inform clinical understanding of the disorder and patient management.

1.1 Visual Snow Syndrome

The following section will provide an overview of the diagnostic criteria for VSS, commonly co-occurring sensory and psychiatric symptoms, and what is currently known about the aetiology and clinical course of the disorder. Potential pathophysiological mechanisms will also be discussed.

1.1.1 Development of diagnostic criteria

Schankin, Maniyar, Digre, et al. (2014) observed that almost all patients presenting with VS also complained of additional visual disturbances, and based on patient descriptions

proposed a set of diagnostic criteria for VSS which have come to be relied upon in both clinical practice and research, and have been included in the International Classification of Headache Disorders ("The International Classification of Headache Disorders, 3rd edition," 2013). The diagnostic criteria for VSS (presented in Table 1.1) require the presence of VS plus at least two additional visual symptoms from four categories. The symptoms must persist for at least 3 months and cannot be attributable to migraine aura or another disorder.

Table 1.1

Diagnostic criteria for VSS

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

*modified from Schankin, Maniyar, Digre, et al. (2014)

The prevalence of VSS is difficult to estimate due to how poorly recognised the disorder has historically been. Initially assumed to be a rare syndrome, recent research suggests VS may be a relatively common symptom in the population (Kondziella, Olsen, & Dreier, 2020). An epidemiological study surveying 1015 adults from the UK found that 3.7% reported visual symptoms compatible with VSS, with 2.2% appearing to meet the diagnostic

criteria for VSS (Kondziella et al., 2020). In contrast to migraine, which has a female sex prevalence, VSS does not appear to have a sex prevalence (Fraser, 2022).

The diagnosis of VSS has been questioned by some, with critics arguing that It unnecessarily pathologizes a common and generally benign visual disturbance (Kondziella, 2022). While it is important to recognise that VS/VSS varies in severity and impact (Schankin, Puledda, & Goadsby, 2020; A. C. Thompson, Goodbourn, & Forte, 2023), with some individuals who experience VS unconcerned by their symptoms, many patients with VSS are profoundly affected. For those individuals whose visual disturbances are mild and ignorable, reassurance that there is no dangerous or progressive underlying pathology may be sufficient treatment. However, for others, VSS can be highly distressing and debilitating, with significant ramifications for academic, occupational, and social functioning (Fraser, 2022; Fraser & White, 2019). Understanding the impact VSS can have on patients is important, as patient distress may be compounded by a lack of recognition and dismissive attitudes from professionals (Hildenbrand, Perrault, & Rnoh, 2021; McManimen, McClellan, Stoothoff, Gleason, & Jason, 2019).

1.1.2 Visual symptomology

Visual Snow

The defining symptom of VSS, VS refers to the perception of continuous, innumerable flickering dots throughout the entire visual field. Descriptions of VS can vary significantly between patients. VS may appear monochromatic, transparent, colourful, or a combination thereof (Lauschke, Plant, & Fraser, 2016; F. Puledda, Schankin, & Goadsby, 2020; Schankin, Maniyar, Digre, et al., 2014). Generally, VS is reported to be more prominent in the dark and on plain or untextured surfaces, and is present with the eyes both open and closed. Factors that may aggravate visual snow include stress, fatigue, or high-

contrast text; fewer alleviating factors are reported, the most common being altering ambient lighting (Lauschke et al., 2016; Schankin, Maniyar, Digre, et al., 2014).

As most VSS patients show no signs of retinal pathology, and continue to perceive VS with their eyes closed, the symptom is assumed to arise from dysfunctional visual information processing (Lauschke et al., 2016; McKendrick et al., 2017; Schankin, Maniyar, Digre, et al., 2014). The nature and localisation of dysfunction is unclear, but is suggested to involve aberrant hyperexcitability of cortical regions, and/or thalamic dysfunction (Fraser, 2022; Fraser & Lueck, 2021).

Not all individuals who perceive VS meet the criteria for VSS (F. Puledda, C. Schankin, et al., 2020). Uncommonly, episodic VS may be experienced during migraine attacks (Hodak, Fischer, Bassetti, & Schankin, 2020). VS may also be perceived in the context of other neurological or ophthalmological disorders, leading some authors to classify cases of VS as either 'primary' or 'secondary' (Barral, Martins Silva, García-Azorín, Viana, & Puledda, 2023; Metzler & Robertson, 2018), although it is unclear whether these disorders cause VS, or whether in some cases the co-occurrence of VS may be coincidental.

Secondary VS is most commonly reported by individuals with hallucinogen persisting perception disorder (HPPD) (Lerner, Rudinski, Bor, & Goodman, 2014; Martinotti et al., 2018). HPPD is a poorly understood syndrome characterised by prolonged or recurring perceptual symptoms beginning after, and reminiscent of, hallucinogenic drug consumption (Martinotti et al., 2018). Cases of HPPD can present very similarly to VSS, however recent studies have identified differences between these cohorts, including a significantly lower prevalence of migraine among HPPD patients, and a male sex prevalence in HPPD (Fraser, 2022; van Dongen, Alderliefste, Onderwater, Ferrari, & Terwindt, 2021). Other neurological disorders where secondary VS has been reported include acute ischemic stroke (Scutelnic et al., 2023), idiopathic intracranial hypertension (Yoo, Yang, Choi, Kim, & Hwang, 2020),

occipital lobe epilepsy (Hang, Leishangthem, & Yan, 2021), multiple sclerosis (D. G. Mehta, Garza, & Robertson, 2021), and Creutzfeldt–Jakob disease (B. S. Chen, Lance, Lallu, & Anderson, 2019).

Palinopsia

Palinopsia refers to the persistence of visual images after the stimulus has disappeared. The term encompasses both afterimages and visual trailing, which are reported by ~80% and ~60% of VSS patients respectively (F. Puledda, C. Schankin, et al., 2020; Schankin, Maniyar, Digre, et al., 2014). Palinopsia has been associated with various neurological and psychiatric disorders (including migraine), lesions affecting the occipital, temporal, or parietal lobes, head injury, certain prescription medications, and illicit drug use (Abert & Ilsen, 2010; Kalita, Uniyal, & Bhoi, 2016). According to Gersztenkorn and Lee (2015) palinopsia as described in VSS would be categorised as 'illusory palinopsia'- i.e. afterimages which are of low resolution and affected by ambient lighting and movement. Gersztenkorn and Lee (2015) theorised that palinopsia during VSS and migraine may reflect a dysfunction of visual perception related to alterations in neuronal excitability.

Enhanced entoptic phenomenon

Entoptic phenomenon were classically defined as visual perceptions arising from the structure of the eye (Brewerton, 1930), however Schankin, Maniyar, Digre, et al. (2014) employed a revised definition of entoptic phenomenon from Tyler (1978) as 'phenomena arising from [any] structure of the visual system'. This revised definition includes photopsia and self-light of the eye, in addition to floaters and blue field entoptic phenomena (BFEP). The persistent presence of floaters is reported by over 80% of VS patients, blue field entoptic phenomenon (BFEP) by ~70%, spontaneous photopsia by ~60%, and self-light of the eye by 50-70%% (F. Puledda, C. Schankin, et al., 2020; Schankin, Maniyar, Digre, et al., 2014; Yildiz, Turkyilmaz, & Unal-Cevik, 2019).

Floaters, the most commonly observed entoptic phenomenon, are the perception of strands of vitreous floating in the vitreous humour of the eye; generally seen when looking at a white or blue background, they take the appearance of irregularly shaped grey and transparent ellipses (Voke, 2010). Less commonly reported are BFEP, the perception of white blood cells flowing through capillaries over the retina; these are perceived as tiny white dots darting around on squiggly paths across the visual field (Riva & Petrig, 1980). As the name suggests, BFEP are typically only seen when gazing at a blue background (generally the sky), however VSS patients report perceiving BFEP frequently and in everyday situations.

Photopsia refers to the perception of flashes of light in the absence of an external light source. A common symptom of various ophthalmological conditions, as well as migraine, photopsia generally occur as a result of direct retinal stimulation but can also originate from elements of the visual system posterior to the eye- as is likely the case during migraine and VSS (Brown, Brown, & Fischer, 2015). Self-light of the eye refers to the perception of 'luminous clouds' moving in waves when the eyes are closed, often described as 'swirls, clouds, or waves' by patients (Marshall, 1935; Schankin, Maniyar, Digre, et al., 2014). The origin and significance of this perception is unclear.

In healthy individuals, entoptic phenomena are generally filtered out and perceived only under specific circumstances (Schankin, Maniyar, Digre, et al., 2014; Tyler, 1978). The excessive presence of entoptic phenomena during VSS suggests dysfunction in the subcortical or cortical filtering mechanisms which would normally prevent their perception (White et al., 2018). It has been suggested neuronal excitability may underlie this dysfunction, resulting in the perception of normally sub-threshold visual stimuli (Lauschke et al., 2016).

Nyctalopia

Nyctalopia refers to a reduced capacity to see in low light conditions, and is experienced by 40-80% of VSS patients (McKendrick et al., 2017; F. Puledda, C. Schankin, et al., 2020; Schankin, Maniyar, Digre, et al., 2014; Yildiz et al., 2019). In the general population, nyctalopia typically is associated with rod dysfunction caused by retinal degeneration (Hansen, Mendoza-Santiesteban, & Hedges, 2018; Munk et al., 2014; Ohba & Ohba, 2006), but there is no evidence for this explanation in VSS. White et al. (2018) suggested that nyctalopia in VSS may be caused by impaired central interpretation of input from rod photoreceptors. F. Puledda, Schankin, Digre, and Goadsby (2018) noted that some patients attributed their poor night vision to a heightened intrusiveness of their visual snow, palinopsia, entopic phenomena, or some combination thereof in low-light conditions.

Photophobia

Photophobia is defined as an abnormal sensitivity to light, manifesting as discomfort or pain caused by normally tolerable light levels (Digre & Brennan, 2012). A common symptom of many ophthalmic and neurological disorders, photophobia is reported to occur in 55-80% of VSS patients (F. Puledda, C. Schankin, et al., 2020; Schankin, Maniyar, Digre, et al., 2014; Yildiz et al., 2019). Despite its prevalence, photophobia is poorly understood and its pathophysiology has not been clearly defined (Main, Vlachonikolis, & Dowson, 2000). Photophobia is one of the major diagnostic criteria for migraine, reported by up to 80-85% of migraine patients during an attack (Boulloche et al., 2010; Digre & Brennan, 2012). VSS patients have been reported to experience photophobia equivalent to that reported by patients with chronic migraine during attacks (Ozan E Eren, Ruscheweyh, Straube, & Schankin, 2020). Interestingly, photophobia during migraine attacks has been linked to the lingual gyrus, a region which has also shown increased activity during VSS (Boulloche et al., 2010; Schankin, Maniyar, Sprenger, et al., 2014).

1.1.3 Associated sensory symptoms and disorders

Other sensory symptoms

Tinnitus is the most common non-visual sensory symptom associated with VSS, present in 60-86% of cases and generally described as bilateral, continuous, and high-pitched (Lauschke et al., 2016; McKendrick et al., 2017; F. Puledda, C. Schankin, et al., 2020; Schankin, Maniyar, Digre, et al., 2014). The aetiology of tinnitus is multifactorial and can involve structural damage and/or neurological dysfunction (Langguth, Kreuzer, Kleinjung, & De Ridder, 2013). Schankin, Maniyar, Sprenger, et al. (2014) noted that tinnitus could be considered the auditory equivalent of visual snow; both present as continuous, low-level 'noise' within their respective sensory systems.

The ubiquitous presence of tinnitus in VSS patients indicates the neural areas affected during the syndrome may be multi-sensory rather than solely visual, reflecting a central mishandling of sensory signals. In line with this theory, additional sensory symptoms such as paraesthesia, numbness, tremor, and balance issues such as dizziness and vertigo are also commonly reported by patients, albeit less commonly than tinnitus (Lauschke et al., 2016; D. G. Mehta et al., 2021; Metzler & Robertson, 2018).

VSS and Migraine

Migraine is frequently comorbid with VSS, experienced by 50-70% of VSS patients (Kondziella et al., 2020; Lauschke et al., 2016; F. Puledda, C. Schankin, et al., 2020; Schankin, Maniyar, Sprenger, et al., 2014; Zambrowski, Ingster-Moati, Vignal-Clermont, & Robert, 2014). Migraine is a neurovascular disorder characterized by episodes of unilateral throbbing head pain accompanied by a range of neurological symptoms. Symptoms may include nausea, sensitivity to light and sound, and cognitive, emotional, or motor disturbances (Noseda & Burstein, 2013). Approximately one third of migraine patients experience

additional neurological symptoms preceding the headache (most commonly visual) referred to as migraine aura (Noseda & Burstein, 2013).

The initial assumption that VSS was a variant of migraine aura was discounted due to both the large number of VSS patients without a history of migraine, and significant differences in the phenotype of each condition (Fraser, 2022). Migrainous visual disturbances are typically unilateral and occur mostly (although not exclusively) in the leadup to a migraine headache (A. Charles, 2018). The 'classic' visual aura presents as a scintillating scotoma or zig-zag line; flashing lights, isolated scotomas and other distortions of vision may also occur (A. Charles, 2018; Queiroz et al., 1997). The typical duration of a visual aura is approximately 30 minutes; prolonged auras lasting longer than 60 minutes are unusual (Wang et al., 2008). In contrast, VS occupies the entire visual field and is ongoing, and often temporally unrelated to migraine in regard to symptom onset or fluctuation.

Despite these differences, there is evidently a relationship between migraine and VSS. The two conditions show a number of overlapping symptoms including photophobia, photopsia, and depersonalization (Cahill & Murphy, 2004; Schankin & Goadsby, 2015). In addition, VSS patients often report a family history of migraine (Yildiz et al., 2019). These factors support the theory that VSS and migraine may share a similar underlying pathophysiology.

Migraine aura is widely supposed to be caused by cortical spreading depression (CSD), a slowly propagated wave of depolarization that spreads across the cortex (A. C. Charles & Baca, 2013). CSD is an unlikely explanation for VSS due to the persistent nature of visual symptoms, as CSD is generally short-lived (Lauritzen et al., 2011). A more probable explanation is that VSS and migraine may both involve altered cortical excitability; increased excitability has been demonstrated in migraine patients using a variety of electrophysiological measures (Ambrosini, de Noordhout, Sandor, & Schoenen, 2003), and

indirect evidence indicates similarly heightened excitability in VSS (Bou Ghannam & Pelak, 2017; McKendrick et al., 2017).

There is some evidence to suggest that VSS may present more severely in patients with comorbid migraine (Schankin, Maniyar, Sprenger, et al., 2014).

VSS and other sensory processing disorders

In addition to the frequent co-occurrence of migraine and tinnitus with VSS, other sensory processing disorders including fibromyalgia and persistent postural-perceptual dizziness are often comorbid with VSS (A. Klein & Schankin, 2021; Metzler & Robertson, 2018). It has been proposed that VSS and these disorders may exist on a spectrum of perceptual disorders sharing migraine as a common risk factor (A. Klein & Schankin, 2021). The authors argue that the disorders on this proposed spectrum share several features including increased sensory sensitivity, reduced sensory thresholds, and a high prevalence of psychiatric comorbidities, and therefore are likely to share similar pathophysiological mechanisms (A. Klein & Schankin, 2021).

1.1.4 Associated psychiatric symptoms and disorders

The earliest papers defining and characterising VSS found that many patients reported diagnoses of anxiety and depressive disorders (Schankin, Maniyar, Digre, et al., 2014; Unal-Cevik & Yildiz, 2015). Lifetime prevalence of diagnosed anxiety and depressive disorders have both been reported at approximately 40% in VSS patients (Lauschke et al., 2016; van Dongen et al., 2019). However, using a screening questionnaire van Dongen et al. (2019) found that over 50% of patients exhibited current significant anxiety or depressive symptomology, indicating the true prevalence may be higher. Irritability has been reported by 37-43% of patients (Schankin, Maniyar, Digre, et al., 2014; Yildiz et al., 2019), which is notable as heightened irritability is associated with a range of psychiatric disorders, and is

theorized to represent a transdiagnostic vulnerability factor for psychopathology (Beauchaine & Tackett, 2020).

VSS patients have also been reported to experience lethargy (Schankin, Maniyar, Digre, et al., 2014), fatigue (Metzler & Robertson, 2018), sleep disturbances (A. Klein & Schankin, 2021) brain fog (Metzler & Robertson, 2018), and concentration difficulties/distractibility (Schankin, Maniyar, Digre, et al., 2014; Yildiz et al., 2019). Interestingly, a case series of 248 VSS patients also reported that 30 (14.3%) of their patients who had been treated for VSS were recorded as having a diagnosis of Attention Deficit Disorder (ADD) or Attention Deficit Hyperactivity Disorder (ADHD) (D. G. Mehta et al., 2021).

Many VSS patients describe dissociative experiences (specifically, depersonalization and derealization) following VSS onset (D. G. Mehta et al., 2021; "Visual snow syndrome," 2018). Depersonalization and derealization are frequently co-occurring forms of dissociation. Depersonalization refers to subjective feelings of being detached from the physical body and mental processes, and may involve a diminished sense of agency or feelings of being 'robotic'. Derealization is characterized by feelings that the surrounding world is unreal or unfamiliar; the world may be perceived as artificial, 2D, or colourless (Simeon et al., 2008).

Depersonalization and derealization occur during a wide range of psychiatric and neurological conditions including depression and anxiety disorders (Baker et al., 2003; Michal et al., 2016), schizophrenia, temporal lobe epilepsy, hallucinogen persisting perception disorder, and migraine (Cahill & Murphy, 2004; Lambert, Sierra, Phillips, & David, 2002; Martinotti et al., 2018; Sierk et al., 2018). Interestingly, there are a number of potential references to visual snow in the literature on depersonalization and migraine. Cahill and Murphy (2004) suggested that some cases of depersonalization-derealization disorder may represent undiagnosed incidences of prolonged migraine aura status, and other authours

have reported that patients with depersonalization-derealization disorder often report a range of bilateral visual symptoms including 'visual snow' or 'tv static', as well as the perception of 'flashes of light' (photopsia) (Baker et al., 2003; Mauricio Sierra, 2009; M. Sierra, Medford, Wyatt, & David, 2012). Depersonalisation is also a defining symptom of hallucinogen persisting perception disorder, the only disorder apart from VSS where visual snow has frequently been described as a symptom (Martinotti et al., 2018).

The psychiatric symptoms associated with VSS have so far received little investigation; their prevalence and potential associations with migraine and sensory symptomology has not been systematically characterized. It is possible that comorbid migraine might contribute to a higher frequency of psychiatric symptoms in VSS, as migraine is consistently associated with comorbid mood and anxiety disorders, sleep problems, and fatigue, as well as depersonalization and derealization (Cahill & Murphy, 2004; Karsan & Goadsby, 2021; Minen et al., 2016). As is assumed to be the case with migraine, psychiatric symptoms may also be elevated in VSS due to a combination of other factors: distress related to symptoms and their impact on quality of life, shared genetic susceptibility, and/or pathophysiological changes that underlie both sensory and psychiatric pathology (Minen et al., 2016). An improved understanding of psychiatric symptoms in VSS, and any association with sensory disturbances, would be useful to inform psychiatric assessment of patients and treatment approaches.

1.1.5 Aetiology, prognosis and treatments

Aetiology

The aetiology of VSS remains largely unknown. Schankin, Maniyar, Digre, et al. (2014) reported that 10% of their VSS cohort claimed one or more close family members also experienced VSS, and Lauschke et al. (2016) found that one of their twenty VSS patients

reported the same. These findings, in conjunction with reports that 15%-76% of VSS patients have a family history of migraine, which is known to have a heritable risk (Lauschke et al., 2016; Yildiz et al., 2019), suggest that heritable genetic factors may contribute to the likelihood of developing VSS (Fraser, 2022).

Approximately 40% of VSS patients report their visual symptoms have been present since childhood, or as long as they can remember, indicating their VSS may be lifelong (McKendrick et al., 2017; Schankin & Goadsby, 2015; van Dongen et al., 2019). For patients with a later onset of VSS, symptoms generally begin in the second or third decade of life (McKendrick et al., 2017; D. G. Mehta et al., 2021; Schankin, Maniyar, Digre, et al., 2014; Yildiz et al., 2019), although ages of onset as old as 48 and 55 have been recorded (Bessero & Plant, 2014; Lauschke et al., 2016).

In many cases, patients cannot link the onset of their symptoms to a clear trigger. When patients can recall a trigger, the most common inciting events include migraine attacks, medication use, head trauma, and infection (D. G. Mehta et al., 2021; F. Puledda, C. Schankin, et al., 2020). Case reports of VSS describe onsets related to traumatic brain injury (Metzler & Robertson, 2018; Werner & Gustafson, 2022), severe pneumonia (Ciuffreda, Han, & Tannen, 2019), Covid-19 infection (Braceros, Asahi, & Gallemore, 2021), brain cyst removal surgery (Ciuffreda et al., 2019), and LASIK surgery (Keppel & Randleman, 2022).

Prognosis

Prognostic information for VSS is limited. In the majority of patients with VSS the syndrome appears to be chronic, with one longitudinal study finding that all 40 patients available for a follow-up interview 8 years following VSS diagnosis still met full criteria (Graber et al., 2022). According to most case reports, VSS is non-progressive and generally benign (Scutelnic et al., 2023), however symptom severity may fluctuate over time (Yildiz et al., 2019). There are no recorded cases of complete vision loss or obscurement due to VSS.

Treatments

VSS can be refractory to pharmacological treatment, however most medications show limited effectiveness (Francesca Puledda, Nicolas Vandenbussche, et al., 2021; van Dongen et al., 2019). The evidence for pharmacological VSS treatments is also scarce, with current knowledge coming largely from case series and reports, or retrospective case reviews (Rusztyn, Stańska, Torbus, & Maciejewicz, 2023).

Lamotrigine, an anticonvulsant medication generally used to treat epilepsy, is most frequently recommended for treating VSS, and has shown past success in treating positive visual symptoms associated with migraine (W. T. Chen, Fuh, Lu, & Wang, 2001; D'Andrea, Nordera, & Allais, 2006), but inconsistent effectiveness for VSS. Unal-Cevik and Yildiz (2015) reported the case study of a 25-year-old woman with VSS who experienced complete remission after lamotrigine treatment, however this success has not been replicated in the literature. More recent studies investigating lamotrigine for VSS have found that only ~20% of patients report symptom improvement (Francesca Puledda, Nicolas Vandenbussche, et al., 2021; van Dongen et al., 2019). In addition, lamotrigine can cause significant side-effects including nausea, fatigue, and nystagmus (Bou Ghannam & Pelak, 2017). Half of the patients in van Dongen et al. (2019)'s study reported experiencing adverse effects from the drug.

Other medications which have shown success in reducing symptoms for some patients include antidepressants and benzodiazepines, triptans, gabapentin, beta-blockers, topiramate, acetazolamide (D. G. Mehta et al., 2021; Francesca Puledda, Nicolas Vandenbussche, et al., 2021; van Dongen et al., 2019).

Aside from medical treatments, wearing tinted lenses may help some patients cope by reducing the appearance or intensity of visual symptoms. Intuitive colourimetry involves selecting the optimal coloured tint of lenses to alleviate symptoms of visual stress or other perceptual disorders, and has been used for migraine and photosensitive epilepsy (Huang et

al., 2011; Wilkins et al., 1999). Lauschke et al. (2016) reported that 92% of twelve VSS patients reported symptom reduction using coloured lenses, with 83% favouring lenses in the yellow-blue colour spectrum.

When VS is secondary to other disorders, management of the primary condition may help alleviate visual disturbances (Fraser, 2022; D. G. Mehta et al., 2021). Reassurance that VSS is not progressive or life-threatening, and education on the current state of VSS research may also give patients understanding and peace of mind (Fraser, 2022).

One study has reported on the efficacy of neuro-optometric rehabilitation therapy for treating VSS, which involves patients completing neurosensory and neuromuscular exercised aimed at improving ocular motor function. The authors reported that VSS patients experienced significant increases in QOL following the intervention, however a reduction in visual symptoms was not found (Tsang, Shidlofsky, & Mora, 2022). This highlights an important weakness of research into VSS treatments, which is the reliance on self-reports of symptom severity to judge efficacy. Lacking an objective measure of VS severity, patient reports of treatment effectiveness are inherently subjective and susceptible to expectancy and placebo effects.

1.2 The visual system and pathophysiology of VSS

Although understanding of VSS pathophysiology remains in the early stages, a number of potential mechanisms have been proposed, including alterations to cortical excitability and dysfunction in thalamocortical networks (Fraser, 2022). Prior to discussing these theories, a brief overview of relevant structures and dynamics of the visual system will be given. Given that visual processing is a highly complex function, this overview will be necessarily simplified.

1.2.1 The visual system

Visual processing refers to the brain's ability to receive, integrate, and give meaning to visual information (Purpura & Tinelli, 2020). This encompasses both detection of basic visual properties such as shape, colour and motion, as well as higher-level visual functions such as recognition of objects and faces (M. Hoffmann, 2016).The visual system is comprised of both feedforward and feedback connections. The following overview will outline the well-characterized feedforward connections, which convey visual information through the hierarchy of visual processing regions (Briggs, 2020; Prasad & Galetta, 2011). However, the visual system additionally features extensive feedback connections, which are assumed to exert a modulatory influence from higher-order areas on the earlier stages of visual processing (Bastos et al., 2015; Briggs, 2020). All visual processing regions, with the sole exception of the retina, are subject to feedback influences (Bastos et al., 2015; Gilbert & Li, 2013).

Subcortical visual processing

Visual information is initially received by photoreceptor cells (rods and cones) in the retina, and from there is transmitted by the optic nerve to the lateral geniculate nucleus (LGN) (Huff, Mahabadi, & Tadi, 2021; Prasad & Galetta, 2011). Transmission of visual information from the retina occurs primarily via three specialized visual pathways: the parvocellular, magnocellular, and koniocellular pathways (Nassi & Callaway, 2009). Each pathway carries input from different photoreceptor cells in the retina to be processed in specialized layers of the LGN (Huff et al., 2021).

The thalamus plays an important role in the initial filtering and processing of visual and sensory information (Yuri B. Saalmann & Kastner, 2011; Usrey & Alitto, 2015). The visual thalamus comprises three nuclei: the thalamic reticular nucleus (TRN), the pulvinar,

and the LGN (Yuri B. Saalmann & Kastner, 2011). The TRN receives projections from cortical and subcortical regions, but projects exclusively to thalamic regions, suggesting a primary function of inhibiting thalamo-cortical transmission (Yuri B. Saalmann & Kastner, 2011). The pulvinar is extensively connected to the cortex, and may regulate cortico-cortico transmission (Yuri B. Saalmann & Kastner, 2011; Usrey & Alitto, 2015). Finally, the LGN relays visual information received from the retina to the cortex, gating and modulating the flow of this information based on projections from surrounding subcortical structures and the visual cortex (Prasad & Galetta, 2011; Yuri B. Saalmann & Kastner, 2011).

Cortical visual processing

Cortical processing of visual information is organized hierarchically, with visual representations increasing in complexity as information ascends in parallel pathways through specialized cortical regions (Katzner & Weigelt, 2013). Visual information is initially received by the primary visual cortex (V1), also referred to as the striate cortex (Huff et al., 2021). From the primary visual cortex, visual information is distributed through secondary visual processing regions in the visual cortex (V2, V3, V4, V5), referred to collectively as the visual association cortex or extrastriate cortex (Fraser & Lueck, 2021).

Two parallel, interconnected visual pathways carry information through the visual processing hierarchy: the ventral pathway, also known as the ‘what’ pathway, which is implicated in object recognition, and the dorsal pathway, also known as the ‘where’ pathway, which is implicated in visual motion and spatial orientation (Gilbert & Li, 2013). Ultimately, information from the dorsal and ventral pathways is transmitted to higher level cortical areas for further processing (Prasad & Galetta, 2011).

1.2.2 VSS pathophysiology

It is unclear what stage(s) or aspect(s) of the visual processing system is implicated in VSS. Neuroimaging studies conducted in VSS have shown evidence of widespread neuroanatomical and functional differences relative to controls, which affect both cortical and subcortical visual processing structures, and extend beyond the visual system (Fraser, 2022; Raviskanthan, Ray, Mortensen, & Lee, 2022).

Cortical hyperexcitability

Evidence of heightened cortical excitability has been reported in migraine and tinnitus (Burstein, Noseda, & Borsook, 2015; Schecklmann et al., 2014), and is thought to be a part of VSS pathophysiology (Fraser, 2022; Schankin, Maniyar, Sprenger, et al., 2014). Persistent, diffuse overactivation of neurons in visual regions could conceivably produce the visual 'noise' characteristic of VSS, and affect the filtering of visual information, resulting in the perception of normally sub-threshold visual stimuli (i.e., entoptic phenomena) (Lauschke et al., 2016).

Neuroimaging studies have provided support for altered cortical excitability. Structural neurological differences identified in VSS such as localized increases in grey matter volume, and white matter abnormalities, could be a consequence of hyperexcitation (Michels et al., 2021; Francesca Puledda et al., 2020; Schankin, Maniyar, et al., 2020). PET studies have found hypermetabolism in the lingual gyrus of VSS patients, as well as in the cerebellum and regions of the parietal and temporal lobe (Schankin, Maniyar, et al., 2020; Schankin, Maniyar, Sprenger, et al., 2014). The lingual gyrus is a region of the extrastriate cortex implicated in photophobia and migraine aura (Barral et al., 2023), and has also been reported to show increased lactate levels, potentially a consequence of increased activation (F. Puledda, D. Ffytche, et al., 2020).

Other studies have examined blood oxygenation level dependent (BOLD) activity and regional cerebral blood flow in VSS to detect areas of altered activation (F. Puledda, D. Ffytche, et al., 2020; Francesca Puledda, Christoph J. Schankin, et al., 2021). Reduced BOLD responses were found in the insula of VSS participants while viewing simulated VS, which suggests there may be heightened insula activity at baseline (F. Puledda, D. Ffytche, et al., 2020). The insula is an essential structure in the salience network (F. Puledda, D. Ffytche, et al., 2020). Areas of increased regional cerebral blood flow in VSS participants were identified in the cerebellum, fusiform gyrus, areas of the frontal cortex, and the posterior cingulate cortex (Francesca Puledda, Christoph J. Schankin, et al., 2021).

Neurophysiological and behavioural studies have also shown evidence for an excitable cortex. In patients with migraine, occipital cortex hyperexcitability has been shown to correlate with lower phosphene thresholds and potentiation (as opposed to habituation) to repetitive visual stimulation compared to controls (Afra, Cecchini, De Pasqua, Albert, & Schoenen, 1998; Ambrosini et al., 2003; Aurora, Ahmad, Welch, Bhardhwaj, & Ramadan, 1998; W. T. Chen et al., 2011). Yildiz et al. (2019) found that phosphene thresholds were significantly lower in VSS patients compared to healthy controls, and that VSS patients were more likely than controls to experience phosphenes during the study. VSS patients have also shown differences in visual evoked potentials (O. Eren, Rauschel, Ruscheweyh, Straube, & Schankin, 2018). Using behavioural perceptual measures, McKendrick et al. (2017) found differences in VSS results consistent with an imbalance of inhibition/excitation in the visual cortex.

Fraser (2022) suggested that a genetic predisposition towards neuronal hyperexcitability might contribute to VSS susceptibility, possible involving genes implicated in regulating gluamatergic excitement and synaptic transmission. This predisposition could be

shared with migraine and HPPD, explaining the diagnostic and symptom overlap among these disorders (Fraser, 2022).

Thalamocortical dysrhythmia

Lauschke et al. (2016) proposed that thalamocortical dysrhythmia (TCD), potentially triggered by cortical hyperexcitability, may underlie VSS symptoms. The thalamus acts as a sensory relay, receiving and filtering incoming sensory information and transmitting it to the cortex (Usrey & Alitto, 2015). It is a vital structure serving sensory perception and consciousness, and is extensively connected to brain area involved in attentional and arousal regulation (Bollimunta, Mo, Schroeder, & Ding, 2011; R. R. Llinas, Ribary, Jeanmonod, Kronberg, & Mitra, 1999; Y. B. Saalmann & Kastner, 2009). The thalamus is highly interconnected with the cortex through feedback loops characterised by oscillatory activity, which functions to regulate information transmission to and within the cortex, and coordinate the activity of different cortical regions (De Ridder, Vanneste, Langguth, & Llinas, 2015; Zobeiri, van Luijtelaar, Budde, & Sysoev, 2019).

TCD is a form of pathological oscillatory activity in these neural networks linking the thalamus and cortex; more specifically, an increase in low-frequency oscillations during states of wakefulness coupled with an increase in surrounding high-frequency activity, alongside heightened thalamocortical coherence (Fuggetta & Noh, 2013; Vanneste, Song, & De Ridder, 2018; Zobeiri et al., 2019). The consequence of TCD is disruption in normal state-dependent thalamocortical communication, which may result in a range of negative and positive symptoms depending on the localisation of dysfunction (Malekmohammadi, Elias, & Pouratian, 2015). A number of diverse psychiatric and neurological disorders have been linked with TCD including Parkinson's disease, schizophrenia, depression, tremors, tinnitus, and migraine (De Ridder et al., 2015; Pratt & Morris, 2015; Vanneste et al., 2018).

In VSS, it has been suggested that TCD might be related to abnormalities in koniocellular pathway function (Hepschke, Martin, & Fraser, 2021; Lauschke et al., 2016). The koniocellular pathway transmits information from short-wave (S-cone) cells in the retina, which serve yellow-blue colour vision, and may exert a modulatory influence on magnocellular and parvocellular pathway function (J. L. Hepschke et al., 2021). This theory is based on findings that VSS patients prefer tinted lenses on the yellow-blue spectrum to reduce the perception of visual symptoms, that coloured lenses which increase s-cone excitation aggravate visual symptoms (J. L. Hepschke et al., 2021; Lauschke et al., 2016).

While TCD has not been directly shown in VSS patients, a magnetoencephalography study found significantly increased primary visual cortex gamma power, and reduced phase-amplitude coupling. These results are suggestive of a hyperexcitable visual cortex, and theoretically consistent with the presence of TCD (Jenny L. Hepschke et al., 2021a).

Other theories

Metzler and Robertson (2018) suggested that stochastic resonance may play a role in VSS symptoms. Stochastic resonance is a phenomenon in which the addition of sensory 'noise' improves signal-to-noise ratio and enhances the detection of weak stimulus (Manjarrez, Mendez, Martinez, Flores, & Mirasso, 2007; Moss, Ward, & Sannita, 2004). Stochastic resonance occurs in all sensory modalities, including visual, and can function cross modally; the addition of noise to one sensory system can improve the sensitivity of another (Manjarrez et al., 2007). It is theorised that, during VSS, the presence of visual 'noise' may increase the sensitivity of other sensory systems, resulting in the heightened perception of sub-threshold or non-existent stimuli such as tinnitus (Metzler & Robertson, 2018).

Summary

The pathophysiology of VSS appears to be complex and widespread. Thalamic dysfunction is a compelling theory given that disruption to sensory processing at this early

stage may gave flow-on effects to cortical processing regions, and contribute to the development of co-occuring sensory and psychiatric symptoms (Fraser, 2022). Altered activity and connectivity of visual processing regions in the cortex may trigger thalamic dysfunction, or represent a consequence of it (Lauschke et al., 2016). Francesca Puledda, Ffytche, O'Daly, and Goadsby (2019) suggested that a combination of subcortical, cortical, and peripheral dysfunction contribute to VSS pathophysiology, potentially to differing extents in different individuals and stages of the syndrome.

1.3 Ocular motor assessment

Ocular motor assessment may offer a method of assessing the integrity of visual networks in VSS. The visual system and ocular motor network are highly interdependent, and rely on overlapping neural pathways and structures. Eye movements represent the efferent output of the visual system, while also serving a vital function for visual perception by acquiring information for processing (R. John Leigh & Zee, 2015; Prasad & Galetta, 2011).

There are a number of advantages to ocular motor measures. The anatomical structures and physiological processes involved in ocular motor control are among the most clearly understood neural networks in the brain (Anderson et al., 1994; Hikosaka, Takikawa, & Kawagoe, 2000; R. John Leigh & Zee, 2015; Pelisson, Alahyane, Panouilleres, & Tilikete, 2010). Consequently, abnormalities in ocular motor performance in clinical patient groups can provide clues as to the localization and nature of neurological dysfunction (Tatler, 2013). Ocular motor methods have proven to be highly sensitive in detecting neurological changes in sub-clinical populations such as a clinically isolated syndrome of demyelination, during which neurological changes may be subtle and pass undetected by less sensitive measures (J. Fielding et al., 2015). In addition, ocular motor tasks are typically brief, reproducible, and well-tolerated by patients (Hutton, 2008b).

Due to both the overlap with the visual system, and high level of sensitivity, ocular motor assessment is well positioned to detect neurological changes in VSS. Differences in ocular motor performance in VSS may further illuminate the pathophysiology of the condition, and could offer an objective measure of disorder presence or severity.

1.3.1 Saccadic eye movements

Saccadic tasks are commonly used when assessing ocular motor function. Saccades are rapid, conjugate movements of the eyes, which function to position objects or regions of interest in the visual field on the fovea, the region of the retina responsible for high acuity vision (R. John Leigh & Zee, 2015). The latency of saccades (i.e., time taken to generate a saccade) is often a metric of interest in saccadic tasks, as saccade latencies are thought reflect not only the time needed to determine where to look and trigger saccade onset, but also the time taken to decide whether it is worth looking to a location at all (R. H. Carpenter, 1994; Wolf & Lappe, 2021). This decision making process is heavily reliant on attentional processes (Godijn & Theeuwes, 2003).

Attention and ocular motor control

Attention is closely associated with both visual processing and ocular motor control (Awh, Armstrong, & Moore, 2006; Moore & Fallah, 2001; Wu, 2014). The visual environment contains an overwhelming amount of information, of which only a limited amount can be processed concurrently (Godijn & Theeuwes, 2003). Visual attention acts as a selection mechanism, informing decisions of where to direct gaze and therefore visual processing resources (Wu, 2014). Generally, where an individual is looking is also where their attention is directed, although this is not always the case. Attention can be oriented overtly (with an accompanying eye movement) or covertly (without a shift of gaze) (Singh, Upadhyay, & Singh, 2016).

Both orienting of attention and saccade generation are reliant on the balancing and integration of endogenous and exogenous attentional processes. Exogenous orienting refers to bottom-up, stimulus-driven capture of attention by visual stimuli, whereas endogenous orienting refers to top-own, intentional allocation of attention based on current goals (Hutton, 2008b; Mayer, Dorflinger, Rao, & Seidenberg, 2004).

Saccades can be classified into two broad conceptual categories- reflexive saccades and volitional saccades- which parallel exogenous and endogenous attentional processes respectively. Reflexive saccades are triggered automatically by the sudden onset of a sensory stimulus (Mort et al., 2003). Conversely, volitional saccades are generated internally in accordance with the observer's motivations; they represent an intentional decision to shift gaze (R. J. Leigh & Kennard, 2004; McDowell, Dyckman, Austin, & Clementz, 2008). The distinction between reflexive and volitional saccades stems is observed in their distinct behavioural characteristics (Walker, Walker, Husain, & Kennard, 2000), and differing activation of neural circuitry underlying saccade generation (Mort et al., 2003; Schraa-Tam et al., 2009).

1.3.2 Saccade neural circuitry

An extensive body of literature has described the various neural regions and processes involved in generating and controlling saccadic eye movements (Grosbras, Laird, & Paus, 2005; R. John Leigh & Zee, 2015; Munoz, Dorris, Pare, & Everling, 2000). After visual information is received and processed by the retina, LGN, and visual cortex, top-down saccade processing utilizes a complex network of cortical, subcortical, and brainstem regions (Munoz & Everling, 2004). Key cortical regions for saccadic control are found mostly the frontal and parietal cortices (particularly respective eye fields). Subcortically, the superior

colliculus, basal ganglia, cerebellum, and brainstem reticular formation play critical roles (R. John Leigh & Zee, 2015).

Two parallel but interconnected pathways underlie reflexive and volitional saccade generation, linking frontal and parietal eye fields with the superior colliculus- the pre-motor command centre for saccades in the brainstem. The first pathway is implicated primarily in the generation of reflexive saccades, and projects directly from the parietal eye fields to the superior colliculus (Gaymard, Lynch, Ploner, Condy, & Rivaud-Pechoux, 2003; Stanton, Goldberg, & Bruce, 1988). The second pathway is involved primarily in the generation of volitional saccades, reciprocally connecting frontal regions (including the frontal eye fields, supplementary eye fields, and dorsolateral prefrontal cortex), and projecting both directly and indirectly to the superior colliculus via the basal ganglia (McDowell et al., 2008). The following section will discuss the contribution of significant neural regions to the generation of horizontal saccades, as is relevant for this thesis.

Cortical saccade network

Parietal eye fields

The parietal eye fields are located in the posterior parietal cortex; the posterior parietal cortex serves as a sensorimotor interface in the saccade network, and is important for orienting visual attention (with or without an accompanying saccade) (Corbetta et al., 1998; Pierrot-Deseilligny, Milea, & Muri, 2004). Neurons in the PEF show strong activation in response to visually salient stimuli, congruent with their role in orienting attention and the generation of reflexive saccades (Barash, Bracewell, Fogassi, Gnadt, & Andersen, 1991; Wardak, Olivier, & Duhamel, 2002). The PEF are also important for the sensorimotor transformation of retinotopic information into saccade commands, and contribute to maintaining visual targets in working memory; PEF neurons remain active throughout reflexive and volitional saccades (Barash et al., 1991; Corbetta, Kincade, & Shulman, 2002).

Frontal regions

There are three main regions of the frontal lobe important for eye movement control: the frontal eye fields, supplementary eye fields, and prefrontal cortex, which show reciprocal connections with each other, and other cortical regions underlying saccade control (Pouget, 2015). The SEF are located anterior to the supplementary motor cortex, and appear to be important for motor preparation of saccades (Pouget, 2015). They may also play a supervisory role in saccade control, monitoring performance and the relationship between saccadic behaviours and their outcomes (Stuphorn, 2015).

The prefrontal cortices are crucial for the regulation of all goal-directed behaviour, including saccades. Afferent projections from cortical regions involved in attention, motivation, and emotion are received and integrated in the prefrontal cortices and transmitted on to the SC and cortical eye fields (Gaymard, Ploner, Rivaud, Vermersch, & Pierrot-Deseilligny, 1998; R. John Leigh & Zee, 2015; Pierrot-Deseilligny et al., 2004). Anatomically, the prefrontal cortices can be divided into ventral (vlPFC) and dorsal (dlPFC) regions. The dlPFC in particular is implicated in inhibition of unwanted reflexive saccades (Pierrot-Deseilligny et al., 2003).

The FEF is primarily implicated in the more complex, cognitive aspects of volitional saccade generation (Pierrot-Deseilligny et al., 2004). Activation of the FEF is seen during both reflexive and volitional saccades, but increased activation is observed during tasks with higher cognitive demands (Everling & Munoz, 2000). The FEF are also thought to be involved in the integration of top-down cognitive information with bottom-up sensory input, and in inhibiting inappropriate reflexive saccades (Everling & Munoz, 2000; R. John Leigh & Zee, 2015; K. G. Thompson, Bichot, & Sato, 2005).

Anterior cingulate cortex

The anterior cingulate cortex (ACC) shows pre-saccadic activation preceding a range of volitional eye movements (F. R. Robinson & Fuchs, 2001). Although the precise role of the ACC is unclear, it has been proposed that ACC activation prior to an eye movement could reflect intention to perform a saccade and the ensuing preparation of ocular motor areas. This preparation may be achieved through enhancing activity and facilitating neural transmission in motor areas employed by saccades (Gaymard, Rivaud, et al., 1998). The ACC is also thought to play a role in monitoring saccade performance; activation has been observed following errors and reinforcement during saccade tasks (Ito, Stuphorn, Brown, & Schall, 2003).

Subcortical saccade network

Brainstem: saccade generator

All eye movements are driven by the synergistic action of three pairs of extraocular muscles (Enderle, 2002; Wright, 2003). Input from a circuit of ocular motor brainstem regions (including the abducens nucleus, oculomotor nucleus, medial longitudinal fasciculus, and pontine reticular formation) acts as a burst generator, and controls the extraocular muscles (Scudder, Kaneko, & Fuchs, 2002; Wolf & Lappe, 2021). These ocular motor brainstem regions are responsible for the transition between saccades and fixation, primarily based on direct projections from the SC (Scudder et al., 2002; Wolf & Lappe, 2021).

Superior colliculus

The superior colliculus (SC) receives and integrates inputs from various cortical and subcortical areas involved in sensory, motor, and attentional processing, and projects extensively to the brainstem circuity involved in saccade initiation (Munoz et al., 2000; Trappenberg, Dorris, Munoz, & Klein, 2001). Located in the midbrain, the SC is comprised of seven layers which can be viewed as two regions. The superficial ‘visual’ region receives

direct projections from the retina and visual cortex (D. L. Robinson & McClurkin, 1989). The dorsal region receive input from various cortical and subcortical regions including the basal ganglia, frontal eye fields, supplementary eye fields, and parietal cortex (Wolf & Lappe, 2021).

The balance of excitatory and inhibitory inputs to the SC and subsequent activity of neuronal populations within the SC determines the timing and spatial coordinates of saccades (R. John Leigh & Zee, 2015; Munoz & Wurtz, 1993). Excitatory inputs originate from frontal and parietal cortical areas (Gaymard et al., 2003), and the cerebellum (Johnston & Everling, 2008; Lynch, Hoover, & Strick, 1994). Inhibitory inputs originate primarily from the basal ganglia and specific cortical areas (Hikosaka et al., 2000; Sparks & Hartwich-Young, 1989).

Cerebellum

The primary role of the cerebellum in regards to saccadic control is monitoring and adjusting ocular motor command signals to ensure saccadic accuracy (Kheradmand & Zee, 2011; F. R. Robinson & Fuchs, 2001). The cerebellum receives information from virtually all cortical and subcortical areas important for saccade control, and in the short-term modulates activity along ocular-motor command pathways to ensure objects of interest are placed promptly and correctly on the fovea. Long-term, the cerebellum is involved in motor learning and saccadic adaptation to changing environmental demands or damage to saccadic structures (Kheradmand & Zee, 2011; Peterburs et al., 2015; Prevosto, Graf, & Ugolini, 2010)

Basal ganglia

The basal ganglia are a significant component of ocular motor circuitry, contributing primarily to the control of volitional saccades (Hikosaka, 2007). Anatomically, four distinct structures comprise the BG: the striatum, the globus pallidus, the substantia nigra, and the subthalamic nucleus (STN) (Lanciego, Luquin, & Obeso, 2012). Collectively these structures function to modulate cortical projections to the SC and influence goal-directed behaviour.

The BG is implicated in both saccade initiation and inhibition of unwanted saccades; cortical projections via the BG regulate activity in the SC, and are thought to influence the generation and inhibition of saccades based on top-down cognitive processes and goals (Isoda & Hikosaka, 2011).

The dorsal region of the striatum is comprised of the caudate nucleus and putamen, and functions as a major input processing and integration station for the BG (Lanciego et al., 2012). Cortical and subcortical inputs converge on the striatum, and in turn the striatum projects to BG output structures, the gPi and SNr (Hikosaka et al., 2000; Yoshida & Tanaka, 2009). The gPi is the internal segment of the globus pallidus, and is theorised to play a role in saccadic control (Middleton & Strick, 2001; Shin & Sommer, 2010). The SNr is part of the substantia nigra and functions as the final relay station of the BG to the SC, playing a pivotal role in saccade suppression (Hikosaka et al., 2000). These structures project to the SC, influencing SC inhibition and disinhibition and the suppression of initiation of saccades (Hikosaka et al., 2000; Isoda & Hikosaka, 2011).

1.3.3 Ocular motor tasks and psychiatric symptoms

Ocular motor assessment is valuable due to the high sensitivity of the ocular motor system to subtle neurological dysfunction; however, as a consequence, saccadic characteristics may be influenced by neurological or psychiatric comorbidities (Bocca, Marie, & Chavoix, 2014; Carvalho et al., 2015). The potential influence of psychiatric disturbances is an important consideration for the use of ocular motor measures in VSS, given the frequent comorbidity of psychiatric symptoms. Previous research assessing the influence of psychiatric conditions on ocular motor performance has provided mixed results.

Depressive disorders have been associated with longer prosaccade latencies and higher antisaccade error rates (Carvalho et al., 2015; A. Hoffmann, Ettinger, Montoro,

Gustavo, & Duschek, 2019). These changes are speculated to be a consequence of impaired executive control processes (Snyder, 2013), lower levels of motivation resulting in reduced attentional engagement (Bittencourt et al., 2013), or psychomotor retardation (Carvalho et al., 2015). However, other studies have found no influence of depression (Sereno & Holzman, 1993; Sweeney, Strojwas, Mann, & Thase, 1998), or have reported that only a specific subtype of depression is associated with prolonged latencies (Winograd-Gurvich, Georgiou-Karistianis, Fitzgerald, Millist, & White, 2006). Notably, most of these studies also included only patients with diagnosed depressive disorders, whose results may not be generalisable to the wider population. In a community sample of 207 participants, level of depressive symptomology as assessed by a self-report scale not influence antisaccade performance (Todd, Notebaert, & Clarke, 2022).

Anxiety is often associated with distractibility and impaired attentional control (Lapointe et al., 2013; Shi, Sharpe, & Abbott, 2019); anxiety disorders have been linked with prolonged antisaccade latencies (Ansari & Derakshan, 2011; Derakshan, Ansari, Hansard, Shoker, & Eysenck, 2009; Liang, 2018), and increased antisaccade error rates (Garner, Ainsworth, Gould, Gardner, & Baldwin, 2009; Hepsomali, Hadwin, Liversedge, & Garner, 2017; Wieser, Pauli, & Mühlberger, 2009), however the latter has been reported only in tasks where emotive stimuli (e.g., an emotionally expressive faces) have been used as stimuli instead of neutral cues and targets (e.g. arrows, crosses). The differing methods and task designs utilised complicate generalization of results.

Neurodevelopmental disorders including ADHD have also been associated with alterations to saccadic characteristics (Canu et al., 2022; Maron et al., 2021). Most often these alterations are attributed to top-down processing deficits and include increased antisaccade error rates and latencies, and difficulty inhibiting inappropriate anticipatory saccades (Canu et al., 2022; Maron et al., 2021).

Sleep deprivation and fatigue may also impact saccade generation, either through neurophysiological effects on saccade circuitry related to low arousal (Di Stasi, Catena, Cañas, Macknik, & Martinez-Conde, 2013; Zils, Sprenger, Heide, Born, & Gais, 2005), or impairment of executive functioning and attentional control (Bocca et al., 2014; Durmer & Dinges, 2005). The most consistent effect of sleep deprivation and fatigue is alterations to saccade peak velocity, with changes to latencies and error rates found inconsistently (Bafna & Hansen, 2021; Connell et al., 2016).

While it is evident from these studies that psychiatric symptoms can influence ocular motor characteristics, it is not clear whether these effects would be seen across typical and moderately elevated levels of these symptoms throughout the population, or whether they are only apparent in the context of diagnosed conditions (e.g. depressive and anxiety disorders, ADHD) or when experimentally induced in unnatural conditions (e.g. total sleep deprivation).

1.3.4 Summary

The cortical and subcortical networks underlying ocular motor control are well characterized, highly sensitive to dysfunction, and share an obligatory anatomical and functional overlap with visual processing networks (R. John Leigh & Zee, 2015; Prasad & Galetta, 2011). In addition, regions of the cortex and subcortex important for eye movement control have been implicated in VSS neuroimaging studies, including the frontal eye fields, anterior cingulate cortex, cerebellum, and caudate nucleus (Francesca Puledda, Christoph J. Schankin, et al., 2021; Schankin, Maniyar, et al., 2020). Assessment of ocular motor function therefore represents a promising method of assessing changes to visual and attentional networks in VSS, and providing reproducible, objective behavioural markers of dysfunction.

It is unknown what alterations to ocular motor behaviour might be observed in VSS. Given that attentional deficits have been associated with the disorder, difficulty inhibiting eye

movements (poorer inhibitory control), may be observed. Changes to attentional and visual processing could also manifest as differences in the speed of saccade initiation (i.e., latency). A potential limitation of ocular motor measures is that they may be affected by comorbid neurological or psychiatric diagnoses. As psychiatric comorbidity appears to be common in VSS (Fraser, 2022; D. G. Mehta et al., 2021), the possible influence of co-occurring psychiatric symptoms on ocular motor characteristics also needs to be established.

1.5 Rationale for thesis

VSS is poorly understood with no effective treatment options. There is a clear need for an improved understanding of VSS pathophysiology, and the identification of objective markers of dysfunction, to facilitate investigation of treatment strategies. Due to the high level of sensitivity that ocular motor measures offer, and the interdependency of ocular motor visual processing networks, ocular motor tasks may offer a method of achieving both. Alterations to ocular motor behaviour could elucidate visual processing changes in VSS, and provide an objective behavioural marker of dysfunction in visual and attentional networks.

In addition, management of VSS patients may be improved by better characterising and understanding the commonly co-occurring psychiatric symptoms, and how they relate to sensory dysfunction. Given that current treatments aimed at reducing visual disturbances are infrequently effective, treating psychiatric comorbidities may offer an alternate approach to alleviating patient distress.

1.5.1 Aims

The principal aims of this thesis were (1) to investigate the utility of ocular motor measures in identifying visual processing dysfunction in VSS, and (2) to determine the prevalence of commonly reported psychiatric symptoms in VSS and their association with sensory dysfunction. A further aim was to determine whether common psychiatric symptoms in VSS participants influenced OM performance.

To achieve this, a battery of OM tasks was utilised to examine the generation of saccades under different task conditions that evaluated the impact of endogenously or exogenously reorienting attention. A battery of self-report questionnaires was also administered to assess sensory symptoms experienced by participants, as well as current

levels of common psychiatric symptoms (depression, anxiety, stress, sleep, fatigue, depersonalization/derealization, and inattentive and hyperactive/impulsive symptoms).

Chapter Two: General methods

This chapter provides an overview of the general methodology for all experiments included in this thesis. Specific methodologies are provided in each chapter, however, they are brief due to the word limits imposed by journals. This chapter will extend upon the methodology information provided in each chapter and give a cohesive overview of ethics, recruitment procedures, screening techniques, participant information, and the measures used. By necessity, the experimental chapters of this thesis will reiterate some information covered here.

2.1 Ethics

Ethics approval for this study was granted from the Monash University Human Research Ethics Committee (MUHREC, Project ID: 9495). In accordance with the requirements of MUHREC and the Helsinki Declaration, all participants provided informed consent. When participants were under the age of 18, a legal guardian also provided informed consent.

2.2 Recruitment

2.2.1 Healthy control participants

Healthy control participants were recruited primarily through researcher social circles. A small number of control participants were friends or family of VSS participants (with no biological relationship), or were recruited through recruitment flyers placed around the Central Clinical School at the Alfred Centre. Recruitment flyers included a brief explanation of the study, basic inclusion/exclusion criteria, and a contact email for the researcher. Potential control participants were screened for inclusion in the study either in-person or over a phone call, and were emailed the explanatory statement prior to giving informed consent.

Compensation

Healthy control participants were not compensated for participating in the study. Parking vouchers were offered if required.

2.2.2 Visual snow syndrome participants

Participants with VSS were recruited using a number of methods. Prof. Owen White, a neuro-ophthalmologist and co-supervisor for this study, assisted with recruitment by identifying suitable patients from his clinical practice and providing them with information about the study aims and what participation would entail. If patients indicated their interest, they were put in contact with a researcher who sent them the explanatory statement for the project over email, and answered any questions about study methodology and time commitments. A number of VSS patients were also referred to the study by other neurologists, with the same recruitment procedure used. Patients were made aware that their decision to participate or decline would not affect their treatment.

The study was additionally advertised during television and radio interviews regarding the ongoing visual snow research at Monash University, and over online platforms, specifically in online support groups for people with visual snow. Individuals who reached out and expressed their interest following these advertisements were put in contact with a researcher who conducted an initial screening. The purpose of this initial screening was to ascertain whether the interested individual had been diagnosed with VSS, and if not, whether their symptoms and experiences were consistent with a VSS diagnosis, as well as enquiring about other inclusion/exclusion criteria.

Potential VSS participants who had been diagnosed were asked to provide the name of the professional who diagnosed them. Those who had not been diagnosed, but passed the initial screening, were asked to complete a detailed online questionnaire regarding their

visual symptoms and other clinical features and information relevant for VSS diagnosis. Their responses to this questionnaire were reviewed by Prof. Owen White to determine whether a diagnosis of VSS was probable.

Compensation

VSS participants were not compensated for completing the study, but were offered parking vouchers if they preferred to drive.

2.3 Participant characteristics

Specific demographic and clinical information for healthy control participants and VSS participants is presented within each experimental chapter.

2.3.1 Healthy control participants

37 healthy control participants were included in the ocular motor component (Chapters 3, 4, & 6) of this thesis. The inclusion criteria were as follows:

- Between the ages of 16 and 65 years old
- No history of concussion or traumatic brain injury
- Not currently diagnosed with a neurological disorder
- No significant issues affecting eyesight (beyond standard problems that can be addressed with corrective lenses)
- Has not ingested recreational drugs within the past 12 months, and does not have a history of regular recreational drug use

2.3.2 Visual snow syndrome participants

189 VSS participants in total were included across the studies in this thesis. 88 VSS participants completed some or all of the ocular motor tasks, and 167 VSS participants

completed some or all of the online questionnaires. The following inclusion criteria were used:

- Diagnosis of VSS from a neurologist, OR completion of a screening questionnaire with responses reviewed by a neurologist
- Onset of VSS not linked to recreational drug use (no recreational drug use within the 6 months prior to VSS onset)
- Onset of VSS not linked to head injury
- No history of concussion or traumatic brain injury
- No diagnosis of, or history of potentially confounding neurological or ophthalmological condition
- Between the ages of 16 and 65

2.3.2 Reported medication use among VSS participants

An additional exclusion criterion for OM tasks was consumption of medication likely to affect OM results. Based on research showing selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants do not have a significant influence on saccade latencies or inhibitory error rates (Green, King, & Trimble, 2000; Reilly, Lencer, Bishop, Keedy, & Sweeney, 2008), VSS participants reporting use of SSRIs, SNRIs, and tricyclic antidepressants were permitted to participate in OM studies. Other medications prescribed for psychiatric or neurological conditions were considered exclusion criteria, either due to published evidence that they impact saccade latencies and inhibitory control (e.g. benzodiazepines, stimulant medication, and antipsychotic medication), or due to a lack of evidence regarding any impact on saccadic characteristics (e.g. tetracyclic antidepressants, lamotrigine) (Arkell et al., 2022; Reilly et al., 2008). The number and percentage of patients taking medication included in each ocular motor study are outlined below.

- Chapter Three: SSRIs (7 participants), SNRIs (4 participants), tricyclic antidepressants (1 participants). In total, 12 (18.8%) of the 64 VSS participants.
- Chapter Four: SSRIs (6 participants), SNRIs (4 participants), tricyclic antidepressants (2 participants). In total, 12 (17.9%) of the 67 VSS participants.
- Chapter Six: SSRIs (7 participants), SNRIs (4 participants), tricyclic antidepressants (2 participants). In total, 13 (21.3%) of the 61 VSS participants.

Prescribed medications reported by VSS participants across all studies are listed in Table 2.1.

Table 2.1

Prescribed medications reported by VSS participants

Medication	Number of participants	Exclusion criterion for ocular motor studies
SSRIs:		
Citalopram	2	No
Escitalopram	3	No
Sertraline	7	No
Paroxetine	1	No
Fluvoxamine	1	No
Vortioxetine	1	No
SNRIs:		
Desvenlafaxine	3	No
Duloxetine	2	No
Venlafaxine	1	No
Tricyclic antidepressants:		
Dosulepin	1	No
Amitriptyline	1	No
Other antidepressants:		
Bupropion	4	Yes
Mirtazapine	2	Yes
Moclobemide	1	Yes

Antipsychotic medication:		
Quetiapine	1	Yes
Migraine/seizure medication:		
Lamotrigine	3	Yes
Lamictal	2	Yes
Erenumab	1	Yes
Stimulants:		
Amphetamines	2	Yes
Methylphenidate	1	Yes
Other:		
Proton pump inhibitors	3	No
Beta blockers	2	No
Levothyroxine	2	No
Allopurinol	1	No
Minoxidil	1	No

Notes. SSRIs: Selective serotonin reuptake inhibitors; SNRIs: Serotonin–norepinephrine reuptake inhibitor

2.4 Measures

2.4.1 Symptom questionnaires

VSS questionnaire / screening questionnaire

The VSS questionnaire was completed by all participants with VS, and can be found in full in Appendix A. The VSS questionnaire was used both to characterise the symptoms and experiences of participants with a confirmed VSS diagnosis, and to screen participants who had not been formally diagnosed. Consequently, some of the included questions were primarily relevant for the screening process. For example, patients were asked to confirm if they had even been formally diagnosed with VSS, and if so which tests they could recall

having undergone during the diagnosis process. They were also asked if they had ever used illicit drugs, and if yes, whether illicit drugs had been consumed prior to VSS onset.

To characterise the symptoms and experiences of VSS participants, they were asked their age at symptom onset, and to indicate from a list which additional visual and non-visual symptoms they commonly experienced. Participants also rated the intensity, disruptiveness, and impact on quality of life (QOL) of their VS on Likert scales. Intensity was rated on a scale from 1-6, using an image displaying varying intensities of static as a guide. Disruptiveness and impact on QOL were rated on a scale from 1-7, with 1 being the mildest (Not at all disruptive / No impact) and 7 being the most severe (Severely disruptive / Severely reduced quality of life).

Other questions concerned whether participants had a relative with VSS, or a family history of VSS or migraine. A number of open-ended questions were also included, where participants were asked to describe their VS and associated visual symptoms, and indicate whether any life activities were impacted by their VSS, and whether they had identified any factors that improved or worsened their symptoms.

Migraine questionnaire

The migraine questionnaire can also be found in full in Appendix A. This questionnaire comprised questions asking about the frequency and duration of migraine episodes, and what symptoms were typically experienced during or leading up to migraines. Additionally, participants were asked whether they experienced migraine visual aura, and if so typical the frequency, duration, and nature of their visual auras.

2.4.2 Psychiatric and control measures

National Adult Reading Test (NART)

The NART is a verbal pronunciation test which provide an indication of intelligence and general cognitive ability (Nelson & Willison, 1991). The NART is reported to show good internal consistency (α = .93), and test-retest reliability (*r* = .98) (Nelson & Willison, 1991), and is valid as a measure of general intelligence (Crawford, Stewart, Parker, Besson, & Cochrane, 1989). Participants completed the NART to control for any confounding influence of intelligence on ocular motor tasks.

The NART was administered in-person, prior to ocular motor testing. The test comprises a list of 50 irregularly spelled words (e.g. naïve, thyme) of increasing complexity. Participants were asked to read each word aloud and pronounce the word to the best of their ability. The researcher, with the use of a pronunciation guide, recorded which words were or were not correctly pronounced.

The NART is scored by summing the number of errors (i.e., the number of incorrectly pronounced words) to create a total error score. The total error score is then converted using an equation (127.7 – 0.826 X total error score) to a standardised Full Scale IQ (FSIQ) (Nelson & Willison, 1991).

Alcohol Use Disorders Identification Test (AUDIT)

The AUDIT was used as a screening instrument for harmful or hazardous alcohol consumption among participants over the year prior to testing (Saunders, Aasland, Babor, De La Fuente, & Grant, 1993). It is reported to show high internal consistency (α = .94) and good test-retest reliability (*r* = .84) (de Meneses-Gaya, Zuardi, Loureiro, & Crippa, 2009). The AUDIT comprises 10 self-report items, which cover the amount and frequency of typical

alcohol consumption, as well as alcohol-related behaviours and reactions from friends and family.

Participants respond to each item by selecting one of five responses for the first 8 items, and one of 3 responses for the final 2 items, that best describes their level of agreement with the item. The responses for the first 8 items are scored from 0-5, and the final 2 items as 0, 2, or 4. Scores from individual items are summed together to form a total score with a maximum score of 40. Higher scores indicate higher levels of alcohol consumption. Total scores of 8 or more indicate potentially hazardous or harmful alcohol consumption (Saunders et al., 1993).

Drug Use Disorders Identification Test (DUDIT)

The DUDIT was used to screen for problematic illicit drug use among participants over the preceding year (Berman, Bergman, Palmstierna, & Schlyter, 2005). Internal consistency estimates for the DUDIT (α) are generally >.90, and estimates of sensitivity and specificity are favourable (Hildebrand, 2015). It comprises 11 self-report items, which cover topics such as the frequency of illicit drug use, drug-related behaviours and actions, and reactions from friends and family.

Participants respond to each item by selecting one of five responses for questions 1-9, and one of three responses for questions 10 and 11, that best describes their level of agreement with the statement. The first 9 items are scores from 0-4, and the remaining 2 as 0, 2, or 4. Individual item scores are summed to form a total score with a maximum score of 44. Higher scores indicate more frequent or severe illicit drug use. Total scores of 2 + for women or 6+ for men indicate drug-related problems (Berman et al., 2005).

Depression Anxiety Stress Scale (DASS)

The Depression Anxiety Stress Scale was employed to assess the extent of self-reported negative emotions over the week prior to testing (Lovibond & Lovibond, 1995). The DASS is reliable and valid for measurement of depression (α = .96), anxiety (α = .89), and stress (α = .93) (Basha & Kaya, 2016). It comprises 42 items in total which form 3 subscales: Depression, Anxiety, and Stress, each consisting of 14 self-report items. Each item takes the form of a statement, including sentiments related to sadness, feelings of worthless, irritability, and bodily sensations such as breathlessness. An example item is 'I couldn't seem to experience any positive feeling at all'.

Participants respond to each item by selecting one of four responses indicating how strongly they feel the statement applies to them (Did not apply to me at all, Applied to me to some degree, or some of the time, Applied to me to a considerable degree, or a good part of the time, and Applied to me very much, or most of the time). Responses are scores from 0-3, and scores for each subscale are calculated by summing the scores of the 14 items which comprise the subscale. Higher scores reflect higher levels of depression, anxiety, or stress. Score ranges for each subscale as recommended by the DASS manual are displayed in Table 2.2.

Table 2.2

Depression Anxiety Stress Scale (DASS) score ranges

	Depression	Anxiety	Stress
Normal	0-9	0-7	0-14
Mild	10-13	8-9	15-18
Moderate	14-20	10-14	19-25
Severe	21-27	15-19	26-33
Extremely severe	28+	20+	34+

Pittsburgh Sleep Quality Index (PSQI)

The PSQI was used to assess self-reported sleep quality and sleep patterns over the preceding month, and identify sleep dysfunction (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). It is the most widely used sleep health measure, with good internal consistency (α = .76) and test-retest reliability (*r* = .64), and good construct validity (Fabbri et al., 2021). The PSQI comprises 19 items, which form seven subscales: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficacy, sleep disturbances, use of sleeping medication, and daytime dysfunction.

Items are either responded to on a 0-3 Likert scale, (e.g. 'During the past month, how would you rate your sleep quality?) or are open-ended questions (e.g. 'During the past month, when have you usually gotten up in the morning?) where responses are converted to a 0-3 scale. Subscale scores range from 0-3, with higher scores indicating more severe sleep difficulties. A global score ranging from 0-21 can also be generated by summing the seven subscale scores.

A global cut-off score of 5+ is typically recommended to identify clinical levels of sleep disturbances in the general population. However, a more conservative cut-off score of 8+ has been recommended for clinical populations, and was used for this study (J. S. Carpenter & Andrykowski, 1998).

Fatigue Severity Scale (FSS)

The FSS was used to assesses the impact of self-reported trait fatigue on day-to-day activities over the preceding week (Krupp, LaRocca, Muir-Nash, & Steinberg, 1989). It is reported to show good internal consistency (α = .81 - .89) and test-retest reliability (*r* = .68), and good convergent validity (Shahid, Shen, & Shapiro, 2010). The FSS comprises 9 items,

each item a statement of the impact of fatigue on physical, cognitive, or general functioning, such as 'Fatigue interferes with my work, family, or social life'. Participants respond to each item by selecting one of 7 responses on a Likert scale, where 1 = Strongly disagree and 7 = Strongly agree.

Responses to each item are summed to form a total score with a maximum score of 63. Higher scores reflect a greater impact of fatigue on day-to-day functioning. A cut-off score of 36 was used was used to indicate clinical levels of fatigue, equivalent to the cut-off score recommended by the original authors (Krupp et al., 1989).

Cambridge Depersonalisation Scale (CDS)

The CDS was used to measure self-reported experiences of depersonalization and derealization over the previous 6 months (M. Sierra & Berrios, 2000). It has high internal consistency ($\alpha = .81$) and good construct validity (M. Sierra & Berrios, 2000). The CDS includes 29 items, each item a statement describing an experience linked to depersonalisation or derealisation, such as 'I have the feeling of being outside my body', or 'what I see looks 'flat' or 'lifeless', as if I were looking at a picture'.

Participants respond to each statement on two scales, one scale relating to the frequency of these experiences (0-4), and the other their typical duration (1-6). Higher scores reflect more frequent/long-lasting experiences of depersonalisation/derealisation. Scores from both scales are summed to form a total score, with scores above 70 indicating a possible depersonalization disorder (M. Sierra & Berrios, 2000).

Short Form 36 Health Survey (SF-36)

The SF-36 was utilised to assess self-reported health-related quality of life over the preceding month. It has good internal consistency ($\alpha > .70$), test-retest reliability ($r > .70$) and

convergent validity (Yarlas et al., 2018). The SF-36 comprises 36 items which form 8 subscales covering different health concepts: physical functioning (10 items), role limitations due to physical problems (4 items), social functioning (2 items), bodily pain (2 items), mental health (5 items), role limitations due to emotional problems (3 items), vitality (4 items), and general health perceptions (5 items) (Ware, 2000). An example item is, 'During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?'

Participants respond to each item on a 3 or 5 point Likert scale, with higher scores reflecting better health-related quality of life. Scores for each subscale are transformed using an equation to fall on a 0-100 scale ((raw subscale score - minimum subscale score)/subscale range) x 100), with 0 corresponding to the worst possible health-related QOL, and 100 to the best possible health-related QOL. A total score was also calculated by summing raw subscale scores, and similarly transforming to fall on a 0-100 scale.

Adult ADHD Self-report Scale (ASRS)

The ASRS was used to measure inattentive and hyperactive/impulsive symptoms. The scale was developed by the World Health Organisation to assesses symptom levels in adults over the preceding 6 months (Kessler et al., 2005), and is a valid measure of ADHD symptoms with high internal consistency ($\alpha = .88$) (L. A. Adler et al., 2006). The scale comprises 18 items in total, which correspond to symptoms included in the DSM-V diagnostic criteria for ADHD. The two subscales (inattentiveness and hyperactivity/impulsivity) include 9 items each, and reflect the two symptom domains of ADHD. Example items are 'How often are you distracted by activity or noise around you?', and 'How often do you feel restless or fidgety?', for the inattentive and hyperactive/impulsive subscales respectively.

Participants responded to each item by indicating how frequently the experience occurs on a 5 point Likert scale (0 = “never”, 1 = “rarely”, 2 = “sometimes”, 3 = “often”, and 4 = “very often”). Different scoring methods can be used for the ASRS (Kessler et al., 2005). In this study, subscale scores ranging from 0-36 were generated by summing item responses for the 9 items in each subscale. A total score was also generated ranging from 0-72.

However, to identify participants with significantly high levels of inattentive and hyperactive/impulsive symptoms, a shortened 6 item screening version of the ASRS (the ASRS-Screener, ASRS-S) has been reported to outperform the full scale (Kessler et al., 2005). This employs a different scoring method, where item responses are dichotomised based on whether they indicate significant difficulties with the symptom or not. An endorsement of 4 or more of the 6 items using this scoring method is strongly suggestive of ADHD, and this cut-off was used to identify participants with clinically significant levels of symptoms.

2.4.3 Ocular motor apparatus

Ocular motor testing took place at the Central Clinical School in the Alfred Centre, Participants completed all tasks seated on a height-adjustable chair in a darkened room. A head and chin rest were used to stabilise eye position during testing, with the participants eyes situated 950mm from the display monitor (resolution:1920 × 1080). Horizontal displacement of the eyes was recorded binocularly using a desktop-mounted Eyelink 1,000+ dark pupil video-oculography system. The Eyelink 1000 system features a high acquisition rate (1,000 Hz) and a high resolution (noise limited at <0.001°). While the movements of both eyes were recorded, only data from one eye (typically the right eye) was analysed. If the recording of the right eye was comprised in some manner, then data from the left eye was use. Prior to each ocular motor task, an automated calibration program was used. Task stimuli

(1.5° visual angle) are described in detail for each task below, and were presented on a black background.

2.4.4 Analysis of ocular motor data

Ocular motor data output from the Eyelink 1000 was analysed using customised MATLAB software (Zoomtool). Zoomtool is a semi-automated program, and detected four key points for each trial: the time of trial onset, saccade onset, saccade offset, and final eye position. However, all trials had to be manually screened to ensure the accuracy of these points, and edited if required. In addition, trials where an error occurred had to be manually identified and documented. The metrics of interest across all ocular motor tasks were latency and error rate.

Errors were classified into the following categories:

- Task relevant errors: specific to each task, reflecting participant failure to follow task requirements.
- Blinks: a blink occurred <200ms prior to trial onset, or interrupted saccade onset
- Unstable baseline: participants were not fixated on the central cue at trial onset
- System error: a loss of signal or interruption to the eye movement trace

Depending on the task, a task-relevant error was defined as an eye movement exceeding 1.5° in the incorrect direction (Directional error), or an eye movement exceeding 1.5° generated prior to target presentation (Anticipatory error). Task-relevant errors were summed for each task and converted into the proportion of trials (%).

Saccade latency was defined as the temporal difference between trial onset and saccade onset. Saccade onset and offset were identified by positional change in the eye

movement trace corresponding to a change in velocity exceeding 30° per second. Final eye position was the average position of the eye trace during fixation on the target location.

2.5.5 Ocular motor tasks

The following section provides an overview of all five ocular motor tasks completed by participants. The tasks were (1) a visually-guided prosaccade task, (2) an antisaccade task, (3) an interleaved prosaccade-antisaccade task, (4) an endogenously cued saccade task, and (5) a saccadic Simon task.

Visually-guided prosaccade task

The visually-guided PS task simply required the generation of a reflexive eye movement towards a suddenly appearing peripheral target. It comprised 48 trials in total which were presented in a single block in a randomised order. Participants were instructed to begin the task by fixating on the central green cross, and to follow the cross with their eyes as it shifted horizontally to one of four peripheral locations (5 or 10 degrees to the left or right of centre) and then back to centre. The central green cross was presented for a randomised time period to reduce anticipatory responding (1000, 1250, or 1500ms). The peripheral targets were presented for 1500ms, following which the central green cross would be presented again, to indicate participants should return their gaze to the centre to begin the next trial.

For the PS task, only latency was analysed. While errors may occasionally be generated on the PS task, they are infrequent and not generally informative, occurring due to technical errors or a brief moments of participant distraction.

Antisaccade task

The antisaccade task is simple in concept but can be challenging to complete. It requires the inhibition of a reflexive saccade towards a suddenly appearing peripheral target, in favour of a volitionally generated saccade. For this study, the AS task comprised 48 trials in total, split between 2 blocks of 24 trials each with a brief rest in between. As with the PS task, trials were presented in a randomised order. Participants were instructed to begin each trial fixating on a central green cross, which was presented for a variable fore-period to reduce anticipatory responding (1000, 1250, or 1600ms). Concurrent with the disappearance of the central cross, a peripheral green cross was presented in one of four peripheral positions (5 or 10 degrees to the left or right of centre) for 1500ms. Participants were instructed not to look towards the peripheral cross when it appeared, and to look towards the mirror opposite horizontal location instead. When the peripheral cross disappeared, the central cross would reappear, cueing the participant to return their gaze to centre.

Both latency and errors were examined for the AS task. The most common type of errors on the AS task are directional errors, where the participant erroneously looks towards the peripheral cross instead of to the opposite position.

Interleaved prosaccade-antisaccade task

The interleaved PS-AS task presented both prosaccade and antisaccade trials within the same task, with a cue at the initiation of each trial informing the participant which response was required. Interleaving prosaccade and antisaccade trials in this manner increases the cognitive demands and therefore difficulty of the task, as participants must retain the task instructions in their mind and switch quickly between required responses (Ayala & Niechwiej-Szwedo, 2021).

The interleaved PS-AS task comprised 96 trials presented across 3 blocks, with 2 brief rest periods in between. An equal number of PS and AS trials were presented in a pseudo-random order. Participants were instructed to fixate on the central cross at the beginning of each trial, which was presented for a randomised period of 1000, 1250, or 1500ms. Concomitant with the disappearance of the central cross, a peripheral green cross appeared in one of four locations (5 or 10 degrees to the left or right of centre) for 1500ms. At the end of each trial the peripheral cross disappeared and a white box appeared in the centre, to indicate that the participant should return their gaze to baseline.

The colour of the central fixation cross signified whether the participant should generate a prosaccade or antisaccade. Participants were instructed to look towards the peripheral cross if the central cross was green (prosaccade trial), and to look to the mirror opposite position of the peripheral cross if the central cross was purple (AS trial). A guided example of each trial type and a practice block of 10 trials (5 PS and 5 AS trials) was used to familiarise participants with the task requirements.

Trials on the interleaved PS-AS task are classified into four trial types based on whether they were PS or AS, and repeat or switch trials. A repeat trial is a trial following the same type: e.g. a PS following a PS, or AS following an AS. A switch trial is a trial of the opposite type to previous, e.g. a PS following an AS, or AS following a PS. The four trial types were therefore Repeat PS, Switch PS, Repeat AS, and Switch AS. The first trial of each block was excluded from analyses of switch/repeat trial type as they were neither a switch nor repeat trial.

For this task, the latencies of each trial type were analysed, as well as directional errors on AS trials. Errors were not analysed for PS trials due to the simplicity of PS, and therefore small number of erroneous trials.

Endogenously cued saccade task

The endogenously cued saccade task was based on the classic Posner paradigm (Posner, 1980). The task was used to examine the effect of endogenously orienting visual attention either towards or away from the location of an upcoming target.

The endogenously cued saccade task utilised in this study comprised 120 trials split equally into 2 blocks, with a brief rest period in between. Participants were instructed to begin by fixating on a central green cross, which was presented for 400ms. The central cross was flanked by two white boxes located 10 degrees to the left and right of centre. Following 400ms, the cross was replaced by an arrow for 500ms indicating either the right or left box. Participants were told to ignore the arrow and remain fixated on the centre until the arrow disappeared concomitant with the appearance of a target cross in either the box indicated by the arrow (validly cued trial) or in the opposite box (invalidly cued trial). At that point, participants were instructed to look towards the target cross.

Presenting a cue prior to target appearance triggers a covert shift of visual attention towards the cued location. This facilitates the subsequent generation of a saccade towards that location, resulting in shortened reaction times on validly cued trials, and results in lengthened reaction times on invalidly cued trials due to a delay caused by the need to reorient attention (Posner, 1980). The majority of trials (75%) were validly cued, to encourage the expectation that the arrow will correctly predict the upcoming target.

A guided example and practice block of 10 trials (5 validly cued trials and 5 invalidly cued trials) was used to familiarise participants with the task. The metrics of interest for this task were the latencies of each trial type, the cue effect (calculated as invalidly cued trial latency – validly cued trial latency), and the proportion of anticipatory errors. Anticipatory errors occurred when the participant failed to keep their gaze fixed on the centre when the

arrow appeared, and erroneously generated a saccade in the direction indicated by the arrow prior to the cue appearance.

Saccadic Simon task

The Saccadic Simon task similarly manipulates endogenous control of attention, examining the effect of an informative cue located spatially congruent or incongruent with the cued location (Ridderinkhof, 2002). The saccadic Simon task comprised 4 blocks of 32 trials (128 trials in total) with a rest period in between each block. Trials were presented in a pseudo-random order.

To begin the task, participants were instructed to fixated on a central white cross, which was flanked by two white boxes located 10 degrees to the left and right of centre. Following 1000ms, an informative cue in the form a shape (either a circle or a square) was presented in either the left or right box. In the opposite box to the shape, a filler stimuli (three stacked horizontal lines) was presented simultaneously. This was to minimise the likelihood of a reflexive saccade towards the shape. Shape and filler stimuli were presented for 3000ms.

The participant was instructed to look towards the right box if the square appeared, and towards the left box if the circle appeared, regardless of which side they were presented on. They were informed that the circle/square would sometimes appear in the cued location, and sometimes in the opposite location, and that they should maintain their gaze on the central cross until they had interpreted the cue and made a decision about where to look. Participants were familiarised with the task instructions using a guided example, and a practice block of 10 trials.

Trials on the saccadic Simon task are considered congruent if the shape and cued location are corresponding (i.e., a square presented in the right box or a circle presented in the left box) and incongruent if the shape and cued location are opposite (i.e., a square presented

in the left box or a circle presented in the right box). The latencies of incongruent trials are typically longer, an effect known as the 'Simon effect'. However, the Simon effect is only observed in trials following a correctly executed congruent trial (Ridderinkhof, 2002). Latencies for this task are therefore analysed for four trial types, based on the congruency of the previous and current trial: congruent-**congruent** trials, congruent-**incongruent** trials, incongruent-**congruent** trials, and incongruent-**incongruent** trials (bold denotes current trial). The Simon effect is calculated as congruent-**incongruent** latency – congruent-**congruent** latency. Participants typically make a number of directional errors on the saccadic Simon task. Errors are more common on incongruent trials, where the participant erroneously looks towards the shape instead of the cued location.

2.5 General procedure

Ocular motor testing was conducted at the Central Clinical School at the Alfred Centre in Melbourne. Testing sessions were approximately one hour, varying in length based on how many breaks participants required between tasks. All participants were offered a break period halfway through testing (after the third ocular motor task). The ocular motor tasks were completed in the same order for each participant, in approximate order of increasing complexity:

1. Visually guided prosaccade task
2. Antisaccade task
3. Endogenously cued saccade task

(Break)

4. Interleaved prosaccade-antisaccade task
5. Saccadic Simon task

During 2020 and 2021, many VSS participants were recruited remotely to complete the questionnaires, and did not complete the ocular motor testing. All questionnaires were completed online in the participant's own time, with the exception of the NART, which was only administered to participants who completed ocular motor testing.

The majority of the questionnaires were included in an initial online test battery, which was emailed to the participant to complete prior to or immediately following ocular motor testing, or (for remote participants) following an initial brief screening. The CDS and ASRS were completed in separate online questionnaires.

- Online questionnaire battery 1: VSS questionnaire, migraine questionnaire, AUDIT (alcohol use), DUDIT (drug use), DASS (depression, anxiety, stress), PSQI (sleep quality), FSS (fatigue), and SF-36 (quality of life)
- Online questionnaire 2: CDS (depersonalization/derealization)
- Online questionnaire 3: ASRS (inattentive & hyperactive/impulsive symptoms)

The studies presented in this thesis used a cross-sectional design, where data was collected at one time point and compared between groups.

Chapter Three: Ocular motor measures of visual processing changes in visual snow syndrome

The following chapter was written up as a manuscript and published in the journal, *Neurology*, titled *Ocular motor measures of visual processing changes in visual snow syndrome.*

This paper was the first ever publication of its kind in VSS. Two basic and widely used ocular motor tasks, the prosaccade and antisaccade tasks, were chosen to commence characterising the ocular motor profile of VSS patients. The prosaccade task required a simple reorienting of gaze. In contrast, the antisaccade task challenged attentional control by requiring inhibition of a reflexive eye movement in favour of a volitional one. A third task which interleaved prosaccades and antisaccades was also included, to examine these saccade types in a more cognitively demanding context, where participants were required to remember and switch between task rules.

3.1 Abstract

Objective: To determine whether changes to cortical processing of visual information can be evaluated objectively using 3 simple ocular motor tasks to measure performance in patients with visual snow syndrome (VSS).

Methods: Sixty-four patients with VSS (32 with migraine and 32 with no migraine) and 23 controls participated. Three ocular motor tasks were included: prosaccade (PS), antisaccade (AS), and interleaved AS-PS tasks. All these tasks have been used extensively in both neurologically healthy and diseased states.

Results: We demonstrated that, compared to controls, the VSS group generated significantly shortened PS latencies ($p = 0.029$) and an increased rate of AS errors ($p = 0.001$), irrespective of the demands placed on visual processing (i.e., task context). Switch costs, a feature of the AS-PS task, were comparable across groups, and a significant correlation was found between shortened PS latencies and increased AS error rates for patients with VSS ($r = 0.404$).

Conclusion: We identified objective and quantifiable measures of visual processing changes in patients with VSS. The absence of any additional switch cost on the AS-PS task in VSS suggests that the PS latency and AS error differences are attributable to a speeded PS response rather than to impaired executive processes more commonly implicated in poorer AS performance. We propose that this combination of latency and error deficits, in conjunction with intact switching performance, will provide a VS behavioural signature that contributes to our understanding of VSS and may assist in determining the efficacy of therapeutic interventions.

3.2 Introduction

Visual snow (VS) is a persistent visual disturbance characterized by the continuous perception of flickering “static” across the entire visual field. The presence of at least 2 additional visual symptoms, from palinopsia, enhanced entoptic phenomena, photophobia, and nyctalopia, satisfies the diagnostic criteria for VS syndrome (VSS) (Schankin, Maniyar, Digre, et al., 2014), although a range of other visual and nonvisual symptoms (e.g., migraine, tinnitus) commonly co- occur. Currently, little is understood about the neuropathologic underpinnings of VSS; however, the diverse range of visual symptoms suggests that VSS represents disturbance to visual processing, theorized as involving excitability changes within the visual processing areas of cortex (Schankin, Maniyar, Sprenger, et al., 2014), and/or dysfunction within interconnected thalamocortical networks (Lauschke et al., 2016).

Visual processing may be examined by assessing the integrity of the ocular motor (OM) network, which features both afferent processing and an efferent motor response within the same system (R. John Leigh & Zee, 2015). Two classic OM tasks, the prosaccade (PS) and antisaccade (AS) tasks, place differential demands on visual processing, with a simpler PS requiring the generation of a saccade to a suddenly appearing stimulus, and the more difficult AS requiring the generation of a saccade to a stimuli’s mirror opposite location. By modulating task demands (i.e., interleaving PS and AS within the same task), a wider visual processing network is implicated, allowing the assessment of the interaction between visual cortex networks and wider cortico-thalamocortical networks known to underlie these tasks (McDowell et al., 2008). Consequently, the changes within these networks proposed to underlie VSS should manifest as measurable differences on these OM tasks that worsen commensurate with task demands.

3.3 Method

3.3.1 Participants

We recruited 64 patients diagnosed with VSS by a neurologist according to the International Classification of Headache Disorders (ICHD-3, Table 3.1) criteria, through a combination of online, radio, and television advertising.

Table 3.1

Visual snow syndrome diagnostic criteria

International Classification of Headache Disorders (ICHD-3) criteria for a diagnosis of visual snow
A. Visual snow: dynamic, continuous dots in the entire visual field, persisting for > 3 months
B. Additional visual of at least two of the following four types:
V. Palinopsia
VI. Enhanced entoptic phenomena
VII. Photophobia
VIII. Impaired night vision (nyctalopia)
C. Symptoms are not consistent with typical migraine visual aura
D. Symptoms are not better accounted for by another disorder

We recruited equal numbers of patients with VSS with and without a history of migraine. None reported experiencing a migraine or migraine aura symptoms at the time of testing, or within 3 days prior to or after testing. To ascertain whether any of our results might be attributable to or confounded by the presence of migraine, which commonly co-occurs with VSS, we conducted a series of one-way analyses of variance (ANOVAs) between patients with VSS with and without migraine. No significant differences were found between groups on any experimental measure. All patients with VSS were subsequently combined into a single VSS group (Table 3.2).

Table 3.2

Visual snow (VS) group means (SDs) for all ocular motor task variables

	VSS *Mean* (SD) *n*=32	VSS + Migraine *Mean* (SD) *n*=32
Prosaccade latencies (ms)		
PS block	200.07 (20.9)	202.72 (17.3)
Repeat PS	213.57 (28.5)	210.27 (25.9)
Switch PS	232.14 (38.1)	221.34 (28.9)
Prosaccade error rate (%)		
Repeat PS	1.41 (3.2)	1.09 (2.1)
Switch PS	5 (4.7)	3 (3.8)
Antisaccade latencies (ms)		
AS block	333.93 (43.8)	334.23 (43.5)
Repeat AS	326.18 (40.7)	317.99 (32.7)
Switch AS	314.49 (37.7)	312.23 (28.77)
AS block error latency	230.1 (47.13)	230.14 (41.96)
Antisaccade error rate (%)		
AS block	15.49 (15.7)	18.62 (13.6)
Repeat AS	15.08 (9.9)	13.04 (8.8)
Switch AS	19.38 (14.8)	12.88 (11.4)

Notes. PS: prosaccade; AS: antisaccade.

All patients with VSS underwent a full ophthalmic examination to rule out afferent visual processing deficits, which included an assessment of visual acuity, colour vision, and normal retinal anatomy and function. Patients were also excluded if they reported a confounding neurologic condition or were using medications likely to affect visual or cognitive function.

We recruited 23 neurologically healthy controls from the community. Exclusion criteria were a history of migraine, a known visual or neurologic condition, deuteranopia, and consumption of medications known to affect visual or cognitive function.

We screened all participants to exclude substance abuse disorders using the Alcohol Use Disorders Identification Test (Saunders et al., 1993) and the Drug Use Disorder Identification Test (Berman et al., 2005); scores on these measures did not differ significantly between controls and patients. Estimated intelligence was assessed using the National Adult Reading Test (NART) (Nelson & Willison, 1991), and levels of depression, anxiety, and stress using the Depression Anxiety Stress Scale (DASS) (Lovibond & Lovibond, 1995). Patients with VSS exhibited higher NART ($F_{1,77} = 5.85$, $p = 0.018$) and DASS scores than controls ($F_{1,71} = 12.06$, $p = 0.001$). Participant groups did not differ in mean age. A summary of demographic information for all participants, including a breakdown of the frequency of co-occurring visual symptoms associated with VSS, is provided in Table 3.3.

Table 3.3

Demographic information for all participants

	VSS *Mean* (SD) *n*=32	VSS + Migraine *Mean* (SD) *n*=32	Controls *Mean* (SD) *n*=23
Female / Male	12 / 20	21 / 11	14 / 9
Age / distribution	30.56 / 18-57	32.56 / 18-55	28.74 / 21-56
Visual snow			
Duration (years)	17.86 (14.8)	16.24 (14.3)	
Patients with lifelong duration (%)	50	43.3	
Afterimages (%)	73.3	93.3	
Photophobia (%)	46.7	55.2	
Nyctalopia (%)	70	55.2	
Floaters (%)	83.3	89.7	
Blue field entoptic phenomenon (%)	63.3	79.3	
Tinnitus (%)	70	65.5	
Paraesthesia (%)	33.3	27.6	
Family history of migraine (%)	29.6	60.7	
Relative with VS (%)	3.7	7.1	
DASS			
Depression	10.56 (10.2)	8.93 (8.6)	2.94 (3.5)
Anxiety	5.78 (4.6)	6.93 (7.7)	2.28 (2.2)
Overall	9.43 (6.8)	9.17 (7.2)	3.39 (3.4)
AUDIT	5.67 (4.9)	5.39 (5.9)	3.22 (2.1)
DUDIT	1.19 (2.9)	1 (3.6)	0.5 (1.9)
NART	113.72 (6.3)	113.28 (4.9)	116.59 (3.7)

Notes. DASS: Depression Anxiety Stress Scale; AUDIT: Alcohol Use Disorders Identification Test; DUDIT: Drug Use Disorder Identification Test; NART: National Adult Reading Test.

3.3.2 Standard protocol approvals, registrations, and patient consents

Ethics approval was granted by Monash University Human Research Ethics Committee. Participants provided written informed consent prior to participation in the study in accordance with the Declaration of Helsinki.

3.3.3 Data availability

Relevant data not published within the article can be made available by the corresponding author on reasonable request.

3.3.4 Equipment, stimuli, and procedures

All testing took place at the Central Clinical School in the Alfred Centre at Monash University. OM tasks were completed in a darkened room; participants were seated on a height-adjustable chair 950 mm from a monitor (resolution: 1,024 × 768). Horizontal displacement of the eyes was recorded using an Eyelink 1,000 dark pupil video-oculography system. This system has high resolution (noise limited at <0.01°) and an acquisition rate of 1,000 Hz. Participants completed 3 saccade tasks as part of a larger battery. Task stimuli were presented on a black background and comprised green, blue, and purple crosses (1.5° visual angle).

Block prosaccade task

The PS task comprised 48 PS trials in a single block presented in a random order. Participants were instructed to follow a green cross with their eyes as it moved from centre and back to 4 different locations, 5° or 10° to the right or left of centre. The central cross was presented for 1,000, 1,250, or 1,500 ms (timing randomized to reduce anticipatory responding), and the peripheral crosses for 1,500 ms.

Block antisaccade task

The AS task comprised 2 blocks of 24 AS trials presented in a random order. Participants were instructed to begin each trial by fixating on a central green cross; following a variable period (1,000, 1,250, or 1,600 ms), the central cross disappeared, corresponding with the appearance of a green cross 5° or 10° to the left or right of centre for 1,500 ms. Participants were instructed not to look at the peripheral cross but instead look towards its mirror opposite location.

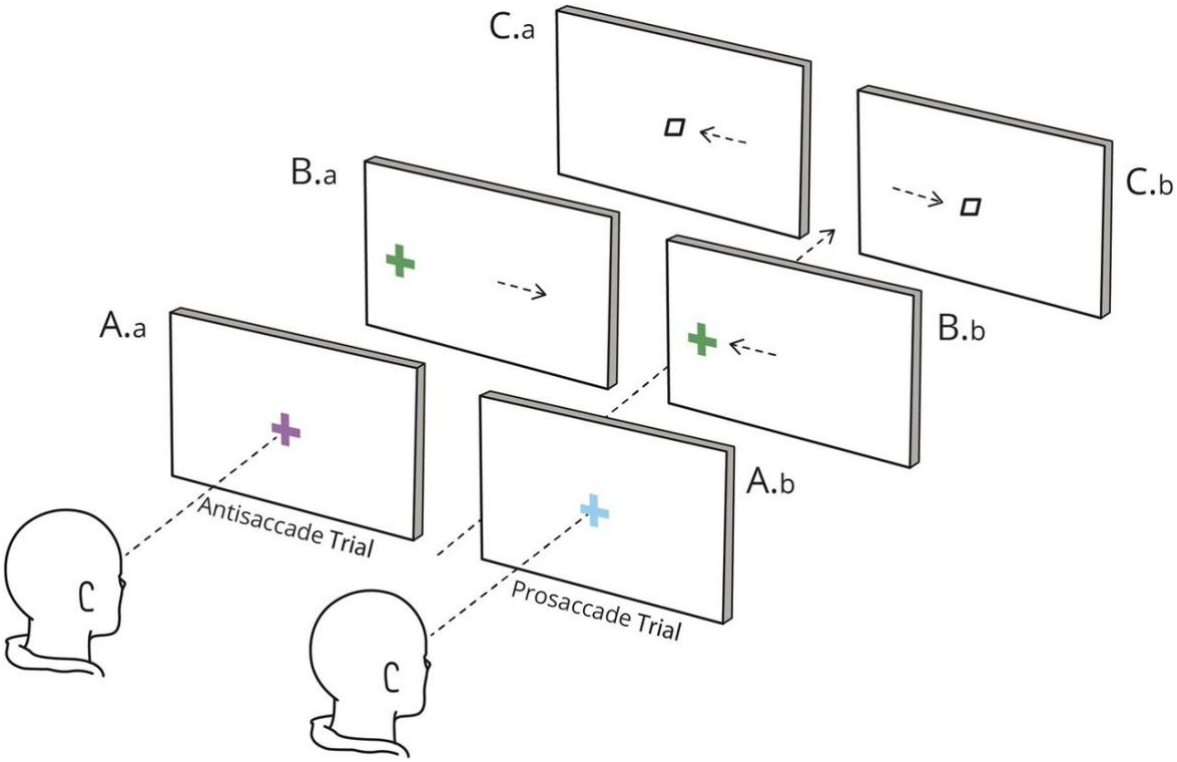
Interleaved AS-PS task

The interleaved AS-PS task comprised 3 blocks of 16 PS trials and 16 AS trials presented in a pseudo-random order. At the beginning of each trial, participants were instructed to fixate on a central green cross for 1,000, 1,250, or 1,500 ms. The colour of the central cross indicated whether the participant should per- form a PS or AS; a blue cross indicated that the participant should look towards the peripheral green cross (PS trial), while a purple cross indicated that the participant should look towards its mirror opposite location (AS trial). A green cross subsequently appeared in 1 of the 4 peripheral locations for 1,500 ms, followed by a white box presented at centre to indicate to return gaze to centre in preparation for the next trial (Figure 3.1).

Participants were familiarized with the interleaved paradigm using a guided example of each trial type and a practice block of 10 trials (5 PS and 5 AS). Trials were classified as either repeat trials (2 consecutive trials of the same type, e.g., PS → PS), or switch trials (a different response required on consecutive trials, e.g., PS → AS). The first trial of each block was excluded from analyses of switch/repeat trial type as they represented neither a switch nor repeat trial.

Figure 3.1

Ocular motor interleaved antisaccade-prosaccade task



Notes. This figure depicts the interleaved antisaccade-prosaccade task. (a) Participants fixate on the central cross, either (A1) a purple cross signifying an antisaccade trial, or (A2) a blue cross signifying a prosaccade trial. With the appearance of a peripheral green cross participants perform an eye movement either to the mirror opposition position of the green cross (C1, antisaccade) or towards the green cross (C2, prosaccade).

3.3.5 Data analysis

We analysed eye movement data offline using a custom MATLAB program. Saccade latency (ms) was calculated from a monocular eye trace as the temporal difference between target onset and saccade onset; saccadic onset was indicated by a visually evident departure from baseline corresponding to a change in the velocity profile of the saccade trace of 30° per second. We excluded trials from analysis of latency where an error was performed, fixation was not maintained within 2 degrees of the central target, a blink occurred during trial onset, or no response was made. For controls, 0.9% of block PS trials, 0.5% of block AS trials, and 8% of interleaved PS-AS trials were removed. For patients with VSS, 2.8%, 1.9%, and 12.6% were removed, respectively.

We defined an error as an eye movement exceeding 1.5° in the incorrect direction; that is, a PS performed during an AS trial or vice versa, and calculated errors as a proportion of total trials. No calculation of error occurred for the block PS task due to the simplicity and automaticity of this task. See Table 3.2 for VS group means and SDs for all OM task variables.

We conducted repeated-measures ANOVAs (group: controls, VSS × trial type: block, switch, repeat) separately for PS and AS latency. For error, a similar approach was taken for AS (group: controls, VSS × trial type: block, switch, repeat); however, for PS, since task-relevant errors do not occur in block trials, the analysis was only performed on interleaved trials (group: controls, VSS × trial type: switch, repeat). In addition, for the interleaved task only, switch cost was calculated for both latency and error and was defined as the relative difference be- tween a switch trial and a repeat trial (i.e., switch trial performance − repeat trial performance). A larger magnitude switch cost indicated increased difficulty with switching and poorer cognitive control. For this task design, previous studies have shown that only PS trials elicit a switch cost (unidirectional switch cost: switch PS − repeat PS), a

consequence of the task set inertia generated by the preceding antisaccade (DeSimone, Weiler, Aber, & Heath, 2014). As such, switch cost was only investigated for PS trials.

Where NART or DASS scores correlated with any experimental variable, we included these scores as a covariate to ensure that they did not confound interpretation of results. Experiment-wise p value corrections were performed according to the Benjamini-Hochberg method (Benjamini & Hochberg, 1995). All data analyses were conducted using IBM SPSS Statistics ("IBM SPSS Statistics for Windows, Version 27.0," 2019).

3.4 Results

Mean latencies and error rates for patients with VSS with and without migraine across all OM tasks can be found in Table 3.2.

Mean latencies and error rates for control and combined patients with VSS across all OM tasks can be found in Table 3.4.

Table 3.4

Means and standard deviations for ocular motor task variables

	Controls *Mean* (SD) *n*=23	VSS *Mean* (SD) *n*=64
Prosaccade latencies (ms)		
Repeat PS	225.05 (25.9)	209.3 (25.9)
Switch PS	243.85 (48.7)	223.4 (32.9)
Prosaccade error rate (%)		
Repeat PS	1.52 (3.5)	1.25 (2.7)
Switch PS	4.87 (4.8)	4 (4.3)
Antisaccade latencies (ms)		
AS block	314.9 (35.5)	335.9 (44.06)
Repeat AS	312.72 (48.9)	320.09 (38.1)
Switch AS	306.14 (47.9)	311.55 (34.5)
AS block error latency	246.06 (11.5)	230.12 (5.6)
Antisaccade error rate (%)		
Repeat AS	6.24 (7.04)	14.06 (9.35)
Switch AS	9.57 (9)	16.13 (13.5)

Notes. PS: prosaccade; AS: antisaccade.

3.4.1 Prosaccades

Latency

As expected, a significant main effect of trial type was found ($F1,70 = 14.23$, $p < 0.001$, $\eta p = 0.169$), with latency increasing commensurate to task difficulty. Block < repeat:

mean difference (MD) = −9.53, 95% CI [−15.99 to −3.07], and repeat < switch: MD = −16.93, 95% CI [−23.27 to −10.58]. This was consistent across groups, with no interaction between trial type and group found.

We found a significant main effect of group ($F_{1,70} = 4.94$, $p = 0.029$, $\eta p = 0.066$, 95% CI [−30.75 to −1.67]), with patients with VSS generating shorter PS latencies than controls. Figure 3.2 displays the latencies of block PS trials for controls and patients with VSS. This difference in latency is not due to a higher number of express saccades, as patients with VSS (median = 0) did not generate significantly more saccades at express latencies (i.e., 80–120 ms) than control participants (median = 0).

With regards to switch cost (interleaved task only), no significant difference in the magnitude was found between groups.

Error

As expected, we found a significant main effect of trial type ($F_{1,85} = 25.258$, $p < 0.000$, $\eta p = 0.229$), with both groups generating more errors on switch trials than repeat trials (MD = 2.7, 95% CI [−0.23 to 5.62]). There was no significant difference between groups in PS error rates, and no interaction between group and trial type.

3.4.2 Antisaccades

Latency

Although AS latencies were longer for patients with VSS, there were no significant effects of group or trial type, and no interaction between group and trial type. This is consistent with the increased variability found for AS.

Error

We did not find a main effect of trial type or interaction between group and trial type. Interestingly, a significant effect of group was found ($F_{1,85} = 11.434$, $p = 0.001$, $\eta p = 0.119$,

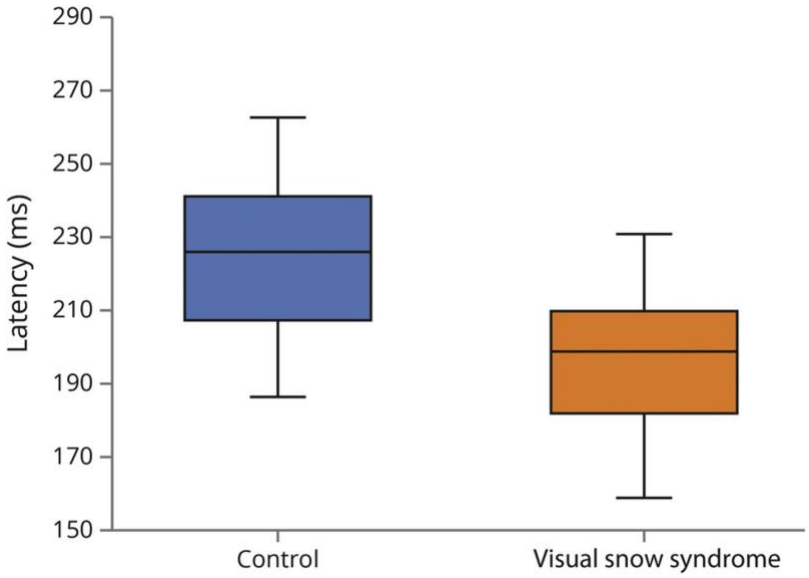
95% CI [4–16.23]), with patients with VSS performing more errors than controls across all conditions. The error rates of controls and VSS patients for AS block trials are presented in Figure 3.3.

AS errors reflect a failure to inhibit a PS, and the latencies of AS error trials are theorized to provide clues as to how or where the inhibitory failure is occurring (Coe & Munoz, 2017). We therefore performed further analyses to compare the latencies of AS error trials to the latencies of block PS trials.

Antisaccade error latencies were significantly longer than block PS latencies for both controls ($t[17] = -3.006$, $p = 0.008$, $d = 0.08$, 95% CI [−54.46 to −9.54]) and patients with VSS ($t[61] = -5.751$, $p < 0.001$, $d = 0.08$, 95% CI [−38.86 to −18.81]). Block AS error latencies correlated with block PS latencies for patients with VSS ($r = 0.404$, $p = 0.003$, $r2 = 16.3\%$) but not controls. Block AS error rates likewise correlated with PS latencies for only patients with VSS ($r = -0.320$, $p = 0.019$, $r2 = 10.2\%$).

Figure 3.2

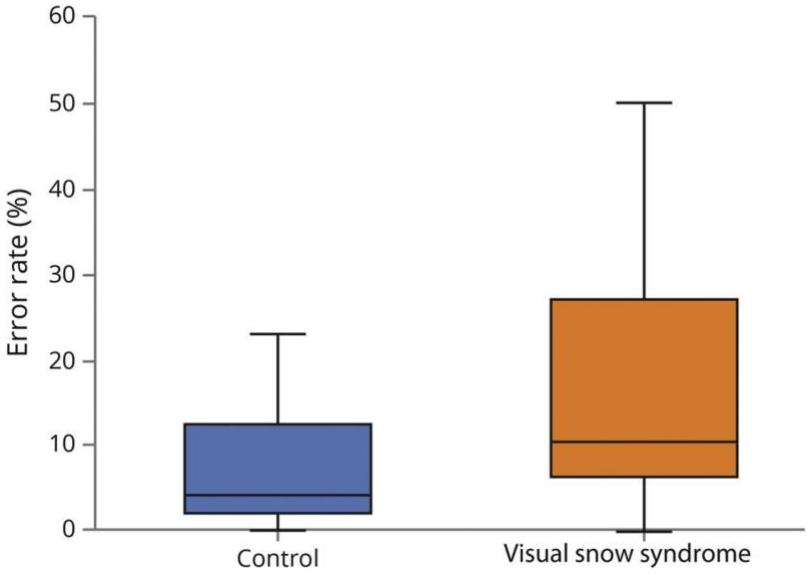
Control and VSS patient latencies on the block prosaccade task



Notes. Boxes represent the median, 25th, and 75th percentile with whiskers showing the range of data points. VSS: Visual snow syndrome.

Figure 3.3

Control and VSS patient error rates on the block antisaccade task



Notes. Boxes represent the median, 25th, and 75th percentile with whiskers showing the range of data points. VSS: Visual snow syndrome.

3.5 Discussion

VSS remains a challenge with respect to formal diagnosis and provision of effective treatment strategies. Currently, both rely solely on subjective patient reports of perceptual changes that cannot be explained by any another condition. We reveal objective and quantifiable behavioural changes in patients with VSS, manifesting in significantly shortened PS latencies and an increased rate of AS errors, irrespective of the demands placed on visual processing (i.e., task difficulty) and controlling for levels of anxiety and depression. Importantly, the shortened latencies of patients with VSS correlated significantly with increased AS error rates, suggesting that these changes might be attributable to a speeded PS response rather than to impaired executive processes more commonly implicated in poorer AS performance.

Individuals generally show longer latencies on AS than PS; AS are also subject to directional errors whereby a PS is generated instead of the required AS. This is thought to reflect the fact than an AS recruits additional (pre)frontal executive processes, a consequence of the added requirements of overriding the more automatic PS response elicited by the visual stimulus in favour of a volitional AS response (McDowell et al., 2008). Notably, increased AS errors and longer latencies are routinely observed in various psychiatric and neurologic conditions with known (pre)frontal executive control deficits (Massen, 2004), including schizophrenia, multiple sclerosis, and attention-deficit/hyperactivity disorder (Curtis, Calkins, Grove, Feil, & Iacono, 2001; J. Fielding et al., 2015; Mahone, Mostofsky, Lasker, Zee, & Denckla, 2009). While a number of models have been proposed to explain AS performance, all essentially assume an “independent race” between decision processes involved in generating a PS or an AS, with some models also proposing a third “stop” process (Cutsuridis, 2017). Unlike a PS, which may be elicited directly by a suddenly appearing stimulus, both AS and stop processes are considered (pre)frontally mediated. Irrespective of

the model, if an AS program reaches the necessary threshold for saccade generation, a PS response is cancelled, and a correct AS is released. However, if processes involved in the generation of a PS occur more quickly relative to the AS or stop responses, an error will occur (Cutsuridis, 2017). Accordingly, increased errors as seen in VSS necessarily reflect either an executively mediated failure, or an overly speeded PS response.

If we assume some form of (pre)frontally mediated stop process is involved in the increased AS VSS error rate, 2 processes may be responsible. Coe and Munoz (2017) propose 2 distinct AS suppression mechanisms: pre-emptive and online. The first occurs in the anticipatory period before the appearance of the peripheral target. If this pre-emptive suppression fails, AS errors are generated with express latencies (90–140 ms). Given that patients with VSS did not generate express latency errors, pre-emptive AS suppression appears intact. The second form of suppression occurs during the programming of a saccade, where a correct volitional response must override an incorrect PS response. A failure here hypothetically results in AS error latencies comparable to PS latencies (Coe & Munoz, 2017). As block AS error latencies were significantly longer than block PS latencies for both controls and patients, with a similar magnitude of difference, online AS suppression also appears intact in VSS, again suggesting that AS errors are not a consequence of dysfunctional (pre)frontal processes.

A pre(frontal) explanation for our AS findings is not supported by patient performance on the interleaved AS-PS task (Massen, 2004). Specifically, patients with VSS performed similarly to controls on this task, which is known to depend crucially on the integrity of (pre)frontal cortices. Both patients with VSS and controls exhibited a PS switch cost, with switch PS trial latencies significantly longer than repeat PS trial latencies, and a higher number of errors on switch PS trials.

The magnitude of the switch cost was similar across groups, indicating that patients with VSS were not differentially affected by the added difficulty of switching between trial types. In addition, AS latencies were not significantly different across groups. We therefore propose that changes we report in VSS appear to be attributable to an overly speeded PS response. This is supported by the shortened latencies of patients with VSS, which were inversely related to AS error rates, and is consistent with an "independent race" model of AS generation, which predicts that overly short PS latencies, relative to AS or stop latencies, would result in a greater number of errors.

Currently, the pathologic processes that might drive these changes in VSS remain unclear. At present, the most prominent theory is that of cortical hyperexcitability, presumably of visual processing areas (McKendrick et al., 2017; Schankin & Goadsby, 2015). The changes we re- port are not inconsistent with such a proposal, with the initial processing of a visual stimulus potentially accelerated in VSS. Previously, a few small scale studies in VSS have proposed cortical hyperexcitability/hyperactivity to explain the persistent potentiation of the visual evoked potentials response, a reduction in N75-P100 amplitudes (W. T. Chen et al., 2011; Luna, Lai, & Harris, 2018; Unal-Cevik & Yildiz, 2015; Yildiz et al., 2019), reduced centre-surround contrast suppression, elevated luminance increment thresholds in noise in a study of perceptual performance (McKendrick et al., 2017), and increased metabolism found within the lingual gyrus using 18F-FDG PET (Schankin, Maniyar, Sprenger, et al., 2014). Stochastic resonance, a sensory phenomenon theorized to play a role in VSS symptomology (Metzler & Robertson, 2018), has also been proposed, resulting in the accelerated detection of a visual stimulus; the addition of noise to a sensory system, up to an optimal level, is thought to enhance the detection of weak stimuli in both the same system and cross-modally (Lugo, Doti, & Faubert, 2008; Manjarrez et al., 2007).

Alternatively, and equally consistent with our data, VSS might represent disruption to thalamocortical processing. Not only does the thalamus regulate the flow of sensory information that is projected to cortex, but via recurrent projections, plays an important role in modulating and supporting ongoing cortical processing (Malekmohammadi et al., 2015; McAlonan, Cavanaugh, & Wurtz, 2008). These roles potentially influence the speed at which a visual image is processed and responded to. Interestingly, Lauschke et al. (2016) reported subjectively reduced symptoms of VS in individuals using yellow–blue colour filters, proposing that VS might represent an imbalance between konio- and parvo/magnocellular pathway processing, and subsequently thalamocortical dysrhythmia (TCD) of the visual pathway. TCD is a model that has been proposed to explain a number of neurologic disorders, including tinnitus and migraine (Vanneste et al., 2018), with Vanneste et al. (2018) showing that different disorders may be characterized by a spectrally equivalent but spatially distinct form of TCD. In our study, patients with and without concomitant migraine performed similarly, ruling out the presence of migraine as potential driver of the reported behavioural changes.

Although our data appear consistent with a speeded PS response, further research is required to provide more direct evidence for this hypothesis, and in particular for divining the source of this change. However, we have provided evidence that we can objectively measure differences in cortical processing in VSS, and have revealed a combination of latency and error differences that, in the absence of executive deficits, may provide a VSS behavioural signature that contributes to our understanding of VSS neuropathophysiology and may assist in determining the efficacy of future therapeutic interventions.

Chapter Four: Eye movement characteristics provide an objective measure of visual processing changes in patients with visual snow syndrome

The following chapter was written up as a manuscript and published in the journal, *Scientific Reports*, titled *Eye movement characteristics provide an objective measure of visual processing changes in patients with visual snow syndrome.* Formatting has been altered to ensure consistency with other chapters.

The preceding chapter (Chapter 3) described an ocular motor signature of VSS comprising shortened prosaccade latencies and increased inhibitory errors. These differences in ocular motor behaviour were thought to represent a consequence of stronger bottom-up attentional capture by visual stimuli, rather than a failure of top-down cognitive control mechanisms.

The following chapter aimed to further refine this signature by examining whether similar changes to ocular motor behaviour are evident in VSS when attention is directed endogenously. Two tasks were included, a Posner-inspired endogenously cued saccade task, and a saccadic Simon task. These tasks directly assess the effect of attentional orienting (Posner) and the effect of cue-target spatial congruency (Simon).

4.1 Abstract

Visual snow syndrome (VSS) is a poorly understood neurological disorder that features a range of disabling sensory changes. Visual processing changes revealed previously in VSS appear consistent with poor attentional control, specifically, with difficulty controlling environmentally driven shifts of attention. This study sought to confirm this proposal by determining whether these changes were similarly evident where attention is internally driven. Sixty seven VSS patients and 37 controls completed two saccade tasks: the endogenously cued saccade task and saccadic Simon task. The endogenously cued saccade task correctly (valid trial) or incorrectly (invalid trial) pre-cues a target location using a centrally presented arrow. VSS patients generated significantly shorter saccade latencies for valid trials ($p = 0.03$), resulting in a greater magnitude *cue effect* ($p = 0.02$), i.e. the difference in latency between valid and invalid trials. The saccadic Simon task presents a peripheral cue which may be spatially congruent or incongruent with the subsequent target location. Latencies on this task were comparable for VSS patients and controls, with a normal *Simon effect*, i.e. shorter latencies for saccades to targets spatially congruent with the preceding cue. On both tasks, VSS patients generated more erroneous saccades than controls towards non-target locations (Endogenously cued saccade task: $p = 0.02$, saccadic Simon task: $p = 0.04$). These results demonstrate that cued shifts of attention differentially affect saccade generation in VSS patients. We propose that these changes are not due to impairment of frontally-mediated inhibitory control, but to heightened saccade-related activity in visual regions. These results contribute to a VSS ocular motor signature that may provide clinical utility as well as an objective measure of dysfunction to facilitate future research.

4.2 Introduction

Visual snow syndrome (VSS) is a poorly understood neurological disorder characterized by a range of debilitating visual symptoms, including visual snow (VS), a persistent perceptual phenomenon that manifests as a veil of flickering dots across the entire visual field ("The International Classification of Headache Disorders, 3rd edition," 2013). Non-visual sensory symptoms commonly co-occur with VSS, including tinnitus, paraesthesia, and migraine (Lauschke et al., 2016; Schankin, Maniyar, Sprenger, et al., 2014). Initially assumed to be a persistent variant of migraine visual aura, VSS is now recognised as a distinct but overlapping disorder. In contrast to migraine aura, which is generally a short-lived visual disturbance preceding a migraine, VS is continuous, and phenotypically distinct from typical descriptions of migraine aura (Schankin, Maniyar, Digre, et al., 2014; Schankin, Maniyar, Sprenger, et al., 2014). Further, a significant number of VSS patients do not experience migraine (F. Puledda, C. Schankin, et al., 2020). Onset of VSS is typically in the second or third decade of life, often without a clear triggering event (Schankin & Goadsby, 2015), although approximately 40% of patients report having always experienced VSS (F. Puledda, C. Schankin, et al., 2020; Schankin & Goadsby, 2015). Standard ophthalmic and neurological examinations, including MRI, are typically normal (Schankin, Maniyar, Sprenger, et al., 2014).

At present, the pathophysiology of VSS remains unknown and there are no objective measures of the disorder, hampering the provision of effective treatments (van Dongen et al., 2019). However, the diverse range of associated visual and other sensory symptoms suggest a central disturbance in the processing of sensory information. Proposed mechanisms include cortical hyperexcitability (Bou Ghannam & Pelak, 2017; Schankin, Maniyar, Digre, et al., 2014), and/or dysfunction of thalamocortical networks associated with sensory processing (O. Eren et al., 2018; Yildiz et al., 2019). These theories are supported by a few small scale

behavioural (McKendrick et al., 2017; Solly et al., 2020), electrophysiological (O. Eren et al., 2018; Yildiz et al., 2019), and imaging studies (F. Puledda, D. Ffytche, et al., 2020; Schankin & Goadsby, 2015).

Given the significant functional and physiological overlap between visual processing and saccade networks in the brain, ocular motor tasks may be used to evaluate the integrity of networks underpinning visual processing impairments (R. J. Leigh & Kennard, 2004; McDowell et al., 2008; Solly et al., 2020). Indeed, our own preliminary work revealed an ocular motor changes in VSS that included significantly faster eye movements towards suddenly-appearing visual stimuli and difficulty inhibiting erroneous eye movements i.e. increased antisaccade errors (Solly et al., 2020). As no evidence of executive impairment was found when participants were required to switch randomly between a simple and more difficult saccadic task, we determined that increased error rate was likely attributable to the faster visually-guided response (Taylor & Hutton, 2008). However, we propose that these changes might also be viewed as a more rapid stimulus-driven (exogenous) shift of attention, with the altered excitability of visual cortical regions in VSS resulting in heightened reactivity to visual stimuli and a correspondingly faster saccade.

Importantly, attention is not only captured exogenously, but also directed endogenously, in line with internal goals and motivations. Here we investigated whether ocular motor changes are evident in VSS patients when attention is endogenously (internally) directed rather than exogenously captured. Two classic ocular motor tasks were implemented: the endogenously cued saccade task and the saccadic Simon task. The endogenously cued saccade task is based on the classic Posner paradigm (Posner, 1980), and examines the effect of manipulating attentional set by presenting a directional cue (i.e. arrow) prior to the appearance of a visual target. The saccadic Simon task examines the effect of presenting an informative cue (i.e. shape) that is either spatially congruent or incongruent with the target

location (Hommel, 2011); participants are required to endogenously shift attention towards, and interpret the cue, prior to making an eye movement.

This study aimed to determine whether increased cortical excitability in VSS impacts endogenous shifts of attention similarly to exogenous shifts of attention, resulting in an increased rate of erroneous saccades to non-target stimuli for both saccade tasks, and shorter latencies for visually guided saccades for the endogenously cued saccade task. We propose that the results herein will contribute to a VSS ocular motor signature that may be used to both further research the neuropathological underpinnings of the disorder, and assist with patient management, in particular, assessment of the efficacy of future treatments. This goal is particularly important given the current lack of objective measures of VSS.

4.3 Materials and methods

4.3.1 Participants

We recruited 67 patients who met the criteria for VSS as specified by the International Classification of Headache Disorders (ICHD-3: see Table 4.1) through a combination of online, radio, and television advertising.

Table 4.1

Visual snow syndrome diagnostic criteria

International Classification of Headache Disorders (ICHD-3) criteria for a diagnosis of visual snow
A. Visual snow: dynamic, continuous dots in the entire visual field, persisting for > 3 months
B. Additional visual symptoms of at least two of the following four types:
1. Palinopsia
2. Enhanced entoptic phenomena
3. Photophobia
4. Impaired night vision (nyctalopia)
C. Symptoms are not consistent with typical migraine visual aura
D. Symptoms are not better accounted for by another disorder

Ophthalmic examination revealed normal visual acuity, colour vision, and retinal anatomy. Thirty seven healthy control participants were recruited from the community. Exclusion criteria for all participants were having experienced a migraine or migraine aura within 3 days preceding or following testing, a confounding neurological or visual condition, or consumption of any medication likely to affect cognitive or visual function.

Participant (control and VSS) numbers differed across tasks due to personal and technical issues. Although VSS patients reported higher depression, anxiety, and stress scores overall on the Depression Anxiety Stress Scale (DASS), $F(1, 80)=-5.91$, $p<.001$), VSS and control groups did not differ in age, measures of substance use/abuse (Drug Use Disorder

Identification Test- DUDIT (Berman et al., 2005), Alcohol Use Disorders Identification Test-AUDIT (Saunders et al., 1993)), or estimated premorbid intelligence (National Adult Reading Test: NART (Nelson & Willison, 1991)). DASS, DUDIT, AUDIT, and NART scores did not correlate with any saccadic variables. Demographic information for all participants is displayed in Table 4.2.

Table 4.2

Demographic information for all participants.

	VSS *Mean* (SD) *n=32*	VSS + Migraine *Mean* (SD) *n*= 35	Controls *Mean* (SD) *n*= 37
Female / Male	12/20	24/11	24/12
Age / distribution	29.38 / 18-54	31.78 / 20-55	27.56 / 18-56
Visual snow			
Duration (years)	14.81 (13.3)	13.42 (11.72)	
Patients with lifelong duration (%)	39.3	34.4	
Afterimages (%)	67.9	93.1	
Photophobia (%)	46.4	62.1	
Nyctalopia (%)	75	58.6	
Floaters (%)	82.1	86.2	
Blue field entoptic phenomenon (%)	67.9	79.3	
Tinnitus (%)	67.9	67.9	
Paraesthesia (%)	25	42.9	
Famiy history of migraine (%)	30.4	59.3	
Relative with VS (%)	4.3	7.4	
DASS			
Depression	12.42 (9.84)	8.41 (8.62)	2.62 (3.72)
Anxiety	6.33 (4.87)	7.07 (7.5)	1.86 (2.2)
Total	10.53 (6.69)	8.57 (6.8)	2.92 (3.24)
AUDIT	3.17 (4.36)	2.45 (1.59)	2.62 (1.57)
DUDIT	1.21 (2.93)	1.24 (3.63)	.52 (1.72)
NART	113.88 (5.95)	114.17 (4.87)	116.15 (5.65)

Notes. VSS: Visual snow syndrome; DASS: Depression Anxiety Stress Scale; AUDIT: Alcohol Use Disorders Identification Test; DUDIT: Drug Use Disorder Identification Test; NART: National Adult Reading Test.

4.3.2 Standard protocol approvals, registrations, and patient consents

Ethics approval was granted by the Monash University Human Research Ethics Committee, and all participants provided written informed consent prior to participation in the study. All methods were performed in accordance with the declaration of Helsinki.

4.3.3 Equipment, stimuli, and procedures

The following ocular motor tasks were conducted at the Alfred Centre, Monash University, Melbourne, over a one hour session. For each task, the latency and accuracy of saccades was measured using an Eyelink 1000 plus dark pupil video-oculography system. This system has a high resolution (noise limited at <0.01°), an acquisition rate of 1,000 Hz, and a refresh rate of 60Hz. Participants were seated in a darkened room, on a height-adjustable chair, with a forehead and chin rest used to stabilise the head during recordings. This situated the participant's eye 950mm from a monitor (resolution:1920 x 1080). Task stimuli were displayed on a black background, and calibration was performed using a five-point grid as per the built-in Eyelink process.

Endogenously cued saccade task

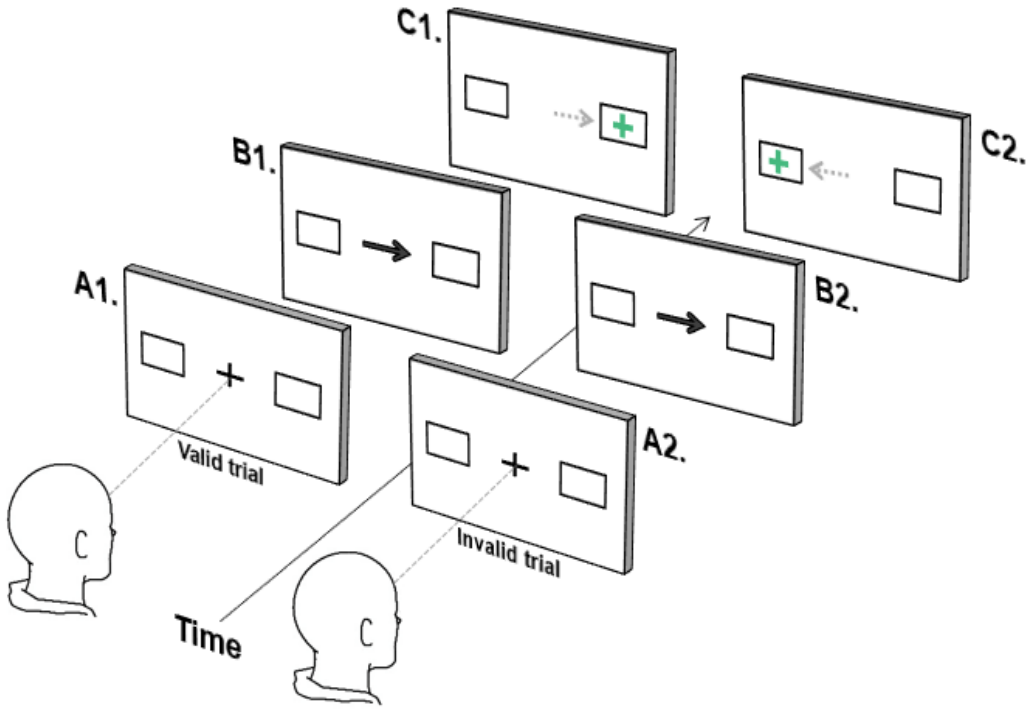
This task derives from Posner's attentional orienting task and explores the impact, on latency, of endogenously redirecting attention prior to target presentation (Posner, 1980). Participants were instructed to fixate a central green cross (1.5°) flanked by 2 white boxes presented 10 degrees right and left of centre. Following 400 ms, the central cross was replaced by an arrow (1.5°) for 500 ms, pointing to either the left or right box. Participants were instructed to 'ignore' the central arrow and maintain fixation at centre until a green cross appeared in the box either indicated by the arrow (valid trial) or in the opposite direction (invalid trial). As soon as the green cross appeared, participants were required to look directly

towards it. Participants were familiarised with the task by way of a guided example (see Figure 4.1).

The task comprised 120 trials (2 blocks of 60 trials), 75% valid trials and 25% invalid trials presented in a random order. The preponderance of valid trials typically creates the expectation that the central arrow correctly predicts the location of the upcoming green cross (Posner, 1980). A 'cue effect' is subsequently observed, where latencies for valid trials are significantly shorter than latencies for invalid trials.

Figure 4.1

Endogenously cued saccade task



Notes. (A) Participants fixate on the central cross, which is replaced by an arrow indicating the left or right box (B). The participant must remain fixated on the centre until a cross appears either in the box indicated by the arrow (C1, valid trial), or in the opposite box (C2, invalid trial) at which point they look towards the cross

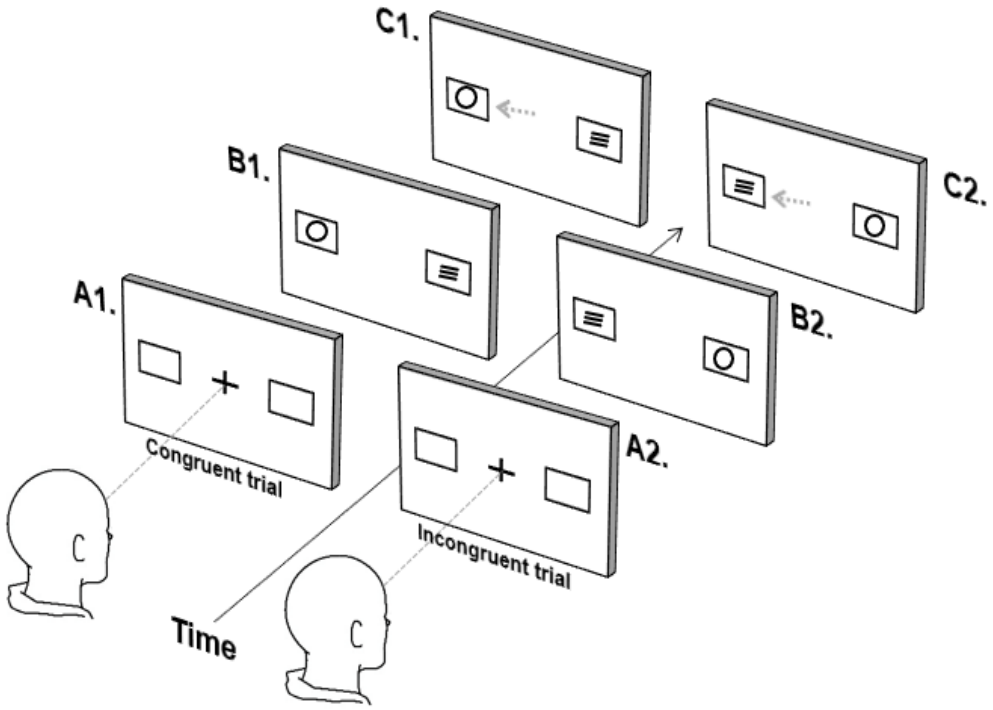
Saccadic Simon task

Participants were instructed to fixate a central white cross flanked by 2 white boxes presented 10 degrees to the right/left of centre. Following 1000 ms, either a 'circle' or a 'square' was presented in one of the peripheral boxes and a filler stimulus (three stacked horizontal lines) presented in the opposite box. The appearance of a circle in either box indicated that the participant should look immediately towards the box on the left hand side, while the appearance of a square in either box indicated that the participant should look immediately towards the box on the right hand side. Shape and filler stimuli were presented for 3000 ms. Trials were either congruent, if the target location and trial stimulus (circle/square) were in the same location, or incongruent, if the target location and trial stimulus were in opposite locations (see Figure 4.2).

Typically, the latency of an incongruent trial is longer than a congruent trial; this is known as the 'Simon effect', although is seen only on those trials following a correctly executed congruent trial (Ridderinkhof, 2002). For analyses, trials were classified according to the congruency of both the previous and current trial. The task comprised 128 trials (4 blocks of 32 trials), with an equal number of each trial type presented in a pseudo-random order. Participants were familiarised with the task with by way of a guided example and a practice block consisting of 10 trials (5 congruent, 5 incongruent).

Figure 4.2

Saccadic Simon task



Notes. Only circle trials depicted. (A) Participants fixates on the central cross, and (B) a shape (circle/square) appears concomitant with the appearance of a 'filler symbol' (three horizontal lines) in the opposite box. The participant determines the direction of the eye movement based on the shape (circle = leftward movement, square = rightwards movement) and (C) performs an eye movement to the corresponding box. (B1/C1) depict a congruent trial, and (B2/C2) depict an incongruent trial.

4.3.4 Data analysis

Analyses of eye movement data were performed offline using a custom Matlab program. Saccade latency (ms) was calculated as the temporal difference between stimulus onset (endogenously cued saccade task: green cross, saccadic Simon task: circle/square) and saccade onset. Saccade onset was indicated by a visually evident departure from baseline corresponding to a change in the velocity profile of the saccade trace of 30° per second. Trials were excluded from latency analysis where an error was performed (see below), fixation was not maintained within 2° of centre, a blink occurred following trial onset, or no response was made.

For the endogenously cued saccade task, latencies were calculated separately for valid and invalid trials. A cue effect was calculated (invalid minus valid trial latencies), and an error rate as the proportion of errors to the total number of trials; an error describes an incorrect saccade exceeding 1.5 degrees in the direction indicated by the central arrow, either prior to or within 100ms following target presentation.

For the saccadic Simon task, latencies were calculated separately for all trial types. Given that congruency effects are contingent upon performance in the previous trial (Ridderinkhof, 2002), trials that directly followed an error were not included in latency analysis. An error was defined as a saccade exceeding 1.5° in the incorrect direction following appearance of the trial stimulus, e.g. a rightward saccade following the appearance of a circle: error rate was calculated as the proportion of errors to the total number of trials. The Simon effect was calculated as incongruent trial latency minus congruent trial latency, for those trials following a correctly executed congruent trial.

Statistical analyses

Data analyses were conducted using IBM SPSS Statistics 26 ("IBM SPSS Statistics for Windows, Version 25.0," 2017). An alpha-level of $p < .05$ was set for all analyses, and

where data was missing, pairwise deletion was used. Repeated measures ANOVA were conducted for both tasks: endogenously cued saccade latency: group (controls, VSS) x trial type (valid, invalid); saccadic Simon task latency and error rate: group (controls, VSS) x previous trial type (congruent, incongruent) x current trial type (congruent, incongruent). Post hoc analyses used either t-tests or one-way ANOVAs. Since errors on the endogenously cued task occurred prior to target presentation (thus prior to the determination of trial type), error rate was compared between groups using a one-way ANOVA. A ROC curve analysis was performed for variables where VSS patients differed significantly from controls: valid latencies on the endogenously cued saccade task, and total error rates for both tasks. Benjamini–Hochberg corrections were made for all multiple comparisons (Benjamini & Hochberg, 1995).

4.4 Results

Although we acknowledge that there may be subtle visual symptoms associated with migraine itself (independent of headache), we revealed no significant differences between VSS patients with migraine (n = 35) and those without migraine (n = 32) on any experimental variable (see Table 4.3). As such all patients were combined into a single VSS group. This is consistent with our previous study (Solly et al., 2020). Mean latencies and error rates for controls and the combined VSS patient group can be found in Table 4.4.

Table 4.3

VSS group means and standard deviations for ocular motor task variables

	VSS no migraine *Mean* (SD) *n*=32	VSS + Migraine *Mean* (SD) *n*=35	*p*
Endogenously cued saccade latencies (ms)			
Valid trials	234.48 (33.21)	235.33 (24.56)	.909
Invalid trials	247.09 (49.42)	248.58 (28.01)	.884
Endogenously cued saccade errors (%)	6.61 (7.68)	6.9 (6.63)	.874
Saccadic Simon task latency (ms)	492.63 (13.12)	517.68 (57.25)	.128
Saccadic Simon task total errors (%)	15.97 (9.21)	12.43 (6.71)	.064

Notes. VSS: Visual snow syndrome

Table 4.4

Means and standard deviations for ocular motor task variables

	Control *Mean* (SD)	VSS *Mean* (SD)	*p*
Endogenously cued saccade latencies (ms)	*n=36*	*n=60*	
Valid trials	248.86 (31.65)	234.94 (28.67)	**.029**
Invalid trials	253.16 (36.18)	247.89 (39.12)	.513
Cue effect	4.3 (12.7)	12.95 (23.16)	**.02**
Endogenously cued saccade errors (%)	3.66 (4.57)	6.76 (7.08)	**.01**
Saccadic Simon task latencies (ms)	*n=28*	*n=66*	
Congruent-congruent trials	490.64 (89.76)	495.1 (69.84)	.796
Congruent-incongruent trials	502.16 (85.82)	518.88 (73.88)	.342
Incongruent-congruent trials	497.71 (89.29)	499.98 (72.56)	.897
Incongruent-incongruent trials	492.24 (77.64)	508.18 (72.8)	.343
Simon effect (ms)	11.51 (32.37)	23.78 (46.46)	.207
Saccadic Simon task errors (%)			
Congruent-congruent trials	7.9 (6.14)	13.22 (8.73)	**.004**
Congruent-incongruent trials	15.27 (11.7)	18.65 (12.04)	.212
Incongruent-congruent trials	10.97 (6.94)	14.88 (9.51)	.053
Incongruent-incongruent trials	9.34 (11.01)	12.25 (10.8)	.239

Notes. VSS: Visual snow syndrome. Underline: indicates the trial of interest.

4.4.1 Endogenously cued saccade task

Latency

A significant main effect of trial type was found, (F(1,94)=16.88, p<.001, ηp=0.152, CI [235.66, 238.14]) with latencies for valid trials significantly shorter than latencies for invalid trials (mean difference = 9.7065). A significant trial type x group interaction was found, (F(1,94)=4.25, p=.042, ηp=.043), with post hoc analyses revealing that while both groups demonstrated the same relationship between valid and invalid trials (invalid > valid: controls: (t(35)=-2.03, p=.05, d=.13, 95% CI [-8.6, .0]); VSS: (t(59)=-4.33, p<.00, d=.38, 95% CI [-18.93, -6.97])), valid trial latencies were significantly shorter for VSS patients than controls (F(1,94)=4.91, p=.029, d=.46, 95% CI [233.99, 246.32]). This was reflected in the significantly larger cue effect found for VSS patients compared to controls, t(93.41)=-2.36, p=.02, d=.43, CI [-15.93, -1.38], see Table 4.4. In contrast, invalid trial latencies were not significantly different between groups. Mean latencies of controls and patients for valid and invalid trials can be viewed in Figure 4.3.

For valid trial latencies, ROC curve analysis indicated that the area under the curve was 0.63 (SE=.06, p=.036, CI [.516, .741]).

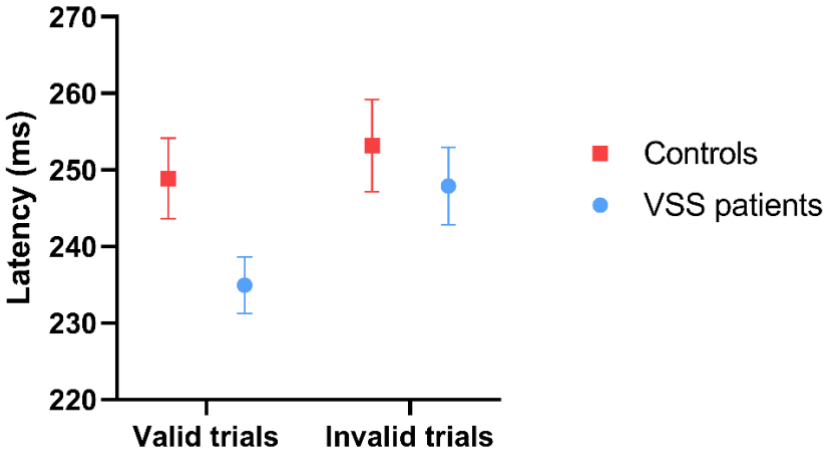
Error Rate

VSS patients generated a significantly higher rate of errors than controls (F(1,94)=5.54, p=.021, d=.52, 95% CI [4.3, 6.9]), see Table 4.4. Mean error rates for controls and patients are displayed in Figure 4.4.

ROC curve analysis indicated that the area under the curve for errors was 0.66 (SE=.07, p=.02, CI [.53, .79]).

Figure 4.3

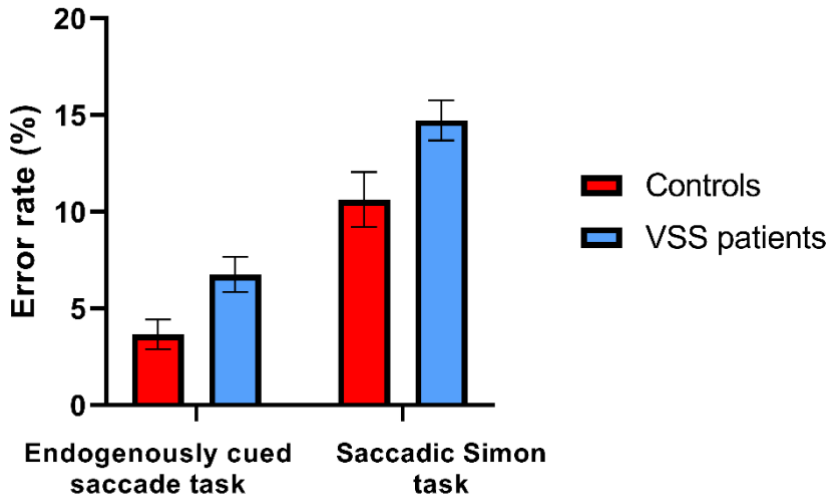
Control and VSS patient latencies on the endogenously cued saccade task



Notes. Mean latencies of controls and VSS patients are shown for valid and invalid trials on the endogenously cued saccade task. Error bars represent standard errors. VSS: Visual snow syndrome.

Figure 4.4

Control and VSS error rates on the endogenously cued saccade task and saccadic Simon task



Notes. Mean error rates of controls and VSS patients are shown for the endogenously cued saccade task and saccadic Simon task. Error bars represent standard errors. VSS: Visual snow syndrome.

4.4.2 Saccadic Simon task

Latency

A significant main effect of current trial was found, with latencies for congruent trials significantly shorter than latencies for incongruent trials ($F(1,92)=5.55$, $p=.021$, $\eta p=0.57$, 95% CI [479.29, 512.43]). On average, incongruent trial latencies were 12.13ms slower than congruent trials. This effect was consistent across groups, with no group x current trial interaction.

A significant previous trial x current trial interaction was found ($F(1,92)=5.17$, $p=.025$, $\eta p=0.53$, CI [466.41, 521.94]); this is in line with the expectation that only trials preceded by a congruent trial should show latency modulation. Specifically, the Simon effect, or longer latencies for incongruent versus congruent trials, was only seen for trials following a congruent trial. This was consistent across groups with no group x previous trial x current trial interaction found. No other interaction or main effect of group was found.

Error rate

A significant main effect of current trial was found, with more errors occurring on incongruent than congruent trials *(*$F(1,92)=5.43$, $p=.022$, $\eta p=0.56$, CI [11.53, 16.24]); this was found to be consistent across groups with no current trial x group interaction found. A significant main effect of previous trial was also found ($F(1,92)=9.89$, $p=.002$, $\eta p=0.97$, CI [10, 13.72]), with less errors occurring on trials following an incongruent trial than a congruent trial; again, this was found to be consistent across groups with no previous trial x group interaction found.

A significant previous trial x current trial interaction was present ($F(1,92)=34.58$, $p<.001$, $\eta p=0.273$, CI [8.75, 12.37], with more errors occurring when the current trial type was different to the previous trial type (i.e. a congruent trial following an incongruent, or an

incongruent trial following a congruent trial). This pattern was consistent across groups with no previous trial x current trial x group interaction found.

A significant main effect of group was found, with VSS patients exhibiting a higher error rate, irrespective of current or previous trial type, compared to controls, ($F(1,92)=4.43$, $p=.038$, $\eta p=0.046$, 95% CI [12.75, 16.75]).

ROC curve analysis indicated that the area under the curve for errors was 0.66 (SE=.07, $p=.019$, CI [.529, .788]).

4.5 Discussion

VSS is a complex disorder of sensory processing, manifesting in a range of visual and non-visual symptoms. Here we sought to determine whether the more rapid stimulus-driven shift of attention we identified previously is evident when attention is internally or endogenously redirected. For the endogenously cued saccade task we revealed a normal *cue effect* in VSS (i.e. shorter latencies for validly cued saccades). However, the magnitude of this effect was significantly larger for VSS patients, a consequence of shorter validly cued saccade latencies. VSS patients also generated significantly more erroneous saccades corresponding with the cue rather than the target. For the saccadic Simon task we revealed a normal *Simon effect* for both groups (i.e. the latency of an incongruent trial was longer than a congruent trial for those trials following a correctly executed congruent trial). Again, VSS patients generated significantly more erroneous saccades, although these errors bore no relationship to the cue stimulus.

These results demonstrate that endogenously driven shifts of attention more strongly influence saccade-related activity in VSS patients compared to controls, leading to greater difficulty controlling a relatively rapid shift of attention. A significant body of research has shown that saccades and attention share an obligatory relationship, both functionally and neuroanatomically (Hutton, 2008a). Directing attention towards a specific spatial location alters the activity of populations of neurons that process stimuli at that location, as well as neurons that generate a saccade towards that location, influencing the direction and timing of a saccade (Wollenberg, Deubel, & Szinte, 2018). This occurs whether attention is captured by a suddenly appearing visual event (exogenously driven) or redirected internally (endogenously driven).

For the endogenously cued saccade task, the preponderance of a centrally presented arrow that correctly predicts the location of an upcoming target, results in a pre-emptive shift

of attention towards the probable location of an upcoming target. Consequently, visual processing is prioritised at the cued location and saccade-related activity enhanced, resulting in relatively shorter latencies (Posner, 2016). Conversely, latencies for invalidly cued saccades are relatively prolonged due to the added requirements of reorienting attention away from the cued location and generating a saccade in the opposite direction (Carrasco, 2011; Posner, 1980). Correct performance of this task also requires the suppression or inhibition of saccade-related activity evoked by a shift of attention until a visual target appears (Posner, 1980).

Shorter latency saccades to validly cued targets suggest that for VSS patients, the balance between saccade-related and inhibition-related activity is shifted compared to controls such that, saccade-related activity sits relatively closer to threshold for release once a corresponding target appears. While an increased proportion of errors suggests that this saccade-related activity breaches threshold for the release more readily (Posner, 1980), it is not possible from this data to determine whether this imbalance is due to reduced inhibitory or increased saccade-related activity. However, we have previously shown that a speeded response is unlikely to be due to executive failure (Solly et al., 2020), and therefore presume that this reflects a stronger response to the cue, corresponding with greater saccade-related activity at the cued location.

For VSS patients, when saccade-related activity provoked by the cue is successfully inhibited and an error prevented, a corresponding saccade to a target is generated more quickly - significantly so for validly cued trials. Although not significantly different to controls, invalidly cued saccade latencies were also shorter, potentially reflecting the added difficulty in redirecting saccade-related activity away from the cued location. Notably, the differences seen between VSS and control latencies for cued saccades, were considerably smaller than previously reported for un-cued saccades (Solly et al., 2020), suggesting a delay

caused by greater difficulty balancing saccade-related and inhibition-related activity, a consequence of the cue. This may reflect additional inhibition-related activity required to maintain this balance in VSS.

The results of our saccadic Simon task appear consistent with this notion. This task requires interpretation of an abstract symbol presented in one of two locations. Here a participant must maintain fixation at centre, and orient attention to both peripheral stimuli to determine, (1) whether the *task* stimulus is a circle or square, and (2) based on this information, decide whether to look left or right. Consequently, and as for the endogenously cued task, a shift of attention results in increased saccade-related activity for neurons encoding the location of that shift, irrespective of direction, and the need to inhibit any response until a decision is made regarding the correct saccade location. VSS patients generated more errors, which like the endogenously cued saccade task, may be perceived as a premature breach of threshold for release of a saccade following the re-orienting of attention. Unlike the endogenously cued saccade task, these errors were not related directly to the cue stimulus, but likely the indiscriminate exploration of task stimuli; again, this suggests that saccade-related activity more readily breaches threshold for release in VSS. Given that a normal Simon effect was found for VSS patients, it is possible that these errors are *not* due to poor frontally-mediated inhibitory control as seen with other patient populations, such as Parkinson's disease (Joanne Fielding, Georgiou-Karistianis, Bradshaw, Millist, & White, 2005) and schizophrenia (Gastaldo, Umiltà, Bianchin, & Prior, 2002), who exhibit significant differences between congruent and incongruent trial latencies. Instead we attribute these errors to increased saccade-related activity, a consequence of a shift of attention (Ridderinkhof, 2002). However, we do acknowledge that the increased number of errors for VSS patients may have reduced our capacity to determine any differential effect of trial type (i.e. a difference in the size of the Simon effect) and temper this proposal accordingly.

VSS latencies on the Simon task were not differentially impacted by cue presentation. This is similar to results from our previous study where antisaccade latencies (Solly et al., 2020), which also require a volitional response following an informative cue, were comparable to controls. Again, although VSS saccade latencies were not significantly different to control latencies, they were relatively prolonged compared to controls. This too may reflect a subtle delay caused by the requirement of maintaining saccade-related activity at sub-threshold levels.

Overall, these results confirm our proposal that attentional changes underpin the visual processing changes we revealed previously, demonstrating that the differences identified in tasks that exogenously direct attention, are similarly found in those that endogenously direct attention. Specifically, both exogenous and endogenous shifts of attention appear to more strongly increase saccade-related activity in VSS, resulting in increased errors and altered saccade latencies. As attention networks are complex and widespread in the cortex, the precise nature and location of dysfunction in VSS cannot be determined from these saccadic tasks alone. However, inferences may be made, and the combination of latency and error differences are consistent with earlier, lower level changes in visual processing, and not later executive processing of visual stimuli.

This heightened activation by either a visual stimulus or endogenous shift of attention may reflect increased excitability directly within visual processing regions, as theorised to occur in VSS (McKendrick et al., 2017; Schankin, Maniyar, et al., 2020; Schankin, Maniyar, Digre, et al., 2014; Yildiz et al., 2019). Lauschke et al. (2016) proposed that cortical hyperexcitability may be associated with disruption to thalamocortical communication. Although simplistic, the thalamus acts as a gatekeeper for the flow of sensory information to cortex, and influences the ongoing cortical processing of sensory information through recurrent feedback loops (Malekmohammadi et al., 2015; McAlonan et al., 2008). We have

previously shown that perceptual surround suppression is altered in those with VSS (McKendrick et al., 2017). While the mechanisms involved in neuronal surround suppression in the primary visual cortex involve both feedforward, horizontal, and feedback connections, the thalamocortical feedforward connections can strongly influence suppression strength (Angelucci et al., 2017). Hence, if thalamocortical communication is altered in VSS, alterations to perceptual surround suppression would be a predicted outcome.. In further support of this theory, tinnitus and migraine, which frequently occur alongside VSS, have also been associated with abnormal thalamocortical communication (Vanneste et al., 2018).

These factors alongside our own findings lead us to hypothesise that a disruption to thalamocortical networks, alongside heightened excitability of associated cortical regions, may underlie the emergence of VSS by impacting the filtering and processing of sensory information. The ocular motor signature of VSS identified by this and our earlier studies may not only provide a quantifiable measure of dysfunction in VSS that can be used to monitor the efficacy of any future treatments, but may also be used to inform future investigation of the mechanisms disrupted in VSS, guided by our hypothesis of disruption to thalamocortical networks.

Chapter Five: The Psychiatric Symptomology of Visual Snow Syndrome

The following chapter was written up as a manuscript and published in the journal, *Frontiers in Neurology*, titled *The Psychiatric Symptomology of Visual Snow Syndrome.* Formatting has been altered to ensure consistency with other chapters.

All participants who completed the ocular motor studies were asked to also complete a battery of online questionnaires regarding their visual and psychiatric symptoms. Additional participants were recruited remotely. The psychiatric symptom questionnaires included in the battery were chosen to capture commonly reported symptoms of VSS, either in the existing literature (anxiety, depression, fatigue), or anecdotally, by patients in the practice of Prof. Owen White (sleep difficulties, depersonalization and derealization).

Although these symptoms had been linked to VSS in the existing literature their prevalence had typically been described in terms of historic diagnoses rather than current symptom levels, and their potential association with sensory dysfunction had not been explored. Additionally, although many VSS patients reported high levels of distress and impairment, there was no published exploration of health-related quality of life in VSS. The following chapter therefore aimed to characterise current psychiatric symptom levels, quality of life, and the association of psychiatric symptoms with quality of life and sensory dysfunction in VSS participants.

5.1 Abstract

Objective: To characterise the psychiatric symptoms of visual snow syndrome (VSS), and determine their relationship to quality of life and severity of visual symptoms.

Methods: One hundred twenty-five patients with VSS completed a battery of questionnaires assessing depression/anxiety, dissociative experiences (depersonalisation), sleep quality, fatigue, and quality of life, as well as a structured clinical interview about their visual and sensory symptoms.

Results: VSS patients showed high rates of anxiety and depression, depersonalisation, fatigue, and poor sleep, which significantly impacted quality of life. Further, psychiatric symptoms, particularly depersonalisation, were related to increased severity of visual symptoms. The severity/frequency of psychiatric symptoms did not differ significantly due to the presence of migraine, patient sex, or timing of VSS onset (lifelong vs. later onset).

Conclusion: Psychiatric symptoms are highly prevalent in patients with VSS and are associated with increased visual symptom severity and reduced quality of life. Importantly, patients with lifelong VSS reported lower levels of distress and milder self-ratings of visual symptoms compared to patients with a later onset, while being equally likely to experience psychiatric symptoms. This suggests that the psychiatric symptoms of VSS are not solely due to distress caused by visual symptoms. While no consistently effective treatments are available for the visual symptomology of VSS, psychiatric symptoms offer an avenue of treatment that is likely to significantly improve patient quality of life and ability to cope with visual symptoms.

5.2 Introduction

Visual snow syndrome (VSS) is a neurological disorder characterised by a range of persistent visual disturbances. Its defining symptom is visual snow (VS), described as constant, flickering static across the entire visual field. Diagnosis of VSS requires the presence of VS for >3 months, alongside at least two of the following visual symptoms: palinopsia, enhanced entoptic phenomena, photophobia, and impaired night vision (nyctalopia) ("The International Classification of Headache Disorders, 3rd edition," 2013). For approximately 40% of patients, the visual disturbances associated with VSS have been present from their earliest memories; the remainder of patients experience a sudden or stepwise onset of symptoms, typically in the second or third decade of life. Symptom onset may be related to a migraine attack, but typically cannot be linked to a clear trigger (F. Puledda, C. Schankin, et al., 2020; Schankin, Maniyar, Digre, et al., 2014).

VSS often presents with a number of comorbidities, most commonly migraine and tinnitus (F. Puledda, C. Schankin, et al., 2020; Schankin, Maniyar, Sprenger, et al., 2014), but also other sensory symptoms, including paraesthesia and dizziness (Lauschke et al., 2016; Solly et al., 2020). Notably, a range of psychiatric symptoms are consistently reported in VSS patients; these include depression and anxiety, (Lauschke et al., 2016; F. Puledda, C. Schankin, et al., 2020; Schankin, Maniyar, Digre, et al., 2014), as well as fatigue, sleep disturbances (Metzler & Robertson, 2018; Yildiz et al., 2019), and depersonalization, a dissociative experience involving a sense of estrangement from the body (Michal et al., 2016). Irritability and difficulty concentrating are also frequent complaints (Schankin, Maniyar, Digre, et al., 2014). It is currently unclear how these psychiatric symptoms relate to each other or to the visual symptoms of the disorder, and ultimately how they impact quality of life. Since there is no cure or effective treatments available for the visual symptoms of

VSS (van Dongen et al., 2019), management of psychiatric symptoms offers a viable means to alleviate the burden of VSS and improve patient quality of life.

Here, we comprehensively characterised the psychiatric symptomology of VSS in a large cohort of patients, using a combination of validated questionnaires and a structured interview. Specifically, we investigated the frequency of psychiatric symptoms and assessed their relationships to each other as well as to visual symptoms. In addition, we evaluated whether psychiatric symptom severity differed as a function of migraine status, onset of visual snow, and sex. Finally, we explored the impact of psychiatric symptoms on the frequency and severity of visual symptoms and their relative contribution to quality of life. The results of this research will provide important information for health professionals who encounter patients with VSS, and help identify treatment options allowing more effective management of the disorder.

5.3 Methods

5.3.1 Participant recruitment

Participants with VSS were recruited primarily through online, radio, and television advertising, with a number of patients also referred by neurologists. Patients who had not been diagnosed with VSS by a neurologist were screened using an online questionnaire to confirm that they met the diagnostic criteria for VSS as specified by the International Classification of Headache Disorders (ICHD) ("The International Classification of Headache Disorders, 3rd edition," 2013). The questionnaire enquired about the onset and characteristics of the participant's VS, other visual symptoms the participant experienced, and whether they had ever undergone ophthalmological or imaging examinations regarding their VS.

Participants also were asked if they had been diagnosed with other ophthalmological, neurological, or psychiatric conditions, to exclude those with potentially confounding disorders. To exclude patients with Hallucinogen Persisting Perception Disorder (HPPD), which can present very similarly to VSS (Abraham, 1983), participants were asked about illicit drug use. Those who reported illicit drug use in the 12 months preceding VSS symptom onset were considered possible HPPD patients and were not included in the study.

Forty-one healthy controls were recruited from the community through researcher social circles. Control data were used to determine normative ranges for the Short-Form 36 Health Survey global score and subscales, as clinical cut-off scores were not available. Exclusion criteria were a diagnosis of a confounding psychiatric, neurological, or ophthalmological condition. The mean age of controls was 27.2 (SD=8.7): 15 (36.6%) male, and 26 (63.4%) female.

Standard Protocol Approvals, Registrations, and Patient Consents

Ethics approval was granted by the Monash University Human Research Ethics Committee. All participants provided written informed consent prior to participation in the study in accordance with the declaration of Helsinki.

5.3.2 Measures

Participants completed a battery of online questionnaires relating to psychiatric symptomology and health-related quality of life. Standard methods for calculating scores and cut-offs for questionnaires were used unless otherwise indicated. In addition, VSS patients provided clinical information regarding age of VSS onset, VS symptom severity, presence of other symptoms (both visual and non-visual), and other relevant health information.

VSS clinical information

VS symptom severity was determined using a figure displaying varying intensities of 'static'. Based on this figure, patients rated their VS intensity on a scale of 1-6, with 1 referring to the lowest intensity image and 6 to the highest intensity image. Patients also rated how disruptive they considered their VS to be on a scale from 1 ('Not at all disruptive') to 7 ('Severely disruptive'), and how much they felt that VS has impacted their life on a scale from 1 ('No impact') to 7 ('Severely reduced quality of life'). Further, they were given the option to list factors that improved or worsened their VS, and any life activities that were directly impacted by their visual symptoms.

A checklist of visual and non-visual symptoms commonly reported with VSS was provided to patients who were asked to nominate which symptoms, if any, they experienced. For symptoms patients may not be familiar with, such as depersonalization and derealization, definitions were provided. Depersonalization was defined as 'feelings of being detached or disconnected from your body', and derealization as 'feelings that your surroundings or the people around you are not real'. Finally, patients reported whether they had ever been

diagnosed with an anxiety or depressive disorder. Demographic and symptom information for VSS patients is presented in Table 5.1.

Table 5.1

Demographic information and symptom prevalence

	VSS patients (n = 125)	
	Number	Percentage
Age (mean, SD)	31.3, 10.4	-
Female (male)	63 (62)	50.4% (49.6%)
Lifelong VSS	45	36%
Later onset VSS:	80	64%
Age of onset (mean, SD)	22.4, 9.8	-
VSS duration (mean, SD)	9.7, 9.9	-
VSS intensity (mean, SD)	3.7, 1.3	-
VSS disruptiveness (mean, SD)	3.6, 1.6	-
VSS impact on quality of life (mean, SD)	3.7, 1.7	-
Migraine	61	48.8%
Family history of migraine	66	52.8%
Relative with VSS	5	4%
Visual symptoms		
Palinopsia: afterimages	108	86.4%
Palinopsia: trailing	66	52.8%
Nyctalopia	88	70.4%
Photophobia	58	46.4%
Floaters	113	90.4%
Blue field entoptic phenomenon	91	72.8%
Halos	83	66.4%
Number of visual symptoms (mean, SD)	5.4, 1.8	-
Non-visual sensory symptoms		
Tinnitus	97	77.6%
Tremor	43	34.4%
Paraesthesia	59	47.2%
Dizziness	44	35.2%

Other symptoms		
Neck pain	63	50.4%
Irritability	70	56%
Concentration problems	99	79.2%
Depersonalization	45	44.1%
Derealization	31	30.4%
Previous or current anxiety disorder	56	44.8%
Previous or current depressive disorder	48	38.4%

Depression Anxiety Stress Scale (DASS)

The DASS is a commonly used measure of anxiety and depression (Lovibond & Lovibond, 1995) assessing self-reported negative emotions over the immediately preceding week. It consists of three scales: depression, anxiety, and stress, with higher scores reflecting higher levels of each symptom. Standard score ranges were used, as recommended by the DASS manual. Depression: Normal (0-9), Mild (10-13), Moderate (14-20), Severe (21-27), Extremely severe (28+). Anxiety: Normal (0-7), Mild (8-9), Moderate (10-14), Severe (15-19), Extremely severe (20+). Stress: Normal (0-14), Mild (15-18), Moderate (19-25), Severe (26-33), Extremely severe (34+).

Cambridge Depersonalization Scale (CDS)

The CDS measures self-reported experiences of depersonalization over the previous 6 months(M. Sierra & Berrios, 2000). Higher scores indicate more frequent and severe depersonalization, scores above 70 indicating clinical levels of depersonalization (M. Sierra & Berrios, 2000).

The Pittsburgh Sleep Quality Index (PSQI)

The PSQI is a questionnaire assessing sleep quality over the past month (Buysse et al., 1989). It consists of 7 subscales, each with a score range of 0-3: sleep quality, sleep latency, sleep duration, habitual sleep efficacy, sleep disturbances, use of sleeping medication, and

daytime dysfunction. A global score ranging from 0-21 is also generated, with higher scores indicating poorer sleep. In the general population a global cut-off score of >5 is normally used, however in this study a more conservative cut-off score of >8 was chosen, as this has been suggested to be more appropriate in clinical populations (J. S. Carpenter & Andrykowski, 1998).

The Fatigue Severity Scale (FSS)

The FSS assesses the impact of fatigue on day to day functioning (Krupp et al., 1989). It is a nine item self-report questionnaire requiring participants to respond on a scale of 1-7, with higher scores indicating higher levels of fatigue. Scores from each item were summed to form a total score ranging from 7-63. A cut-off score of >36 was used, equivalent to the cut-off score recommended by the original authors (Krupp et al., 1989).

The Short-Form 36 Health Survey version 2 (SF-36)

The SF-36 is a commonly used measure of health-related quality of life comprising 8 subscales: physical functioning, role limitations due to physical problems, social functioning, bodily pain, mental health, role limitations due to emotional problems, vitality, and general health perceptions (Ware, 2000). Subscale scores are transformed to a scale from 0-100, with 0 representing the lowest possible score and 100 representing the maximum possible score. Higher scores indicate better health. A global score for the SF-36 was calculated to provide an overall indication of health-related quality of life, by summing the 8 raw subscale scores and similarly transforming to a 0-100 scale.

5.3.3 Data availability statement

Relevant data not published within the article can be made available by the corresponding author upon reasonable request.

5.3.4 Data analysis

Data were analysed using SPSS statistics 27. Group means, standard deviations (SD), and the percentage of patients with scores falling above/below cut-offs were calculated for all questionnaires. Where published cut off scores were not available (SF-36 subscales and global score) control data were used by converting scores to z-scores based on the formula; (patient raw score – control population mean)/control population SD. For the SF-36, a z-score of -1.96 or below was considered indicative of significantly ($p<.05$) poor health relative to normative population scores. Z-scores were not calculated for the Pittsburgh Sleep Quality Index subscales due to the limited range of values for each subscale (0-3).

Where $\geq$25% of VSS patients scored outside defined normative cut-offs, analyses used independent samples t-test to determine whether psychiatric symptom severity differed due to the presence of migraine, patient sex, onset of symptoms (lifelong vs later onset), or presence of depersonalization. Chi square analyses were used to assess the likelihood of visual and non-visual symptoms occurring in each group. Relationships among questionnaire scores, number of visual symptoms, and VS self-ratings were examined using Pearson correlations, or Spearman correlations where appropriate. A backwards stepwise linear regression was run to assess the contributions of questionnaire scores to health-related quality of life (overall SF-36 score), and to VS intensity and the number of visual symptoms. An alpha-level of $p < .05$ was used to determine significance. Adjustments were not made for multiple comparisons.

5.4 Results

Demographic information and prevalence of visual and non-visual symptoms in VSS patients are presented in Table 5.1.

Questionnaire results (mean scores, SDs, number and percentage of patient scores falling above specified cut-offs) are presented in Table 5.2, with SF-36 results presented separately in Table 5.3. The number and percentage of patients in each DASS score range are displayed in Figure 5.1.

Table 5.2

Questionnaire results

Subscale	Mean (SD)	Scores above cut-off (%)
Depression Anxiety Stress scale		
Depression	13.1 (10.9)	-
Anxiety	9.5 (8.4)	-
Stress	14 (9.6)	-
Cambridge Depersonalization Scale	47.9 (41.1)	34 (27.2%)
The Pittsburgh Sleep Quality Index		
Global score	8.6 (3.7)	56 (44.8%)
Subjective sleep quality	1.3 (0.7)	-
Sleep latency	2 (1)	-
Sleep duration	0.8 (0.9)	-
Sleep efficiency	1.7 (1.4)	-
Sleep disturbances	1.4 (0.6)	-
Sleep medication	0.7 (1.1)	-
Daytime dysfunction	0.8 (0.9)	-
Fatigue Severity Scale	35.3 (15.1)	62 (49.6%)

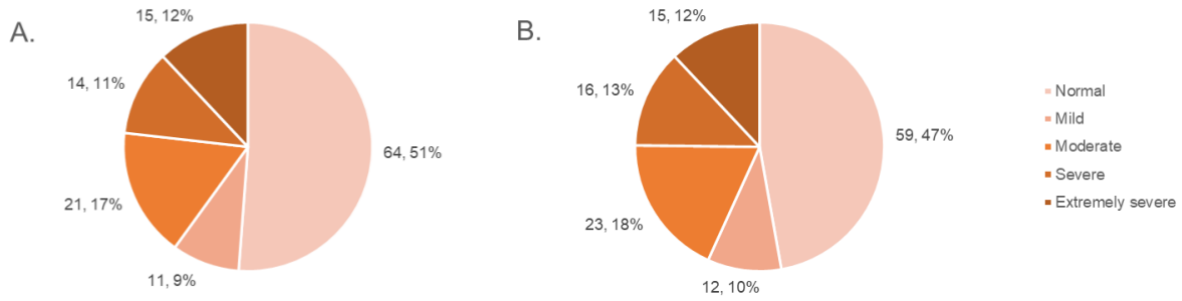
Table 5.3

Short-Form 36 Health Survey results

Subscale	Mean (SD)	Significantly low scores (%)
Global score	58.8 (16.1)	52 (41.6%)
Physical functioning	83 (21.9)	16 (12.8%)
Role: physical	67.9 (32.9)	47 (37.6%)
Role: emotional	48.4 (24.5)	41 (32.8%)
Bodily pain	48.2 (8.3)	3 (2.4%)
General health	52.9 (22)	31 (24.8%)
Vitality	36.2 (20.2)	31 (24.8%)
Social functioning	59.3 (29.2)	36 (28.8%)
Mental health	55.4 (20.2)	52 (41.6%)

Figure 5.1

Patient DASS anxiety and depression subscale scores



Notes. (A) Number and percentage of patients falling within each DASS: anxiety score range, (B) Number and percentage of patients falling within each DASS: depression score range.

5.4.1 Sub-Group comparisons

Migraine

Psychiatric questionnaire scores did not differ between patients with and without migraine.

A higher number of visual symptoms was reported by patients with migraine, (Mean=5.9, SD=1.7), relative to those without (Mean=4.8, SD=1.7), t(123) = -3.6, p<.001, *d*=0.1, 95% CI [-1.68, -0.49].

Patients with migraine were more likely to report photophobia (X^2 (1, N=125) =7.63, *p*=.006), and palinopsia (visual trailing) (X^2 (1, N=125) =5.93, *p*=.015). The prevalence of other visual and non-visual symptoms did not differ.

Sex

Women exhibited higher levels of fatigue (FSS scores) than men, (Mean=39, SD=14.2; Mean=31.6, SD=15.4), t(123) = -2.8, p=.006, *d*=0.5, 95% CI [-12.59, -2.12].

Women also rated the intensity of their VS as more severe (Mean=3.94, SD=1.13) than men (Mean=3.42, SD=1.35), t(123) = -2.3, p=.022, *d*=0.4, 95% CI [-0.96, 0.07]. The prevalence of visual and non-visual symptoms did not differ.

VSS onset

Psychiatric questionnaire scores did not differ between lifelong and later onset VSS patients.

Later onset VSS patients rated their VS as being more disruptive than lifelong VSS patients, (Mean=3.9, SD=1.5; Mean=3, SD=1.5), t(123) =3.18, p=.002, *d*=0.6, 95% CI [0.34, 1.44], with a greater impact on their quality of life (Mean=4.13, SD=1.69) than lifelong VSS patients (Mean=2.82, SD =1.53), t(123) = 4.27, p<.001, *d*=0.8, 95% CI [0.69, 1.91].

Lifelong VSS patients were less likely to report palinopsia (visual trailing), X^2 (1, N=125) = 4.62, *p*=.032. The prevalence of other visual and non-visual symptoms did not differ.

Tinnitus

Psychiatric questionnaire scores did not differ between patients with and without tinnitus.

Patients with tinnitus reported a higher number of visual symptoms (Mean=5.7, SD=1.6), than those without tinnitus (Mean=4.3, SD=1.8), $t(123) = 0.33$, $p<.001$, $d=0.8$, 95% CI [-2.15, -0.75], and rated their VS as being more disruptive (Mean=3.8, SD=1.6), than those without (Mean=2.9, SD=1.3), $t(123) = -2.62$, $p<=.010$, $d=0.6$, 95% CI [-1.5, -0.21].

VSS patients with tinnitus were more likely to experience palinopsia (afterimages) ($X2$ (1, N=125) =10.56, p=.001), floaters ($X2$ (1, N=125) =14.96, p<.001), and BFEP ($X2$ (1, N=125) =9.47, p=.002). They also reported paraesthesia ($X2$ (1, N=125) =23.23, p=<.001), tremor ($X2$ (1, N=125) =6.47, p=.011), concentration problems ($X2$ (1, N=125) =4.87, p=.027), and neck pain ($X2$ (1, N=125) =6.89, p=.009), more often than patients without tinnitus.

Correlations between questionnaire scores, the number of visual symptoms, and self-ratings of VSS severity are presented in Table 5.4.

Table 5.4

Correlations between variables

	SF-36: Global	FSS	PSQI: Global	DASS: Depression	DASS: Anxiety	CDS	No. visual symptoms	VS Intensity	VS disruptiveness	VS impact on QoL
SF-36: Global	-	**-.484 (<.001)**	**-.373 (<.001)**	**-.619 (<.001)**	**-.653 (<.001)**	**-.559 (<.001)**	-.117 (.194)	-.151 (.092)	**-.204 (.023)**	**-.304 (<.001)**
FSS	**-.484 (<.001)**	-	.164 (.067)	**.276 (.002)**	**.299 (<.001)**	**.371 (<.001)**	**.270 (.002)**	.125 (.165)	**.186 (.038)**	**.217 (.015)**
PSQI: Global	**-.373 (<.001)**	.164 (.067)	-	**.265 (.003)**	**.446 (<.001)**	**.290 (<.001)**	.130 (.148)	-.014 (.874)	.008 (.932)	.017 (.852)
DASS: depression	**-.619 (<.001)**	**.276 (.002)**	**.265 (.003)**	-	**.596 (<.001)**	**.488 (<.001)**	-.021 (.815)	.005 (.957)	.068 (.450)	**.187 (.036)**
DASS: Anxiety	**-.653 (<.001)**	**.299 (<.001)**	**.446 (<.001)**	**.596 (<.001)**	-	**.473 (<.001)**	**.177 (.048)**	.069 (.442)	**.190 (.034)**	**.305 (<.001)**
CDS	**-.559 (<.001)**	**.371 (<.001)**	**.290 (<.001)**	**.488 (<.001)**	**.473 (<.001)**	-	**.256 (.004)**	**.288 (<.001)**	**.222 (.013)**	**.284 (.001)**
No. visual symptoms	-.117 (.194)	**.270 (.002)**	.130 (.148)	-.021 (.815)	**.177 (.048)**	**.256 (.004)**	-	**.209 (.019)**	**.455 (<.001)**	**.343 (<.001)**
VS Intensity	-.151 (.092)	.125 (.165)	-.014 (.874)	.005 (.957)	.069 (.442)	**.288 (<.001)**	**.209 (.019)**	-	**.496 (<.001)**	**.283 (.001)**
VS disruptiveness	**-.204 (.023)**	**.186 (.038)**	.008(.932)	.068 (.450)	**.190 (.034)**	**.222 (.013)**	**.455 (<.001)**	**.496 (<.001)**	-	**.725 (.001)**
VS impact on QoL	**-.304 (<.001)**	**.217 (.015)**	.017 (.852)	**.187 (.036)**	**.305 (<.001)**	**.284 (.001)**	**.343 (<.001)**	**.283 (.001)**	**.725 (.001)**	-

Notes. Correlation coefficient (p value). Bold = significant. SF-36: Short Form 36 Health Survey, FSS: Fatigue Severity Scale, PSQI: Pittsburgh Sleep Quality Index, DASS: Depression Anxiety Stress Scale, CDS: Cambridge Depersonalization Scale, VS: Visual snow, QoL: quality of life.

5.4.2 Relationship Between Psychiatric and Visual Symptoms

To estimate the proportion of variance in health-related quality of life (as estimated by the SF-36) that can be accounted for by fatigue (FSS), sleep (PSQI), depression (DASS: Depression), anxiety (DASS: Anxiety), and depersonalization (CDS), we performed a multiple regression analysis using the stepwise backward elimination method. In combination, these variables accounted for a significant 60% of the variability in overall health-related quality of life (SF-36), R^2*=0.6,* adjusted R^2*=.59,* $F(5, 120) = 45.49$, $p < .001$. Unstandardised (*B*) and standardised (β) regression coefficients for each predictor in the regression model are reported in Table 5.5.

Table 5.5

Quality of life regression analysis summary

Variable	***B* [95% CI]**	**β**	***t***	**p**
FSS	-0.26 [-0.39, -0.13]	-0.24	-3.87	**<.001**
PSQI: Global	-	-	-	-
DASS: Depression	-0.39 [-0.61, -0.17]	-0.27	-3.49	**<.001**
DASS: Anxiety	-0.65 [-0.94, -0.37]	-0.34	-4.55	**<.001**
CDS	0.07 [-0.13, 0.02]	-0.18	-2.57	**.011**

FSS: Fatigue severity scale, PSQI: Pittsburgh Sleep Quality Inventory, DASS: Depression Anxiety Stress Scale, CDS: Cambridge Depersonalization Scale.

Further multiple regression analyses using the stepwise backward elimination method were performed to determine the proportion of variance in the number of visual symptoms, and self-reported VS intensity, that can be accounted for by the same variables. In combination, these variables, excluding the PSQI which was again non-significant, accounted for 18% of the variability in the number of visual symptoms, R^2=0.18*,* adjusted R^2=1.5*,* $F(5, 119) = 6.42$, $p<.001$. Unstandardised (*B*) and standardised (β) regression coefficients for each predictor in the regression model are reported in Table 5.6. Depression and depersonalization

accounted for 12% of the variability in VS intensity, R^2=.12, adjusted R^2=0.12, $F(5, 119) = 8.58$, p<.001, with the remaining variables non-significant. Unstandardised (*B*) and standardised (β) regression coefficients for each predictor in the regression model are reported in Table 5.6.

Table 5.6

Visual symptoms regression analysis summaries

Number of visual symptoms				
Variable	***B* [95% CI]**	**β**	***t***	**p**
FSS	0.24 [0, 0.05]	0.21	2.35	**.021**
PSQI: Global	-	-	-	-
DASS: Depression	-0.53 [-0.08, -0.02]	-0.33	-3.07	**.003**
DASS: Anxiety	0.06 [0.13, 0.1]	0.27	2.54	**.012**
CDS	0.01 [0, 0.02]	0.2	1.99	**.049**
VS intensity				
Variable	***B* [95% CI]**	**β**	***t***	**p**
FSS	-	-	-	**-**
PSQI: Global	-	-	-	-
DASS: Depression	-0.02 [-0.05, 0]	-0.21	-2.15	**.034**
DASS: Anxiety	-	-	-	**-**
CDS	0.01 [0.01, 0.02]	0.4	4.14	**<.001**

FSS: Fatigue Severity Scale, PSQI: Pittsburgh Sleep Quality Inventory, DASS: Depression Anxiety Stress Scale, CDS: Cambridge Depersonalization Scale.

5.4.3 Patient experiences of visual snow

Factors that worsened visual snow

Patients identified environmental and individual factors that worsened their VS. The most common environmental factors were dim or low-light conditions, harsh artificial light, bright sunlight, and darkness. The most common individual factors were tiredness/fatigue, stress/anxiety, alcohol consumption, inadequate sleep, exercise, caffeine, and screen use. Other factors mentioned less commonly included migraine, poor diet, dehydration, illness, menstruation, and illicit drug use (historically).

Factors that improved visual snow

Most of the factors listed as improving VS were individual, with the most common, improving sleep, followed by 'accepting' or learning to ignore symptoms ('looking through them rather than at them'), and improving diet. Other factors mentioned less commonly included altering ambient lighting, practicing meditation or mindfulness, improving general mood, reducing stress/anxiety, and regular exercise. The patients who listed exercise as helpful clarified that exercise may intensify VS during physical activity, but led to improved perception of symptoms in the longer term. Patients frequently reported wearing sunglasses to reduce light sensitivity. Two patients reported wearing coloured lenses to reduce the perception of visual symptoms (Lauschke et al., 2016), and 2 reported that focusing on videos of static found online for 2-3 minutes decreased their VS significantly for approximately 30 seconds, although it did not provide long-lasting benefits.

Activities impacted by visual snow

The most common activity impacted by VS was driving, with patients often specifying that driving at night/in the dark was difficult or impossible. Some patients elaborated on this, citing difficulty reading road signs, oncoming headlights being 'too bright', and afterimages of car lights and streetlights interfering with vision.

Patients also reported difficulty reading, with many adding that they avoided reading unless necessary. Issues using screens were also common, with one patient responding that he quit his career due to being unable to work on computers all day as required.

Other activities mentioned as impacted included social activities or sports which take place in bright daylight, going out at night, physical activity due to the temporary exacerbation of symptoms, and being able to enjoy natural scenery or stargazing. A number of patients simply replied broadly that their work, study, or social life were affected.

5.5 Discussion

VSS remains a poorly understood disorder, with even less known about the frequently co-occurring psychiatric symptomology. Given the difficulty in treating the visual symptomology of VSS (van Dongen et al., 2019), understanding how psychiatric symptoms manifest and relate to the visual symptoms of the disorder offers avenues of treatment that may significantly improve quality of life for patients. Here we characterise the psychiatric symptoms most commonly reported by VSS patients, and their relationship with visual symptoms and quality of life (QoL). Our results show that patients with VSS more frequently exhibit clinically significant levels of depression, anxiety, depersonalization, fatigue, and higher incidences of poor sleep, which significantly impact their QoL. Further, these psychiatric symptoms are related to more severe visual symptomology, with depersonalization in particular consistently associated with more severe self-ratings of VS. Interestingly, the timing of VSS onset (lifelong vs later onset), presence of migraine, and patient sex were not found to significantly impact the severity of psychiatric symptoms.

5.5.1 Depression and anxiety

Consistent with previous reports (Lauschke et al., 2016; Schankin, Maniyar, Digre, et al., 2014; Yildiz et al., 2019), a significant proportion of patients exhibited high levels of anxiety and depression, and poor overall mental health (SF-36: mental health subscale). DASS results indicated that 25% of patients exhibited either severe or extremely severe levels of depression, with a similar number exhibiting severe or extremely severe anxiety. Anxiety and depression scores were found to relate significantly to perceived VS severity. As with other neurological disorders, these symptoms might be assumed to reflect distress relating to the symptoms themselves, or may be linked to neurobiological changes underlying the specific disorder (Hesdorffer, 2016; Prisnie et al., 2018). The impact of VSS visual

symptomology on patient QoL can be profound, and is likely to contribute to higher levels of anxiety and depression. Key life activities including driving, reading, and screen use may be impacted, which frequently lead to difficulties with work and study; some patients stated that they changed employment or elected not to pursue further education as a result of their VSS. Social functioning also appears to be affected, with almost 30% of patients reporting significantly low scores on the SF-36 social functioning subscale. Social and recreational activities may be impacted by VSS in a number of ways: exercise, alcohol consumption, and bright or low-light conditions may temporarily exacerbate symptoms, resulting in avoidance of activities involving those factors. Some patients also reported that anxiety associated with visual symptoms affected their ability to leave their home.

In addition to the distressing nature and impact of their visual symptoms, there are many other factors influencing mental health. As VSS is still not widely recognised or understood, many patients struggle to find a diagnosis or explanation for their symptoms. Patients are often told that their symptoms are psychogenic, or presumed to be malingering (Lauschke et al., 2016; White et al., 2018). Some patients involved in this study relayed having fears pre-diagnosis that they might have unidentified brain cancer, or that their visual symptoms would continue to progressively worsen until they became blind. Even following a diagnosis of VSS, most patients experience little if any relief from the few currently available treatments (van Dongen et al., 2019). These factors likely contribute to the prevalence of anxiety and depression in VSS patients.

However, our results indicate that anxiety and depression in VSS patients are not necessarily secondary to their disabling sensory symptoms, but may be, at least partially, inherent to the disorder. We anticipated that patients with lifelong VSS would report lower levels of anxiety and depression than patients with an onset later in life, given that for them, VS is ‘normal’; indeed, many lifelong patients report not realising their vision was abnormal

until adulthood. In support of this, lifelong VSS patients rated their VS as being less disruptive and impacting their quality of life significantly less than patients with a later onset of symptoms. Yet despite being subjectively less concerned by their symptoms, lifelong VSS patients reported equal levels of depression and anxiety with later onset patients. The two groups also did not differ in sleep quality, level of fatigue, experiences of depersonalization, or overall health-related quality of life. This suggests that the negative impact of VSS on mental health, sleep, and energy level is not solely attributable to distress caused by its symptoms.

5.5.2 Sleep and fatigue

Sleep difficulties have not been previously reported in VSS, however they were a frequent complaint among our cohort, and over 40% of patients exhibited sleep scale (PSQI) scores indicative of sleep dysfunction. Anecdotally, our VSS patients often reported difficulty sleeping due to the distracting and prominent nature of their visual symptoms in the dark, which are present with the eyes open or closed. We found that sleep difficulties were not limited to increased time to fall asleep (sleep latency), but also included high rates of sleep disturbances, poor sleep quality, and low sleep efficiency. As sleep reliably shows a bidirectional relationship with anxiety and depression (Alvaro, Roberts, & Harris, 2013), poor sleep may both contribute to and be influenced by poor mental health. Indeed, poor sleep was linked with higher rates of depression and anxiety. Given that many patients cited poor sleep as an aggravating factor for VS, addressing sleep difficulties in patients may lead to improvement in both mental health and the tolerability of visual symptoms.

Fatigue and lethargy have been previously reported in multiple VSS cohorts (Metzler & Robertson, 2018; Schankin, Maniyar, Digre, et al., 2014). Interestingly, we did not find a significant relationship between sleep quality (PSQI) and level of fatigue (FSS), suggesting

that the high levels of fatigue reported by VSS patients were not solely a consequence of poor sleep. Fatigue is highly prevalent in other neurological disorders, including migraine (Chaudhuri & Behan, 2004; Maestri et al., 2020), where it has been linked with more severe migraine symptomology and a greater level of impairment (Maestri et al., 2020). Our results suggest a similar association in VSS, with increased levels of fatigue associated with a higher number of visual symptoms, and poorer self-ratings of VS severity. However, it remains unclear whether fatigue occurs as a consequence of coping with constant sensory dysfunction, whether patients with higher levels of fatigue are less able to ignore their visual symptoms and thus perceive them as worse, or whether fatigue is linked directly to the pathophysiology of VSS.

5.5.3 Depersonalization

Depersonalization (CDS) scores showed the most consistent relationship with the number of visual symptoms and patient ratings of VS severity. CDS scores were also found to contribute significantly to VS intensity and the number of symptoms experienced. Depersonalization refers to subjective feelings of detachment from the physical body and mental processes, and may involve a diminished sense of agency or feelings of being 'robotic' (Simeon et al., 2008). Temporary experiences of depersonalization are common in the general population, but when they are recurrent and distressing a diagnosis of depersonalization-derealization disorder may be considered (Michal et al., 2016). Nearly 45% of VSS patients in this study reported having experienced depersonalization, and over 25% showed scores above the scale cut-off indicating a possible depersonalization disorder. This suggests that depersonalization is not only common in VSS, but is severe in a significant number of patients. Derealization, a dissociative experience characterised by a sense that the surrounding world is unreal or artificial (Simeon et al., 2008), was also reported by

approximately 30% patients. Derealization frequently co-occurs with depersonalization; it is unclear whether they are truly distinct dissociative experiences, or whether derealization may represent a subtype of depersonalization (Baker et al., 2003).

High rates of depersonalization have been reported previously in patients with vestibular dysfunction (Jauregui Renaud, 2015; Yen Pik San, Jauregui-Renaud, Green, Bronstein, & Gresty, 2006), retinal disease (Jauregui-Renaud, Ramos-Toledo, Aguilar-Bolanos, Montano-Velazquez, & Pliego-Maldonado, 2008), and chronic dizziness (Toupet et al., 2019). Here it has been theorised that feelings of depersonalization may be evoked by a discrepancy between expected sensory input (provided by the frame of experience) and actual (aberrant) sensory experience (Jauregui-Renaud et al., 2008); or, alternatively, by a discrepancy between signals from different sensory systems due to one or more being disrupted (Lopez, 2013). A coherent perception of the body and surrounding space requires the seamless integration of inputs from different sensory modalities; conceivably, disturbance of this integration may lead to a disrupted awareness of the self (Lopez, 2013). As depersonalization and derealization are not well-known as symptoms, or as a disorder, patients may lack the language to describe their experiences, or may not realise what they are experiencing is a defined psychological symptom. Health professionals may therefore need to describe these experiences to a patient to ascertain whether they have experienced them.

5.5.4 Pathophysiology of VSS

Although it is unclear whether poorer mental health and difficulties with sleep and fatigue are primary VSS symptoms, or secondary to sensory dysfunction, a shared underlying cause is plausible. The pathophysiology of VSS remains unknown, but is theorised to involve a central disturbance in the processing of sensory information (Lauschke et al., 2016; Schankin, Maniyar, Digre, et al., 2014; White et al., 2018). In our previous studies

investigating ocular motor performance in VSS patients (Solly et al., 2020), we identified attentional changes hypothesised to be consistent with disrupted thalamocortical (TC) communication, potentially a thalamocortical dysrhythmia (Lauschke et al., 2016; Schankin, Maniyar, Digre, et al., 2014). With the exception of the olfactory system, all sensory input passes through the thalamus, which regulates the incoming flow of sensory information to the cortex (Kremkow & Alonso, 2018; Ward, 2013). The thalamus and cortex are highly interconnected through recurring feedback loops. TC circuits are characterised by state-dependent resonant oscillatory activity, which modulates thalamic and cortical functioning (R. Llinas, Ribary, Contreras, & Pedroarena, 1998). The oscillatory activity of TC networks is crucial not only for the processing and integration of sensory information, but also for attention, cognition, and arousal level (Timofeev & Bazhenov, 2005; Zobeiri et al., 2019). As such, alteration in the oscillatory activity of TC networks may conceivably underlie the range of sensory and non-sensory symptoms reported by VSS patients, including disrupted sleep and fatigue. Evidence also exists that dissociative experiences may involve abnormal TC network activity (Vesuna et al., 2020).

Thalamocortical dysrhythmia (TCD) is a form of aberrant TC oscillatory activity proposed to underly a number of neurological and psychiatric disorders including migraine, tinnitus, and depression (De Ridder et al., 2015; Hodkinson et al., 2016; R. R. Llinas et al., 1999; Vanneste et al., 2018). In TC networks, different behavioural states are characterised by specific forms of oscillatory activity (Zobeiri et al., 2019). TCD involves a pathological increase in low-frequency theta waves during states of wakefulness, coupled with surrounding high-frequency gamma waves (R. R. Llinas et al., 1999; Vanneste et al., 2018). These oscillatory changes result in disruption to normal state-dependent communication between the thalamus and cortex, which may manifest as a diverse range of affective, cognitive, and sensory symptoms, depending on which TC network and associated cortical

areas are implicated (Malekmohammadi et al., 2015; Vanneste et al., 2018). TCD occurs due to increased inhibitory or decreased excitatory input at the thalamic level, which may be triggered by bottom-up or top-down processes (R. R. Llinas et al., 1999). It has been theorised that TCD in VSS may be secondary to cortical excitability (Lauschke et al., 2016).

Potential limitations of this study include recruitment bias, and a lack of objective measures of VSS severity. Patients who are more impacted by their symptoms may be more motivated to seek out and engage in research, biasing studies towards reporting more severe cases. Self-ratings of VS are also unlikely to be purely objective, reflecting distress relating to symptoms as well as symptom severity. Correlations between self-ratings of VS and questionnaire scores should therefore be interpreted with the awareness that they may reflect both the impact of VS on quality of life, and the influence of psychiatric symptomology on the perception of symptoms. Indeed, many patients reported that changes in psychiatric symptomology (e.g. in anxiety level or sleep quality) worsened or improved their perception of visual symptoms.

5.5.5 Treatments

Treating the psychiatric symptomology associated with VSS is likely to significantly improve patient QoL, with or without accompanying improvement in visual symptoms. Sleep dysfunction is highly treatable through a number of approaches including lifestyle changes, behavioural therapies, and pharmacological agents (Becker & Sattar, 2009). Addressing sleep dysfunction may also lead to improvements in depression and anxiety due to the bidirectional relationship between sleep and mental health (Alvaro et al., 2013). Identifying and treating patients at risk of severe mental health problems, and possibly suicidality, is also highly important given the rates of severe depression and anxiety associated with VSS. As with sleep dysfunction, a number of treatment avenues are available for anxiety and depression,

both pharmacological and psychological (Andrews et al., 2018; Malhi et al., 2021). While little research has been conducted into treatments for depersonalization, there is some evidence that lamotrigine, currently the medication considered most efficacious in VSS (van Dongen et al., 2019), may be helpful in treating this symptom (Naguy & Al-Enezi, 2019). Psychological therapies commonly used to treat depression and anxiety, such as cognitive behavioural therapy (CBT) may also help patients cope with their visual symptoms.

No study to date has investigated psychological approaches to treating VSS; however, a wealth of research exists on CBT based treatments for tinnitus. Tinnitus is reported by the majority of VSS patients, and has been theorised to represent an auditory analogue of VS; i.e., the constant perception of low level 'noise' in each sensory system (Schankin, Maniyar, Digre, et al., 2014). Given the similarities between tinnitus and VS, and overlap of patients, treatments shown to be effective for tinnitus may also be helpful in VSS. CBT encompasses a wide variety of cognitive and behavioural therapeutic techniques, but simplistically, typically aims to identify and modify negatively biased or irrational reactions to events and experiences, such as the perception of tinnitus (or VS) (Andersson, 2002). CBT has been shown to significantly improve depression, anxiety, insomnia, and overall health-related QoL in tinnitus patients (Landry et al., 2020). Forms of CBT developed to treat tinnitus may be efficacious if adapted for use in VSS.

5.5.6 Conclusion

Our results show that VSS significantly impacts a patient's QoL, affecting various aspects of physical and mental health. Anxiety and depression, depersonalization, disrupted sleep, fatigue, and impaired social functioning were highly prevalent among patients, with poorer scores on these variables typically relating to worse self-ratings of visual symptoms. Although the equivalent QoL scores of lifelong and later onset patients indicate that mental

health, fatigue, and sleep difficulties may be partially inherent to the disorder, they are doubtless exacerbated by the emotional impact of sensory symptoms. Patients reported that poor sleep, tiredness, and anxiety worsened their VS, whereas improving sleep and reducing stress and anxiety were said to improve perception of symptoms. Given the sparsity of effective treatments available for VSS, treating associated mental and physical health symptoms may in some cases be the only and most effective method of assisting patients. Managing the mental health and sleep of patients is likely to improve their overall quality of life and lead to improvement in the perception of visual symptoms.

Chapter Six: Eye movement characteristics are not significantly influenced by psychiatric comorbidities in people with visual snow syndrome

The following chapter was written up as a manuscript and published in the journal, *Journal of the Neurological Sciences*, titled *Eye movement characteristics are not significantly influenced by psychiatric comorbidities in people with visual snow syndrome.* Formatting has been altered to ensure consistency with other chapters.

In Chapter 3 and Chapter 4 it was established that participants with VSS exhibit significant changes to ocular motor behaviour: specifically, faster eye movements and increased inhibitory errors when attention is captured exogenously, or directed endogenously. This ocular motor signature was assumed to reflect dysfunction in visual and attentional networks in VSS.

In Chapter 5, a high prevalence of psychiatric symptoms was confirmed in VSS. Previous research in psychiatric populations has indicated that psychiatric symptoms can influence ocular motor behaviour. However, previous research has mostly used cohorts with diagnosed psychiatric conditions, or extreme forms of the symptoms assessed (e.g., total sleep deprivation). It was unclear whether standard levels of psychiatric symptoms, even elevated as is the case in VSS, would significantly influence ocular motor results.

This possibility was important to explore, to establish whether psychiatric symptoms might represent confounding variables when interpreting ocular motor results. The psychiatric symptoms assessed in Chapter 5 (depression, anxiety, fatigue, sleep quality, and

depersonalization/derealization) were examined in relation to ocular motor task metrics (latencies and error rates) reported in Chapter 3 and Chapter 4.

6.1 Abstract

Visual snow syndrome (VSS) is a neurological disorder primarily affecting the processing of visual information. Using ocular motor (OM) tasks, we previously demonstrated that participants with VSS exhibit altered saccade profiles consistent with visual attention impairments. We subsequently proposed that OM assessments may provide an objective measure of dysfunction in these individuals. However, VSS participants also frequently report significant psychiatric symptoms. Given that that these symptoms have been shown previously to influence performance on OM tasks, the objective of this study was to investigate whether psychiatric symptoms (specifically: depression, anxiety, fatigue, sleep difficulties, and depersonalization) influence the OM metrics found to differ in VSS. Sixty-one VSS participants completed a battery of four OM tasks and a series of online questionnaires assessing psychiatric symptomology. We revealed no significant relationship between psychiatric symptoms and OM metrics on any of the tasks, demonstrating that in participants with VSS, differences in OM behaviour are a feature of the disorder. This supports the utility of OM assessment in characterising deficit in VSS, whether supporting a diagnosis or monitoring future treatment efficacy.

6.2 Introduction

Visual snow (VS) is a persistent positive visual disturbance across the entire visual field, with the co-occurrence of at least two additional visual symptoms supporting a diagnosis of visual snow syndrome (VSS) ("The International Classification of Headache Disorders, 3rd edition," 2013). At present, the aetiology of VSS is unknown and there are no objective clinical markers of the disorder. Recently, we demonstrated that ocular motor (OM) measures provide a method of assessing visual processing changes in the disorder, providing a potential marker of dysfunction that can be used to aid diagnosis and monitor any future treatment outcomes (Solly et al., 2020; Emma J. Solly et al., 2021). Although we found that migraine, a frequent VSS comorbidity, did not impact our OM measures (Solly et al., 2020; Emma J. Solly et al., 2021), it remains unclear whether the varied and common comorbid psychiatric symptoms of VSS (depression, anxiety, poor sleep quality, fatigue, and experiences of depersonalization / derealization) (Solly, Clough, Foletta, White, & Fielding, 2021) do impact performance, as has been reported in other populations (Bafna & Hansen, 2021; Carvalho et al., 2015).

We demonstrated previously that individuals with VSS reorient gaze to a suddenly appearing target more quickly than neurologically healthy individuals (i.e., make faster latency prosaccades) (Solly et al., 2020). VSS participants also exhibit greater difficulty withholding a response to non-target stimuli (i.e., increased antisaccade errors) (Solly et al., 2020) or when attention is endogenously cued to non-target location (increased inhibitory errors on tasks endogenously manipulating attention) (Emma J. Solly et al., 2021). However, these studies did not consider the numerous psychiatric symptoms that are common in VSS.

VSS cohorts consistently report mood (39%) and anxiety (45%) disorders, and we have also shown that they frequently experience fatigue (50%), poor sleep quality (45%), and experiences of dissociation (specifically depersonalization/derealization, 27%) (E. J. Solly et

al., 2021). Depression has been linked previously with slower saccadic latencies and increased inhibitory errors (Carvalho et al., 2015), and individuals with high levels of anxiety have been reported to generate slower antisaccades (Shi et al., 2019). Both sleep deprivation and fatigue have been associated with increased inhibitory errors and/or alterations to saccade latencies (Bafna & Hansen, 2021; Bocca et al., 2014). Depersonalization and derealization have not been specifically investigated using OM tasks, but are known to involve attentional changes (J. Adler et al., 2014) which, given the inextricable link between attention and OM control (Awh et al., 2006) could theoretically impact OM behaviour.

The aim of this study, therefore, was to determine whether depression, anxiety, fatigue, sleep deprivation, and depersonalization/derealization in VSS participants significantly influence OM task performance in these individuals.

6.3 Materials and methods

6.3.1 Participants

61 participants with VSS (29 male, 32 female), aged 16-55 (Mean = 30.3, SD = 10.7), were recruited through a combination of online, radio, and television advertising. All met the criteria for VSS as specified by the International Classification of Headache Disorders("The International Classification of Headache Disorders, 3rd edition," 2013). Exclusion criteria were consumption of medication likely to affect visual or cognitive functioning, a confounding neurological condition, or having experienced a migraine or migraine aura within 3 days prior to or following OM testing. Thirty-three healthy control participants were recruited from the community (11 male, 22 female) aged 19-56 (Mean = 29, SD = 8.7). Exclusion criteria for controls were a diagnosed psychiatric, neurological, or ophthalmological condition. Control and VSS participant numbers varied between OM tasks due to time limitations when completing OM testing and technical difficulties resulting in lost data. The VSS participants and controls included in this study overlapped significantly with those included in our previous OM papers (Solly et al., 2020; Emma J. Solly et al., 2021).

Participants provided written informed consent prior to participation in the study in accordance with the declaration of Helsinki. Ethics approval was granted by the Monash University Human Research Ethics Committee.

As 28 VSS participants (45.9%) reported a history of migraine we conducted a series of one-way analyses of variance to determine whether the presence of migraine confounded any experimental measures. No significant differences were found between groups, consistent with our previous studies(Solly et al., 2020; Emma J. Solly et al., 2021).

6.3.2 Psychiatric symptom measures

Participants completed the following questionnaires online to assess commonly reported psychiatric symptoms in VSS.

The Depression Anxiety Stress Scale (DASS) assesses self-reported negative emotions over the week prior to testing across three subscales: depression, anxiety, and stress. Subscale scores range from 0 to 42, with higher scores indicating higher levels of each symptom (Lovibond & Lovibond, 1995). For each subscale scores can be grouped into five score ranges: normal, mild, moderate, severe, and extremely severe.

The Pittsburgh Sleep Quality Index (PSQI) assesses sleep quality over the preceding month. The global PSQI score ranges from 0 to 21, with higher scores indicating poorer sleep quality (Buysse et al., 1989). A cut-off score of 8 was used to indicate clinically significant levels of poor sleep quality(J. S. Carpenter & Andrykowski, 1998).

The Fatigue Severity Scale (FSS) examines the impact of fatigue day to day functioning. Higher scores indicate higher levels of fatigue, with a total score ranging from 7 to 63. A cut-off score of 36 was used to indicate clinically significant levels of fatigue, equivalent to the cut-off score recommended by the original authors (Krupp et al., 1989).

The Cambridge Depersonalization Scale (CDS) measures self-reported experiences of depersonalization and derealization over the previous 6 months, with scores above 70 signifying clinical levels of depersonalization (M. Sierra & Berrios, 2000). The CDS was completed at a later time point, and consequently data is missing for 15 participants who could not be reached.

6.3.3 Ocular motor testing

All OM testing was conducted at the Alfred Centre, Monash University, Melbourne, using an Eyelink 1000 + dark pupil video-oculography system to record horizontal

displacement of the eye. This system has high resolution (noise limited at <0.01°) and an acquisition rate of 1000 Hz. A forehead/chin rest was used to stabilise the head during testing. An LCD display monitor (resolution:1920 × 1080) was situated 950mm from the participant's eyes, with task stimuli presented on a black background. A brief overview of each OM task is provided below; more detailed explanations can be found in our previous papers (Solly et al., 2020; Emma J. Solly et al., 2021) or upon request.

The prosaccade task assesses simple reorienting of gaze. Participants were instructed to follow a green cross with their eyes as it shifted horizontally from the centre of the screen to one of four peripheral locations (5/10°, left/right) and back to centre.

The antisaccade task is a commonly used measure of inhibitory control. Participants were instructed to begin fixating on a central cross, which subsequently shifted horizontally to one of four peripheral locations (5/10°, left/right). Participants were required to look to the mirror opposite position of the peripheral cross without making an eye movement in its direction.

The endogenously cued saccade task examines the effect of orienting attention prior to the appearance of a target. This task comprises a central fixation cross flanked by two white boxes situated 10° left/right of centre. Prior to the presentation of a target green cross in one of the peripheral boxes, a left or right pointing arrow is presented at centre. Participants were instructed to ignore the arrow and direct gaze to the peripheral green cross. The direction of the arrow either corresponded (valid trial) or not (invalid trial) with the direction of the upcoming target.

The saccadic Simon task investigates the effect of presenting a peripheral cue that is either spatially congruent or spatially incongruent with a target's location. Participants began each trial fixating on a central cross flanked by two white boxes situated 10° left/right of centre. Either a circle or square was presented in one of the boxes. Participants were

instructed to look towards the right box if a square appeared, and the left box if a circle appeared, regardless of the box in which they were presented.

6.3.4 Ocular motor data analysis

OM data were analysed offline using a customised program written in MATLAB. Variables of interest were error rate (%) and saccade latency (ms). An error was defined as an incorrect eye movement exceeding 1.5 degrees. Error rate was calculated as the % of total trials, and was calculated for all tasks except the prosaccade task. Saccade latency was determined from a monocular eye trace as the temporal difference between stimulus onset and saccade onset, with saccade onset corresponding with a change in velocity exceeding 30° per second. Trials were excluded from latency analyses where an error was performed, fixation was not maintained within 2 degrees of centre, a blink occurred, or no response was made.

6.3.5 Statistical analyses

Statistical analyses were conducted using IBM SPSS Statistics 27 ("IBM SPSS Statistics for Windows, Version 27.0," 2019), using an alpha level of $p < .05$. Where data were missing, the pairwise deletion method was used. Group means and standard deviations (SD) were calculated for all variables. The percentage of VSS participants with scores above questionnaire cut-offs, or within score ranges, were calculated for psychiatric questionnaires.

A series of one-way analyses of variance were conducted to compare OM task latencies and error rates between controls and VSS participants to confirm the differences in OM behaviour previously reported. The relationships between psychiatric questionnaire scores and OM variables (latencies and error rates) found to differ significantly between controls and VSS participants were examined using Spearman correlations. To further

investigate whether VSS participants with clinically significant levels of psychiatric symptoms differed from those without, a series of one-way analyses of variance (or Mann-Whitney U tests where data were not normally distributed) were conducted comparing OM variables between VSS participants with scores above defined cut-offs for the CDS, PSQI, and FSS to those with scores below the cut-offs. As the DASS features score ranges rather than a single cut-off score, trend analyses were conducted with one-way ANOVAs to examine whether OM variables vary by level as a function of depression or anxiety scores.

6.4 Results

6.4.1 Psychiatric questionnaire variables

Questionnaire means, standard deviations, and number of VSS participants with scores above clinical cut-offs are presented in Table 6.1. The number of VSS participants in each DASS subscale score range are shown in Table 6.2.

Table 6.1

Psychiatric questionnaire results for VSS participants

Scale	Mean	SD	Number > clinical cut-off (%)
Fatigue Severity Scale	37.6	14.12	35 (58.3%)
Pittsburgh Sleep Quality Index	7.2	2.9	16 (26.7%)
Cambridge Depersonalization Scale	42.24	33	12 (25.5%)

Table 6.2

DASS descriptives and score ranges for VSS participants

DASS subscale	Mean	SD	Number of participants in each score range (%)				
			Normal	Mild	Moderate	Severe	Extremely severe
Depression	9.03	8.71	39 (65%)	3 (5%)	12 (20%)	4 (6.7%)	2 (3.3%)
Anxiety	6.27	7.18	41 (68.3%)	6 (10%)	7 (11.7%)	3 (5%)	3 (5%)
Stress	11.23	8.99	45 (75%)	3 (5%)	5 (8.3%)	5 (8.3%)	2 (3.3%)

Notes. DASS, Depression Anxiety Stress Scale

6.4.2 Ocular motor task variables

Control and VSS participant mean saccadic latencies and error rates for each OM task are presented in Table 6.3. VSS participants exhibited significantly shorter PS latencies, and higher error rates on the antisaccade task, endogenously cued saccade task, and saccadic Simon task.

Table 6.3

Control and VSS descriptives and ANOVA results for ocular motor task variables

	VSS Mean (SD)	Control Mean (SD)	*F*	*p*	η2
Prosaccade task	*n* = 61	*n* = 33			
PS latency	201.51 (17.68)	210.76 (20.21)	5.295	**.024**	.054
Antisaccade task	*n* = 60	*n* = 32			
AS latency	338.29 (43.82)	319.37 (43.48)	3.911	.051	.042
AS error rate	16.15 (13.2)	9.44 (10.46)	6.175	**.015**	.054
Endogenously cued saccade task	*n* = 55	*n* = 32			
Valid latency	243.84 (34.71)	253.71 (33.08)	1.690	.197	.019
Invalid latency	255.75 (41.51)	257.56 (36.49)	.042	.838	.000
Anticipatory error rate	6 (6.71)	2.99 (3.86)	5.370	**.023**	.059
Saccadic Simon task	*n* = 56	*n* = 30			
Congruent latency	512.99 (73.18)	512.67 (100.48)	.000	.987	.000
Incongruent latency	510.05 (78.09)	503.75 (86.49)	.118	.732	.001
Error rate	14.75 (9.51)	10.13 (7)	5.465	**.022**	.061

Notes. **Bold** indicates significance, p<.05. Abbreviations: VSS = visual snow syndrome, AS = antisaccade.

6.4.3 Relationship between psychiatric and ocular motor variables

The OM variables found to differ significantly between controls and VSS participants (PS latency, AS error rate, endogenously cued saccade task error rate, and saccadic Simon task error rate) were investigated in relation to psychiatric symptoms. Given that AS latency was close to significantly different between controls and VSS participants, this variable was also included in analyses.

No significant correlations were found these OM variables and psychiatric questionnaire scores. OM measures also did not significantly differ between participants with and without clinically significant levels of depersonalization, fatigue, and impaired sleep quality, or across score ranges for the DASS anxiety subscale.

A significant linear trend was found between DASS depression score ranges and AS error rate, indicating that the percentage of AS errors increased with higher DASS score range, $F(1, 54)=6.63$, $p=.013$, $\eta^2=.159$, 95% CI [0, .268]. Means and standard deviations for AS error rates across DASS: Depression score ranges are displayed in Table 6.4.

Post-hoc Games-Howell comparisons revealed that VSS participants with extremely severe depression had a significantly higher AS error rate than VSS participants with severe ($p=.012$, 95% CI [7.19, 54.26]) or moderate depression ($p=.021$, 95% CI [9.03, 48.61]). No other comparisons were significantly different, and no other significant trends were found between OM variables and DASS score ranges for depression and anxiety.

Table 6.4

Antisaccade error rate across DASS: Depression subscale score ranges

DASS: Depression score range	Antisaccade error rate	
	Mean	SD
Normal (0-9)	16.56	13.1
Mild (10-13)	11.11	13.87
Moderate (14-20)	13.89	12.16
Severe (21-27)	11.97	7.86
Extremely severe (28+)	42.71	4.42

6.4 Discussion

The objective of this study was to determine whether psychiatric symptoms commonly reported by individuals with VSS impact results on attentional OM tasks. Specifically, depression, anxiety, depersonalization, sleep quality, and fatigue were investigated in relation to OM metrics found to differ between controls and VSS participants. The differences in OM behaviour found were consistent with our previous studies (Solly et al., 2020; Emma J. Solly et al., 2021), with the exception of validly cued trial latencies on the endogenously cued saccade task, which in contrast to our previous findings did not differ significantly between groups. This may be due to differences in sample size. Importantly, none of the psychiatric variables assessed were found to significantly impact OM results. The exception to this was an increased number of antisaccade errors generated by VSS participants with 'extremely severe' depressive symptoms. Given that only two participants showed depressive symptoms in this range, this result may be spurious, but future OM investigations of VSS should control for the possible influence of severe depression. These results support the utility of OM measures in VSS, indicating that the previously reported differences in OM behaviour are indeed reflecting to changes in visual processing, and are not attributable to comorbid psychiatric symptoms.

Previous studies have reported an association between psychiatric variables and OM task performance. However, most previous investigations linking depression and OM behaviour are limited in their generalizability, for example, including relatively small samples comprised only of participants with diagnosed mood disorders (Carvalho et al., 2015). These represent only the extreme end of depressive symptomology. Similarly, when the influence of sleep factors and fatigue have been investigated, this has typically been in the context of assessing either the effects of total sleep deprivation (Bocca et al., 2014) or experimentally induced fatigue (Bafna & Hansen, 2021), which necessarily more strongly impacts

performance than everyday levels of reduced sleep quality or fatigue. While more extreme levels of psychiatric symptoms are likely to impact OM behaviour, our results show that more typical levels of psychiatric symptomology in VSS participants do not influence performance on our OM tasks.

The lack of a significant association between OM and psychiatric variables might also suggest a dissociation between visual and psychiatric symptom severity. Psychiatric symptoms in individuals with VSS may be both an emotional consequence of coping with the disorder , or linked to pathophysiological changes associated with VSS (E. J. Solly et al., 2021). Our finding that OM measures and psychiatric symptoms do not correlate does not necessarily contradict the latter explanation. The neurological changes underlying VSS are not well understood, but the range of symptoms experienced by patients, and heterogenous presentations of the disorder, suggest an idiosyncratic pathophysiology that may influence people in differing ways to differing extents. In addition, individual and environmental factors affecting susceptibility and resilience are likely to influence the expression and experience of psychiatric symptoms.

We theorised previously that the OM differences observed in VSS participants may be a consequence of cortical hyperexcitability and/or dysfunctional thalamocortical communication, two proposed theories of VSS pathophysiology (Fraser, 2022; Jenny L. Hepschke et al., 2021a). Neuro-imaging and neurophysiological studies published since we first reported our VSS signature provide further support for both hypotheses. Increased regional cerebral blood flow (CBF) in people with VSS has been reported throughout an extensive neural network, particularly affecting areas involved in complex sensory processing and attentional control such as regions of the parietal lobe, the frontal eye fields (FEF), the cerebellum, the insula, and regions of the occipital lobe (Francesca Puledda, Christoph J. Schankin, et al., 2021). Widespread alterations to cortical functional connectivity have also

been found (F. Puledda et al., 2021), both between visual processing regions, and with other areas of the cortex including the FEF, the premotor cortex, regions of the parietal lobe, and the cerebellum (F. Puledda et al., 2021). Regarding thalamocortical changes, microstructural changes are present in the thalamic nuclei of VSS patients (Strik et al., In press), as well as altered connectivity between the pulvinar and right lingual gyrus (F. Puledda et al., 2021), implicating thalamic sensory pathways. These studies, alongside earlier studies, indicate that VSS is characterised by subtle but extensive dysfunction affecting sensory, attentional, and salience networks (Fraser, 2022). As OM tasks are dependent on the integrity of these networks, they are well suited to assessing neurological changes in VSS; hyperexcitability affecting visual and attentional networks is consistent with the speeded and more difficult to control saccadic responses that people with VSS exhibit (Solly et al., 2020; Emma J. Solly et al., 2021).

6.4.1 Conclusions

Although the exact pathophysiological mechanisms underlying VSS remain unclear, the results of this study support the utility of OM assessments in providing objective measure of dysfunction in VSS by showing that psychiatric symptoms common in people with VSS do not significantly influence saccadic latencies or inhibitory error rates. Previously we reported that psychiatric symptoms correlated with self-ratings of VS (E. J. Solly et al., 2021), which could reflect either a relationship between psychiatric and visual symptoms, or the negative influence of psychiatric symptoms on participant's subjective ratings of VS. The lack of a significant relationship between OM results and psychiatric variables in this study indicates the latter explanation is more likely, further highlighting the need for objective measures of VS severity that will not be impacted by placebo effects or a patient's emotional state. OM assessment offers a behavioural manifestation and objective marker of hyperexcitability and disinhibition within the visual processing system in VSS (Solly et al., 2020; Emma J. Solly et

al., 2021). While future research is required to confirm the utility of OM measures in tracking the progression or improvement of visual processing dysfunction in VSS, our results show that OM tasks are robust to the influence of common psychiatric symptoms affecting people with VSS.

Chapter Seven: The prevalence and impact of inattentive and hyperactive/impulsive symptoms in people with Visual Snow Syndrome

The following chapter was written up as a manuscript for the journal *Psychiatric and Clinical Neurosciences*, titled *The prevalence and impact of inattentive and hyperactive/impulsive symptoms in people with Visual Snow Syndrome.* It is currently under review following submission of revisions. Formatting has been altered to ensure consistency with other chapters.

Although concentration difficulties and distractibility were a frequent complaint of VSS patients, a plan to assess inattentive and hyperactive/impulsive symptoms was not formed until D. G. Mehta et al. (2021) reported a higher than normal percentage of Attention Deficit Disorder (ADD) and Attention Deficit Hyperactivity Disorder (ADHD) diagnoses in a review of VSS cases.

Given that an ADD diagnosis requires only inattentive symptoms, and an ADHD diagnosis might indicate both significant hyperactive/impulsive *and* inattentive symptoms, or only significant levels of one domain, a diagnosis of either could conceivably be obtained by an individual experiencing only inattentive symptoms (i.e. distractibility and concentration problems). The study did not include details about the participant's diagnosis to answer this question.

While an elevated level of inattentive symptoms would be expected in VSS, elevated hyperactive/impulsive symptoms as well might indicate a genuine comorbidity with ADHD traits. To explore whether both inattentive and hyperactive/impulsive symptoms were

elevated in VSS participants involved in this study, an ADHD self-report scale was given to all participants who had completed the initial psychiatric questionnaire battery.

Inattentive and hyperactive/impulsive symptoms were also examined in relation to other psychiatric symptoms, quality of life, and the sensory symptoms of VSS.

7.1 Abstract

Aim: To determine the prevalence of inattentive and hyperactive/impulsive symptoms in individuals with Visual Snow Syndrome (VSS), and investigate their associations with the clinical features of VSS, quality of life (QOL), and commonly co-occurring psychiatric symptoms.

Methods: 86 participants with VSS completed a battery of questionnaires ascertaining the presence of inattention and hyperactivity/impulsivity symptoms, VSS clinical features, migraine, psychiatric symptoms (depression, anxiety, stress, fatigue, and sleep problems), and QOL.

Results: While 33 participants (38.4%) reported clinically significant levels of inattention and hyperactivity/impulsivity, neither symptom domain was associated with the clinical features of VSS or differed in participants with comorbid migraine. However, among those with comorbid migraine, both symptom domains were associated with more frequent migraines. Higher levels of inattention and hyperactivity/impulsivity were additionally found to show an association with poorer general health, mental health, and sleep quality.

Conclusion: Individuals with VSS frequently report high levels of inattentive and hyperactive/impulsive symptoms, which are associated with more severe co-occurring psychiatric symptoms, and a poorer QOL. These associations are likely to be bidirectional. Both inattentive and hyperactive/impulsive symptoms, as well as psychiatric symptoms, may well be linked to pathophysiological changes underlying VSS. Treating inattentive and hyperactive/impulsive symptoms may improve the QOL of people with VSS, and their ability to cope with their invasive sensory symptoms.

7.2 Introduction

Visual snow (VS) describes the perception of unrelenting flickering static present throughout the visual field. The persistence of VS for at least 3 months, alongside two or more additional visual symptoms, constitutes the diagnostic criteria for visual snow syndrome (VSS) (Schankin, Maniyar, Digre, et al., 2014). VSS may be a lifelong or acquired condition, with onset typically reported in childhood or young adulthood (Fraser, 2022; E. J. Solly et al., 2021). Initially assumed to be a rare condition, a recent epidemiological study on VSS from the UK suggested the prevalence of VSS may be as high as 2% (Kondziella et al., 2020).

A recent case series review of 248 VSS patients reported higher than population prevalence rates of diagnosed attention deficit hyperactivity disorder (ADHD) or the now outdated attention deficit disorder (ADD) (D. G. Mehta et al., 2021). 14.3% of participants in this cohort disclosed a diagnosis of ADHD or ADD, compared to reported population prevalence rates of 5-7% in children (Polanczyk, Willcutt, Salum, Kieling, & Rohde, 2014; Willcutt, 2012), and 2.5-5% in adults (Prakash, Chatterjee, Guha, Srivastava, & Chauhan, 2021). ADHD is a common neurodevelopmental disorder epitomised by clinically significant impairment in controlling attention and/or impulsive/hyperactive behaviours (*Diagnostic and statistical manual of mental disorders: DSM-5™, 5th ed*, 2013). The disorder has either a predominantly combined presentation (with clinically significant inattention *and* hyperactivity/impulsivity), or a predominantly inattentive or predominantly hyperactive/impulsive presentation. The presentation types of patients in the aforementioned study were not reported (D. G. Mehta et al., 2021).

While there is evidence to suggest that individuals with VSS frequently experience difficulties with inattention (Schankin, Maniyar, Digre, et al., 2014; E. J. Solly et al., 2021), it is unknown whether hyperactive/impulsive symptomology is similarly elevated. Importantly, inattention and hyperactivity/impulsivity are dimensional traits that occur to varying

subclinical levels within the general neurotypical population (Franke et al., 2018; Vogel et al., 2018), and thus logically also within the VSS population.

60-80% of individuals with VSS report poor concentration and/or distractibility, central features of attentional control (Schankin, Maniyar, Digre, et al., 2014; E. J. Solly et al., 2021). It is as yet unclear whether this is a consequence of the chronic distracting nature of visual symptoms (Schankin, Maniyar, Digre, et al., 2014), and/or underlying pathophysiological changes to the attentional and salience networks known to be impacted from functional imaging studies (Fraser, 2022; F. Puledda, D. Ffytche, et al., 2020; F. Puledda et al., 2021; Schankin, Maniyar, Digre, et al., 2014) and eye tracking tasks (Solly et al., 2020; Emma J. Solly et al., 2021). Further, psychiatric symptoms such as sleep difficulties, anxiety, and depression are extremely common in VSS (E. J. Solly et al., 2021; van Dongen et al., 2019), and can negatively impact attentional control (Bijlenga, Vollebregt, Kooij, & Arns, 2019; Dunlop, Wu, & Helms, 2018; Pallanti & Salerno, 2020; E. J. Solly et al., 2021). Notably, 50-80% of VSS participants also experience migraine (Fraser, 2022), which has been linked with heightened inattentive and hyperactive/impulsive symptomology as well as ADHD diagnoses (Arruda, Arruda, Guidetti, & Bigal, 2020; Fasmer et al., 2010; T. F. Hansen et al., 2018; Lévêque et al., 2020).

No consistently effective treatments are available for the perceptual symptoms of VSS (van Dongen et al., 2019), and we previously suggested that treating commonly associated psychiatric symptoms provides an avenue to improve quality of life and tolerance of visual disturbances (E. J. Solly et al., 2021). Elevated inattentive and/or hyperactive/impulsive symptoms in VSS would have important implications for psychiatric care, as high levels of these symptoms are associated with poorer treatment responses for anxiety and depression if not also addressed (Barkley & Brown, 2008; Ginsberg, Quintero, Anand, Casillas, & Upadhyaya, 2014).

The aim of this study was to determine the prevalence of inattentive and hyperactive/impulsive symptoms in individuals with VSS, and how both symptom domains relate to the clinical features of the disorder. In addition, this study examined how inattentive and hyperactive/impulsive symptoms in those with VSS are associated with their comorbid features (migraine, depression, anxiety, stress, fatigue, and poor sleep quality) and quality of life.

7.3 Materials and methods

7.3.1 Participant recruitment

Eighty six participants with VSS were recruited through a combination of methods including referrals from neurologists and online, radio, and television advertising. Approximately half of study participants (41, 48%) had been formally diagnosed by a neurologist, and the remaining were screened using an online questionnaire to establish whether they met the diagnostic criteria for VSS. Screening questionnaire responses were reviewed by a neurologist. Exclusion criteria were the presence of a potentially confounding visual or neurological condition, a traumatic brain injury within the 6 months preceding VSS onset, or an onset of VSS within 12 months of illicit drug use, as Hallucinogen Persisting Perception Disorder (HPPD) can present very similarly to VSS (van Dongen et al., 2021) . Clinical information for participants is presented in Table 7.1.

Table 7.1

Clinical information for VSS participants

	VSS participants (*n* = 86)	
	Number	Percentage
Age (range)	31.7 (16 - 57)	-
Female (Male)	49 (37)	57% (43%)
Migraine	42	48.8%
Lifelong VSS (Later onset VSS)	35 (51)	40.2% (59.3%)
Self-ratings of VS (Mean, SD)		
Intensity	4 (1.2)	-
Disruptiveness	3.7 (1.7)	-
Impact on QOL	3.8 (1.9)	-
Visual symptoms		
Palinopsia (afterimages)	73	84.9%
Palinopsia (trailing)	44	51.2%
Nyctalopia	59	68.6%
Photophobia	45	52.3%
Floaters	75	87.2%
Blue-field entoptic phenomena	67	77.9%
No visual symptoms (mean, SD)	5.4, 1.8	-
Other sensory symptoms		
Tinnitus	66	76.7%
Paraesthesia	42	48.8%
Dizziness	23	26.7%
Tremor	23	26.7%
Non-sensory symptoms		
Irritability	43	50%
Concentration difficulties	64	74.4%
Distractibility	58	67.4%

7.3.2 Ethics

Ethics approval was granted by the Monash University Human Research Ethics Committee. All participants provided written informed consent prior to participation in the study in accordance with the declaration of Helsinki.

7.3.3 Data availability

Relevant data not published within the article can be made available by the corresponding author on reasonable request.

7.3.4 Equipment, stimuli, and procedures

VSS and migraine clinical information

All VSS participants completed an online questionnaire regarding their visual and sensory symptoms. Participants rated the severity of their VS using Likert scales. A figure displaying varying intensities of static was used to rate VS intensity on a scale from 1-6, with 1 referring to the lowest intensity image and 6 to the highest intensity image. 'Disruptiveness' of VS was rated on a scale from 1 ("Not at all disruptive") to 7 ("Severely disruptive"). The impact of VS on quality of life was rated on a scale from 1 ("No impact") to 7 ("Severely reduced quality of life").

Participants were also asked whether they experienced migraine, and if so whether they typically experienced visual aura preceding them. They indicated how often they experienced migraine from the following options: "1. Less than once every few months", "2. Once every few months", "3. Once a month", "4. Once a fortnight", "5. Once a week", or "6. More than once a week".

Assessment of ADHD symptoms

All psychiatric and QOL questionnaires were completed by participants online, in their own time. The Adult ADHD Self-report Scale (ASRS) is a widely used questionnaire for the assessment of self-reported ADHD symptoms. It comprises two scales: nine items describe symptoms related to inattention, and nine items describe symptoms related to hyperactivity/impulsivity. Each of the 18 items corresponds to a symptom listed in the DSM-V diagnostic criteria for ADHD (Kessler et al., 2005). Participants respond to each item on a five-point Likert scale indicating the frequency of the symptom (0 = "never", 1 = "rarely", 2 = "sometimes", 3 = "often", and 4 = "very often").

Different scoring methods can be used for the ASRS (Kessler et al., 2005). In this study, subscale scores were calculated by separately summing responses for inattentive and hyperactive/impulsive items, forming subscale scores ranging from 0-36. A total score was calculated ranging from 0-72. A shortened version, the ASRS screener (ASRS-S), comprises 6 items from the full questionnaire and has been found to more effectively differentiate between individuals with and without ADHD (Kessler et al., 2005). The ASRS-S was scored by dichotomizing the 6 item responses based on whether they indicated clinically significant levels of the symptom. The endorsement of four or more items is strongly suggestive of ADHD (Kessler et al., 2005), and this cut-off point was used to identify VSS participants with clinically significant scores.

To explore the question of whether participants experienced problems with inattention prior to developing VSS, or if inattentive symptoms were linked to VSS onset, a subset of participants were contacted for follow up questions based on two criteria; firstly, that they exhibited a significant level of ADHD symptoms (defined as an ADHD diagnosis or a significant score on the ASRS screener), and secondly, that they reported an onset of VSS after the age of 15. 19 participants met these criteria, 16 of whom were willing to answer follow up questions over a brief telephone or online video call. Question responses were

recorded as ‘Yes’ or ‘No’ by the interviewer, with notes made where participants clarified or included additional details in their answers. The questions were as follows:

1. Do you believe that you experience difficulties with concentration or distractibility (relative to others)?
2. Did you experience difficulties with concentration or distractibility (relative to others) prior to developing VSS?
3. Has your ability to concentrate or ignore distractions changed since VSS onset? If so, how?
4. Do you have a family history of ADHD?
5. Have you ever been diagnosed with ADHD?

Psychiatric and quality of life measures

Depression, anxiety, and stress levels were assessed using the Depression Anxiety Stress Scale (DASS), which enquires about symptoms over the week prior to testing. Subscale scores for each symptom range from 0-42, with higher scores indicating more severe symptoms (Lovibond & Lovibond, 1995).

Sleep quality and fatigue were assessed using the Pittsburgh Sleep Quality Index (Buysse et al., 1989) and the Fatigue Severity Scale (Krupp et al., 1989). Total scores on these measures range from 0-21 and 7-63 respectively, with higher scores indicating poorer quality of sleep and higher levels of fatigue.

QOL was assessed using the Short-Form 36 Health Survey Version 2 (SF-36) (Ware, 2000). The SF-36 comprises 8 subscales measuring various QOL domains: physical functioning, role limitations due to physical problems (role: physical), social functioning, bodily pain, mental health, role limitations due to emotional problems (role: emotional), vitality, and general health perceptions. Each raw subscale score was transformed to fall on a

scale from 0-100, with 0 representing the lowest possible score and 100 representing the highest possible score. Higher scores indicate better QOL.

7.3.5 Statistical analyses

All statistical analyses were performed using IBM SPSS Statistics 27 ("IBM SPSS Statistics for Windows, Version 27.0," 2019). An alpha level of $p<.05$ was used, and where data were missing, the pairwise deletion method was used. To determine the prevalence of significant ADHD symptoms, the proportion of participants exhibiting scores above the ASRS-S cut-off was calculated. Differences between sub-groups were determined using one-way ANOVAs. Differences in the percentage of individuals showing scores above the ASRS-S cut-off was determined using chi-square analysis. Trend analyses were run to investigate whether migraine frequency was associated with ASRS scores, and Spearman correlations were used to investigate the association between ASRS scores and measures of VS severity (number of visual symptoms and self-ratings of VS).

A data reduction technique (principal components analysis) was used to reduce the number of variables for following analyses. Psychiatric variables (ASRS subscale scores, DASS subscale scores, PSQI score, and FSS score), QOL variables (SF36 subscale scores), and measures of VSS severity (number of visual symptoms and self-ratings of VS) were entered with a varimax rotation and the eigenvalue-one criterion. Kaiser-Meyer-Olkin (KMO) and Bartlett's test of sphericity were used to determine sample adequacy and sphericity respectively. Component scores were calculated by averaging the z-scores of variables with a loading of .6 or above. Spearman correlations were then performed between components. A backwards stepwise multiple regression was run to determine which components (found to correlate significantly with ADHD symptoms) were significant predictors of ADHD symptoms.

7.4 Results

7.4.1 Prevalence of inattentive and hyperactive/impulsive symptoms

11 participants (12.6%), 6 male and 5 female, reported having an ADHD diagnosis, 5 of whom (2 male and 3 female) also experienced migraine.

33 participants (38.4%) scored 4 or above on the ASRS-S, indicating clinically significant levels of inattentive and hyperactive/impulsive symptoms. Mean scores and SDs for the ASRS overall, and for male and female participants, are presented in Table 7.2. Scores on inattentive and hyperactive/impulsive subscales showed a significant positive correlation, $r(86) = .676$, $p<.001$.

Table 7.2

VSS participant total and subscale ASRS scores

ASRS scores	Overall n = 86	Male n = 37	Female n = 42
Total score	31.72 (13.72)	34.92 (12.42)	29.31 (14.28)
Inattentive symptoms score	17.53 (7.84)	18.81 (6.75)	16.57 (8.51)
Hyperactive/impulsive symptoms score	14.19 (7.15)	16.11 (6.88)	12.73 (7.08)

Male VSS participants were more likely than female participants to score above the ASRS-S cut-off, with 19 male participants (51.4%) scoring above the cut-off compared to 14 female participants (28.6%), $X^2 (1, 86) = 4.67$, $p=.031$. When total and subscale ASRS scores were compared, male participants had significantly higher levels of hyperactive/impulsive symptoms, $F(1, 84) = [4.904]$, $p = .029$, $\eta 2 = .055$, 95% CI (.000, .17). No differences were found for inattentive symptoms or total ASRS scores.

7.4.2 Association of migraine with inattentive and hyperactive/impulsive symptoms

Inattentive and hyperactive/impulsive symptom levels did not differ between VSS participants with no migraine, participants with comorbid migraine, or participants with comorbid migraine + visual aura. ASRS scores for each group are presented in Table 7.3. The groups also did not differ in their likelihood of scoring above the ASRS-S cut-off.

Table 7.3

ASRS scores and migraine

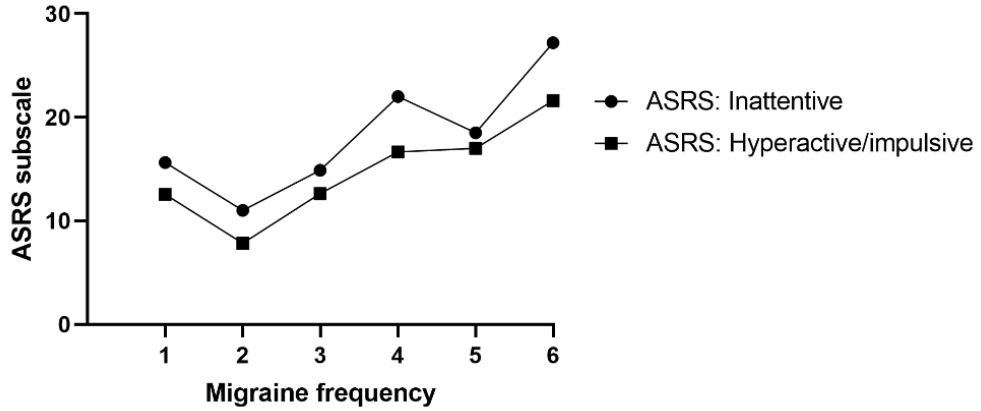
ASRS scores	VSS (no migraine) n = 44	VSS + migraine n = 13	VSS + migraine + visual aura n = 29
Total ADHD symptoms	32.43 (14.34)	34.08 (16.1)	29.59 (11.69)
Inattentive symptoms	17.98 (8.09)	19.15 (8.79)	16.14 (7.03)
Hyperactive/impulsive symptoms	14.45 (7.23)	14.92 (7.91)	13.45 (6.87)

Notes. Abbreviations: VSS = Visual Snow Syndrome.

A significant linear trend was found between migraine frequency and the ASRS inattentive subscale, showing that inattentive symptoms increased with increasing migraine frequency, $F(1, 41)=12.12$, $p=.001$, $\eta^2=.370$, 95% CI [.056, .498]. Scores on the ASRS hyperactive/impulsive subscale similarly increased with migraine frequency, $F(1, 41)=10.172$, $p=.003$, $\eta^2=.304$, 95% CI [.008, .436].

Figure 7.1

Inattentive and hyperactive/impulsive symptoms by migraine frequency



Notes. 1 = less often than once ever few months, 2 = once every few months, 3 = once per month, 4 = once per fortnight, 5 = once per week, 6 = more than once per week.

7.4.3 Association of VSS clinical features with inattentive and hyperactive/impulsive symptoms

Neither inattentive or hyperactive/impulsive symptoms were associated with VSS duration, the number of visual symptoms reported, or with self-ratings of VS (intensity, disruptiveness, and impact on quality of life). Inattentive and hyperactive/impulsive symptoms also did not differ between VSS participants who reported lifelong VSS compared to participants with an onset of symptoms later in life.

VSS participants with scores above the ASRS-S cut-off were not more likely to report experiencing visual symptoms common in VSS (palinopsia, photophobia, floaters, or blue-field entoptic phenomena), or associated sensory symptoms (tinnitus, paraesthesia, dizziness, or tremors). The exception to this was nyctalopia (poor night vision): VSS participants with scores above the cut-off were more likely to report nyctalopia (81%) than those with scores below the cut-off (60%), X^2 (1, N = 86) = 4.341, p=.037.

7.4.4 The association of inattentive and hyperactive/impulsive symptoms with psychiatric symptoms and quality of life

The Kaiser-Meyer-Olkin (KMO) indicated sample adequacy, KMO = 0.746. Bartlett's test of sphericity was significant, which indicated that correlations between variables were sufficiently strong enough for the principal components analysis, $\chi 2\ (171) = 768.192$, $p<.001$. Five components with eigenvalues over 1 were identified, which collectively explained 66.92% of the variance (Table 7.4).

Table 7.4

Principal components analysis

Variables	Components				
	1	2	3	4	5
Visual symptom ratings					
Number of visual symptoms			**.719**		
VS intensity			.585		
VS disruptiveness			**.815**		
Impact of VS on QOL	.349		**.719**		
ADHD symptoms					
Inattentive	.302			**.768**	
Hyperactive/impulsive		.304		**.782**	
Other psychiatric variables					
Depression		**.850**			
Anxiety		**.743**			
Stress		**.790**			
Fatigue	**.710**				
Sleep	.362			.575	
QOL subscales					
Physical functioning	**.781**				
Role: physical	**.787**				
Bodily pain					**.819**
General health	**.694**				
Vitality	**.648**	.408			
Social functioning	**.719**	.418			**.648**
Role: emotional			.372		
Mental health		**.780**			
Percentage variance	31.13	13.198	8.909	7.339	6.256
Eigenvalue	5.930	**2.508**	1.693	1.394	1.189

*Note*s: Factor loadings over 0.60 appear in bold. Abbreviations: VSS = Visual Snow Syndrome, QOL = Quality of Life.

Based on the variables loadings, the extracted components were determined to represent (1) General health and functioning, (2) Mental health, (3) Perceived severity of visual symptoms, and (4) ADHD symptoms. The fifth component (bodily pain and social functioning) was rejected. As PSQI (sleep quality) did not load significantly onto any of the components, but showed a clear association with ADHD symptoms, (5) SSleep quality was included in following analyses as an additional component.

ADHD symptoms were found to correlate with General health and functioning, Mental health, and Sleep quality (Table 7.5).

Table 7.5

Correlations between components

	1. General health and functioning	2. Mental health	3. Visual symptom severity	4. ADHD symptoms	5. Sleep quality
1	-	**.492, <.001****	**.365, <.001****	**.362, <.001****	**.473, <.001****
2	**.492, <.001****	-	.184, .089	**.506, <.001****	**.404, <.001****
3	**.365, <.001****	-.184, .089	-	.134, .218	.114, .294
4	**.362, <.001****	**.506, <.001****	.134, .218	-	**.371, <.001****
5	**.473, <.001****	**.404, <.001****	.114, .294	**.371, <.001****	-

Bold indicates significance, *correlation is significant at the .05 level, ** correlation is significant at the .001 level.

A backwards stepwise linear regression was used to identify significant predictors of ADHD symptoms (from the following: General health and functioning, Mental health, and

Sleep quality). Variables were removed based on *p*-values, with a threshold of .05. General health and functioning did not uniquely contribute to ADHD symptoms and was excluded from the final model, (*Beta = .107, t*(.136) = .197*, p*=.362*)*. The final model (Mental health and Sleep quality) accounted for a significant portion of the variance in ADHD symptoms, $F(2, 83) = 12.017$, $p<.001$, $R^2 = .474$*.*, $R^2_{Adjusted} = .21)$. Mental health significantly predicted ADHD symptoms, (*Beta* = .319*, t(*.111) = 3.039, *p* = .003), as did Sleep Quality, (*Beta* = .248, *t*(.096) = 2.365*, p* = .02).

7.4.5 Follow-up interview: Inattentive symptoms and VSS onset

Half of the 16 participants who responded to the follow-up questions reported they had experienced difficulties with concentration/distractibility (relative to others) prior to VSS onset. Most participants (11, 68.6%) reported that their ability to concentrate/distractibility noticeably worsened following VSS onset. Of these participants, most indicated that the worsening of inattentive symptoms was persistent or had improved only slightly over time as they became accustomed to perceptual symptoms. However, two male participants (1 & 5) described a distinct course of attentional difficulties following VSS onset, where they experienced a particularly severe initial worsening in concentration/distractibility, which then gradually alleviated over a period of months alongside an improvement in their visual symptoms. Most of the 16 participants (11, 68.6%) reported having a family history of ADHD.

The majority of the participants who completed the follow up questions were male (12, 75%). The reason for this sex imbalance seems to be that in addition to being less likely to exhibit significant scores on the ASRS-S, female participants were also more likely to report lifelong VSS symptoms than male, and therefore fewer met the criteria for the follow up interview. Of the 49 female VSS participants who participated in the study, 25 (51%)

reported lifelong symptoms of VSS, compared to 10 (27%) of the 37 male participants.

Details of follow-up participants are presented in Table 7.6.

Table 7.6

Follow-up interview participant details

Participant	Sex	Age	Migraine	Age of VSS onset	ASRS subscales		ADHD diagnosis	ADHD family history	Did you experience concentration problems / distractibility relative to other prior to VSS onset?	Has your ability to concentrate / distractibility changed since VSS onset?
					Inattentive	Hyperactive / impulsive				
1	M	24	No	23	22	22	No	Yes	No	Yes: worsened
2	M	26	Yes	25	16	9	No	No	Unsure	No
3	M	27	Yes	26	18	19	No	No	Unsure	Yes: worsened
4	M	23	No	17	21	16	No	No	Yes	No
5	M	25	Yes	24	15	22	No	No	Unsure	Yes: worsened
6	F	22	Yes	16	24	28	Yes	Yes	Yes	Yes: worsened
7	M	43	Yes	19	20	14	No	Yes	No	Yes: worsened
8	M	40	No	25	28	21	No	Yes	Yes	Yes: worsened
9	M	53	Yes	28	19	30	Yes	Yes	Yes	No
10	M	19	No	19	28	18	No	No	No	Unsure: maybe worsened
11	F	44	Yes	36	32	6	No	Yes	No	Yes: worsened
12	F	49	Yes	35	19	22	No	Yes	Yes	Yes: worsened
13	M	40	No	21	22	22	Yes	Yes	No	Yes: worsened
14	F	33	Yes	32	27	27	No	Yes	Yes	No
15	M	35	No	33	25	25	No	Yes	Yes	Yes: worsened
16	M	23	No	23	16	16	No	Yes	Yes	Yes: worsened

7.5 Discussion

The aim of this study was to determine the prevalence of inattentive and hyperactive/impulsive symptoms in individuals with VSS, and how they relate to the clinical and comorbid symptoms of the disorder. Our results revealed high levels of inattention and hyperactivity/impulsivity in VSS participants compared to typical population prevalence rates. Whilst we found no evidence of an association between inattentive and hyperactive/impulsive symptoms and the clinical features of VSS, we revealed an association between higher symptom levels and poorer general health and functioning, poorer mental health, and poorer sleep quality. Further, for those with migraine, higher symptom levels were linked to more frequent migraines. Our follow-up interviews with a subset of participants indicated that for most, inattentive symptoms worsened following the onset of VSS - however, many reported lifelong difficulties with concentration and distractibility.

7.5.1 Prevalence of inattentive and hyperactive/impulsive symptoms

Of the 86 participants with VSS involved in this study, almost 40% exhibited clinically significant scores on an ADHD screening scale. In contrast, studies examining large community samples report that typically only 5-10% of individuals show scores within a clinically significant range (Caci, Morin, & Tran, 2014; Oerbeck et al., 2019; Vnukova et al., 2020). Clinically significant scores on an ADHD screening scale are not sufficient for a diagnosis of ADHD, and may represent various factors including comorbid psychiatric conditions (Dunlop et al., 2018). However, these results indicate that a large proportion of VSS participants experience levels of inattention and/or hyperactivity/impulsivity that may impair function. Despite the fact that male and female VSS participants equally reported a diagnosis of ADHD, male participants were nearly twice as likely to show clinically significant scores on the screening scale. This appeared driven by higher levels of

hyperactive/impulsive symptoms among male participants, since no sex differences were found for inattentive symptoms. These results are consistent with previous reports of sex differences in ADHD symptom prevalence (Williamson & Johnston, 2015).

7.5.2 Association of migraine with inattentive and hyperactive/impulsive symptoms

In contrast to previous studies reporting an association between migraine and ADHD (Salem et al., 2018), we found that VSS participants with migraine did not differ in inattentive or hyperactive/impulsive symptom level (T. F. Hansen et al., 2018; Salem et al., 2018). This suggests that the presence of comorbid migraine does not explain elevated ADHD symptoms in VSS, nor does it represents an additive risk factor. Among participants with migraine, higher levels of inattentive and hyperactive/impulsive symptoms were associated with more frequent migraines. Cognitive changes including impaired concentration are common during migraine attacks, and may be present for days preceding and following a migraine headache (Gil-Gouveia & Martins, 2018). This may explain the correlation with inattentive symptoms, however hyperactive/impulsive symptoms were also associated with migraine frequency. An alternate explanation is that inattentive or hyperactive/impulsive symptoms might directly or indirectly increase the frequency of migraine triggers: for example, disrupted sleep and stress are commonly reported migraine triggers(Martinelli, Pocora, De Icco, Putortì, & Tassorelli, 2022), and are associated with ADHD symptoms (Das, Cherbuin, Butterworth, Anstey, & Easteal, 2012; Floros et al., 2021)

7.5.3 Association of VSS features with inattentive and hyperactive/impulsive symptoms

The distracting nature of persistent visual symptoms has been proposed as one explanation for concentration problems in VSS (Schankin, Maniyar, Digre, et al., 2014). Our results do not support this. Firstly, no correlations were found between inattentive or hyperactive/impulsive symptoms and self-ratings of visual snow severity, as would be expected if these visual symptoms were related to distractibility. Secondly, inattentive or hyperactive/impulsive symptom levels did not differ between participants with lifelong VSS compared to those with a later onset VSS, despite the latter generally reporting their visual symptoms as being more disruptive (E. J. Solly et al., 2021). In addition, half of the 16 participants who completed the follow-up interview reported experiencing difficulties with distractibility and concentration problems (relative to others) since childhood, preceding the onset of VSS. 11 of the 16 follow-up participants also reported a family history of ADHD, which is notable as inattentive and hyperactive/impulsive symptoms are highly heritable (Brikell, Kuja-Halkola, & Larsson, 2015; Larsson, Chang, D'Onofrio, & Lichtenstein, 2014).

Interview responses raise the possibility that an elevated level of inattentive and hyperactive/impulsive symptoms, or a family history of ADHD, could be a risk factor for developing VSS, and that inattentive symptoms are exacerbated by rather than caused by VSS onset. Notably, ADHD commonly co-occurs with other sensory processing disorders linked to VSS (A. Klein & Schankin, 2021); migraine (Arruda et al., 2020; Fasmer et al., 2010; T. F. Hansen et al., 2018; Lévêque et al., 2020), as aforementioned, as well as tinnitus (Kim, Jeon, Lee, & Kim, 2017; Kumbul, Işik, Kiliç, Sivrice, & Akin, 2022) and fibromyalgia (Pallanti, Porta, & Salerno, 2021; van Rensburg, Meyer, Hitchcock, & Schuler, 2018). However, our results would need to be replicated in a larger sample to support this theory,

preferably with corroborating informant reports of inattentive and hyperactive/impulsive symptoms prior to VSS onset. A limitation of interviewing participants about historical symptoms is the potential for inaccurate recall. Previous studies, for example, suggest adults with ADHD may significantly underestimate their childhood ADHD symptoms compared to parent and informant reports (von Wirth, Mandler, Breuer, & Döpfner, 2021).

7.5.4 Association of psychiatric symptoms and quality of life with inattentive and hyperactive/impulsive symptoms

Higher levels of inattentive and hyperactive/impulsive symptoms in VSS participants were found to correlate with poorer general health (including measures of physical health, fatigue, and social functioning), mental health (depression, anxiety, and stress), and sleep quality, with mental health and sleep quality found to contribute uniquely to inattentive and hyperactive/impulsive symptoms. These results are consistent with a large body of research showing that inattention and hyperactivity/impulsivity, both at clinical and sub-clinical levels, are associated with poorer mental health and sleep quality (Bijlenga et al., 2019; Das et al., 2012; Franke et al., 2018; Vogel et al., 2018). These associations are likely to be bidirectional. Poor mental health and sleep quality may cause or worsen inattentive symptoms (Bijlenga et al., 2019; Dunlop et al., 2018; Van Ameringen, Mancini, Simpson, & Patterson, 2011), however inattentive and hyperactive/impulsive symptoms may also affect sleep and contribute to the development of depressive and anxiety disorders over the lifespan (Gair, Brown, Kang, Grabell, & Harvey, 2021; Riglin et al., 2021). This may be due to a combination of factors including adverse life experiences related to symptoms (such as impairments in social, academic, and vocational functioning), shared genetic liability, and common pathophysiological processes (Brikell et al., 2020; Riglin et al., 2021).

7.5.5 Possible pathophysiological correlates

The pathophysiology of VSS is not well understood, but is proposed to involve cortical hyperexcitability, widespread neuroanatomical alterations, and changes to connectivity throughout the cortex and subcortical regions (Fraser, 2022; F. Puledda et al., 2021; Strik et al., In press). Imaging studies indicate disruption to large scale brain networks, including the dorsal visual network, default mode network, and salience network (Fraser, 2022; F. Puledda et al., 2021). These networks support vision and attentional control, and functionally altered in individuals with clinically significant levels of inattention and hyperactivity (i.e., ADHD) (F. Puledda et al., 2021; Sidlauskaite, Sonuga-Barke, Roeyers, & Wiersema, 2016).

VSS has also been suggested to involve thalamocortical dysrhythmia (TCD), a pathological form of oscillatory activity in thalamocortical networks that modulates the transmission of sensory input to the cortex and ongoing cortical processing (Lauschke et al., 2016; Vanneste et al., 2018). TCD has been identified in several neurological conditions including migraine and tinnitus, as well as in psychiatric conditions such as major depression (De Ridder et al., 2015; Hodkinson et al., 2016; Vanneste et al., 2018). Disruption to thalamocortical communication also been proposed in ADHD (Sukhodolsky, Leckman, Rothenberger, & Scahill, 2007), and thus potentially represents a pathophysiological overlap between VSS, clinical levels of inattentive and hyperactive/impulsive symptoms, and the sensory and psychiatric comorbidities common in VSS.

Shared neurobiological mechanisms could also underly sensory and attentional dysfunction. A frequently proposed theory for the comorbidity between migraine and inattentive and hyperactive/impulsive symptoms is the shared disruption to the dopaminergic system (T. F. Hansen et al., 2018; Paolino, Ferretti, Villa, & Parisi, 2015; Salem et al., 2018).

Dopamine is a catecholamine neurotransmitter important for various essential neurological functions including aspects of attentional control and sensory processing (M. Happel, Deliano, Handschuh, & Ohl, 2014; M. F. K. Happel, 2016; M. O. Klein et al., 2019; Ott & Nieder, 2019; Zaldivar, Goense, Lowe, Logothetis, & Panzeri, 2018). Dopaminergic dysfunction has long been thought to play a role in inattentive and hyperactive/impulsive symptoms (T. R. Mehta, Monegro, Nene, Fayyaz, & Bollu, 2019; Mogavero, Jager, & Glennon, 2018), and there is also evidence that dopaminergic mechanisms contribute to migraine susceptibility and certain migraine symptoms (Paolino et al., 2015). To date, VSS has not been linked to dopaminergic dysfunction, however it is theoretically plausible given that VSS is thought to share pathophysiological mechanisms with migraine (Schankin, Maniyar, Sprenger, et al., 2014).

7.5.6 Limitations

Our results should be interpreted with awareness of the limitations of the study design. Specifically, the reliance on self-report measures for diagnoses as well as sensory and psychiatric symptoms. Although a screening questionnaire (reviewed by a neurologist) was used to determine whether participants who had not been formally diagnosed met the criteria for VSS, this approach is imperfect and could have resulted in the inclusion of some individuals who do not meet the diagnostic criteria. Migraine and migraine aura classification was also reliant on self-reports.

7.5.7 Conclusion

Our results revealed a high prevalence of inattentive and hyperactive/impulsive symptoms in VSS, that were not associated with self-ratings of VS severity or disruptiveness, and were not explained by comorbid migraine. Participants with higher levels of inattention

and hyperactivity/impulsivity were more likely to experience poorer mental health and reduced sleep quality. This association is likely to be bidirectional, although it is also possible that inattentive and hyperactive/impulsive symptoms, psychiatric measures, and sensory processing changes arise from related underlying pathophysiological processes.

Characterising the prevalence of inattentive and hyperactive/impulsive symptoms in VSS, as well as their association with commonly co-occurring sensory and psychiatric symptoms, is important for several reasons. Regarding the clinical management of VSS, we previously found that fatigue, depression, and anxiety were associated with more negative self-ratings of visual snow, and that many individuals with VSS report that managing psychiatric symptoms improves their perception of visual symptoms (E. J. Solly et al., 2021). Identifying and treating clinical or subclinical levels of inattentive and hyperactive/impulsive symptoms in people with VSS may therefore be crucial not only to directly reduce impairment from these symptoms, but to promote general wellbeing and the ability to cope with sensory disturbances. Diagnosing and treating ADHD when present may also result in improved treatment responses for anxiety and depression, with a reduced risk of future anxiety and depressive disorders (Biederman, Monuteaux, Spencer, Wilens, & Faraone, 2009). Additionally, given the current evidence implicating attentional networks in VSS pathophysiology (Fraser, 2022; F. Puledda, D. Ffytche, et al., 2020; F. Puledda et al., 2021; Solly et al., 2020; Emma J. Solly et al., 2021), describing participant experiences of attentional disturbances, and their relation to VSS onset, is valuable to improve our understanding of attentional changes in VSS.

7.6 Additional results: The association between inattentive and hyperactive/impulsive symptoms and ocular motor metrics in Visual Snow Syndrome

7.6.1 Aim

The following unpublished analyses were conducted to determine whether there was an association between inattentive and hyperactive/impulsive symptom levels (as assessed by the ASRS) and ocular motor metrics in VSS.

7.6.2 Analyses and results

Spearman correlations were conducted to determine whether there was any association between ASRS subscale scores (inattentive and hyperactive/impulsive) and saccadic latencies and error rates across four ocular motor tasks (the prosaccade task, antisaccade task, endogenously cued saccade task, and saccadic Simon task). No correlations were found between ASRS subscale scores and any ocular motor variable.

One-way ANOVAS were run to determine whether mean latencies and error rates differed between VSS participants with clinically significant ASRS scores (VSS + high ADHD symptoms) and those who did not show clinically significant ASRS scores (VSS). Descriptives and ANOVA results are presented in Table 7.7.1.

Table 7.6.1

Descriptives and ANOVA results for ocular motor task variables

	VSS Mean (SD)	VSS + high ADHD symptoms Mean (SD)	*F*	*p*	η2
Prosaccade task	*n* = 33	*n* = 11			
PS latency	199.6 (18.7)	194.6 (19.9)	.586	.455	.013
Antisaccade task	*n* = 30	*n* = 11			
AS latency	340.3 (49.8)	329.1 (32.2)	.521	.474	.012
AS error rate	12.02 (9.5)	20.1 (13.9)	4.859	**.033**	.106
Endogenously cued saccade task	*n* = 26	*n* = 8			
Valid latency	258.2 (41.7)	237.2 (39.7)	1.584	.217	.047
Invalid latency	273.9 (52.2)	247.7 (48.9)	1.588	.217	.047
Anticipatory error rate	4.6 (3.1)	3.99 (3.86)	5.116	**.031**	.138
Saccadic Simon task	*n* = 29	*n* = 11			
Congruent latency	505 (66.5)	508.1 (82.7)	.016	.900	.000
Incongruent latency	498.9 (66.2)	518.3 (82.7)	.520	.475	.013
Error rate	12.1 (6.4)	18.4 (10.7)	5.197	**.028**	.118

Notes. **Bold** indicates significance, p<.05. Abbreviations: VSS = visual snow syndrome, AS = antisaccade.

7.6.3 Discussion

The ASRS (ADHD self-report scale) and ocular motor tasks both broadly assess attention. The ASRS assesses self-perceived impairment from inattentive and hyperactive/impulsive symptoms. In contrast, ocular motor tasks assess objective changes to eye movement characteristics associated with control of visual attention. Given these methods measure different aspects of attention, it is unsurprising that ASRS scores were not found to correlate with ocular motor metrics. However, VSS participants with clinically significant ASRS-S scores were more likely to generate inhibitory errors on the antisaccade task, endogenously cued saccade task, and saccadic Simon task. These results suggest that while the subjective attentional deficits reported by VSS participants do not closely reflect objective ocular motor measures of attention, there is an underlying association.

It could be argued that the increased inhibitory errors exhibited by VSS participants with clinically significant ASRS-S scores suggests a potential confounding influence of inattentive and hyperactive/impulsive traits on ocular motor methods in VSS. Increased inhibitory errors were one of the differences found previously between VSS participants and controls (Solly et al., 2020; Emma J. Solly et al., 2021), and previous ocular motor research in ADHD has reported higher antisaccade and anticipatory error rates (Bittencourt et al., 2013; Caldani et al., 2020; Chamorro, Betz, Philipsen, Kambeitz, & Ettinger, 2021; Coe & Munoz, 2017; Levantini et al., 2020; Maron et al., 2021).

However, it is arguably more likely that ASRS scores and ocular motor inhibitory errors are instead both reflecting underlying deficits in attentional control associated with VSS. Neuroimaging studies have demonstrated aberrant salience and attentional network function in VSS, and attentional dysfunction may represent a core deficit of the condition (Fraser, 2022; Menon & Uddin, 2010).

These analyses, and the conclusions drawn from them are limited by the fact that participants were grouped based on screening scale scores (ASRS scores) rather than formal assessment of ADHD. Hence, it cannot be inferred one way or the other from these results whether ADHD diagnoses and traits impact ocular motor results, or if both are measuring underlying pathophysiological changes to attentional networks. The only conclusion that can be drawn is that there appears to be an association between self-reported impairment from attentional dysfunction and reduced inhibitory control of saccades in VSS.

Chapter Eight: General Discussion

Visual snow syndrome (VSS) is a visual processing disorder that typically presents with a constellation of additional sensory and psychiatric disturbances (Schankin, Maniyar, Digre, et al., 2014). A diagnosis of VSS, and assessment of symptom severity, is currently based solely on self-reports of symptoms, with clinical tests used only to rule out other explanations (Sampatakakis et al., 2022; Traber, Piccirelli, & Michels, 2020). Treating VSS poses a challenge to medical professionals. Most patients do not respond to pharmacological treatments, that even when partially effective are often accompanied by significant side effects (Francesca Puledda, Nicolas Vandenbussche, et al., 2021; van Dongen et al., 2019). Along with a poor understanding of the pathophysiology of VSS, the lack of objective measures of VSS significantly impacts any investigation of therapeutic strategies (Traber et al., 2020).

There were two primary aims of this thesis. The first was to investigate the utility of ocular motor methods in VSS, to determine whether ocular motor characteristics might offer objective markers of dysfunction, and potentially shed light on pathophysiological changes underlying the condition. Eye movement control is both guided by and serves visual processing, relying on overlapping neural structures and pathways (Gegenfurtner, 2016; R. John Leigh & Zee, 2015; Prasad & Galetta, 2011). Previous research into the utility of ocular motor measures in other neurological conditions has shown that ocular motor tasks are highly sensitive to subtle pathological changes (J. Fielding et al., 2015; Tatler, 2013). This aim was addressed using a battery of five saccadic tasks was used, assessing both exogenously triggered and endogenously generated saccadic eye movements.

The second aim of this thesis was to characterise the psychiatric sequalae linked to VSS. Previous research had reported a high prevalence of anxiety and depressive disorder, as well as complaints of fatigue and concentration difficulties (Lauschke et al., 2016; Metzler &

Robertson, 2018; Schankin, Maniyar, Digre, et al., 2014; Yildiz et al., 2019). However, there had not previously been a focused characterisation of the varied psychiatric symptoms reported by VSS patients, and their association with sensory dysfunction. Determining the prevalence of common psychiatric symptoms is important to guide clinical evaluation and management of VSS patients. In addition, assessing how psychiatric disturbances and sensory dysfunction might be associated is important to understand the origin of psychiatric symptoms, which might impact treatment approaches. This aim was addressed using a battery of self-report psychiatric symptom questionnaires assessing sensory disturbances and psychiatric symptom levels (specifically: depression, anxiety, stress, fatigue, sleep quality, depersonalization/derealization, and inattentiveness and hyperactivity/impulsivity).

The relationship between ocular motor measures and psychiatric symptoms was also examined to determine whether psychiatric symptoms influence ocular motor performance. While there is some evidence in healthy and psychiatric populations that psychiatric diagnoses can influence eye movement characteristics (Ainsworth & Garner, 2013; Bafna & Hansen, 2021; Bocca et al., 2014), not all studies have found this to be the case (Todd et al., 2022).

8.1 Summary of results

8.1.1 Migraine comorbidity

It is notable that throughout the experimental chapters presented in this thesis, no significant differences were found between VSS participants with and without migraine in ocular motor performance, or psychiatric symptom presentation. The only difference identified was a higher number of self-reported visual symptoms, on average, in VSS participants with migraine. Previous studies examining comorbid migraine in VSS have similarly reported that participants with migraine report more visual symptoms (F. Puledda,

C. Schankin, et al., 2020; Unal-Cevik & Yildiz, 2015). Based on this, it has been suggested that comorbid migraine is associated with a more severe form of VSS. However, the results of this thesis suggest that although migraine is linked to a higher number of visual symptoms, it may not be associated with a generalised increase in VSS severity.

8.1.2 Summary of experimental chapters

A summary of the key findings from each experimental chapter, as well as an overview of the main conclusions, are presented in Table 8.1.

Table 8.1

Summary of key findings and conclusions from each experimental chapter

Chapter		Key findings	Conclusions
3	Ocular motor measures of visual processing changes in visual snow syndrome	VSS participants generated eye movements more quickly to suddenly appearing targets (shorter prosaccade latencies), and showed difficulty inhibiting unwanted eye movements towards targets (increased antisaccade errors).	OM tasks can demonstrate objective evidence of visual processing changes in VSS. Results are consistent with a stronger capture of visual attention and/or speeded eye movement generation.
4	Eye movement characteristics provide an objective measure of visual processing changes in patients with visual snow syndrome	VSS participants generated faster eye movements towards pre-cued targets, and made more erroneous eye movements on tasks where attention was endogenously directed to non-target locations.	Similar differences in eye movements characteristics are observed in VSS when attention is endogenously oriented rather than exogenously captured, supporting an attentional explanation for findings.
5	The Psychiatric Symptomology of Visual Snow Syndrome	VSS participants report high levels of depression, anxiety, stress, sleep difficulties, fatigue, and depersonalization/derealization, which are associated with reduced quality of life, and poorer self-ratings of visual snow severity.	Psychiatric symptoms are highly prevalent in VSS. Treating them may improve quality of life and coping ability.
6	Eye movement characteristics are not significantly influenced by psychiatric comorbidities in people with visual snow syndrome	Psychiatric symptoms common in VSS (depression, anxiety, stress, sleep difficulties, fatigue, and depersonalization/derealization) did not influence ocular motor task results, with the exception of very severe depression.	Psychiatric symptoms are unlikely to significantly influence ocular motor performance in VSS.
7	The prevalence and impact of inattentive and hyperactive/impulsive symptoms in people with Visual Snow Syndrome	Nearly 40% of VSS participants showed significant levels of inattentiveness and hyperactivity/impulsivity, which were associated with poorer mental health and reduced quality of life.	Inattentive and hyperactive/impulsive symptoms are highly prevalent in VSS, with consequences for mental health and quality of life.

The results presented in Table 8.1 show that ocular motor assessment is sensitive to visual/attentional dysfunction in VSS. Participants with VSS exhibited significant differences in ocular motor control relative to controls: their results were consistent with a faster or stronger capture of visual attention, resulting in shorter latency eye movements and difficulty inhibiting unwanted eye movements. These differences were evident when attention was exogenously captured or endogenously directed, and were not attributable to comorbid psychiatric symptomology.

VSS participants also reported high levels of common psychiatric symptoms, which were associated with reduced quality of life. Interestingly, psychiatric symptom levels and quality of life did not differ between participants with lifelong VSS and later onset VSS, despite participants with lifelong VSS indicating that they found their visual symptoms significantly less disruptive and reporting that they impacted their quality of life less. This discrepancy suggests that psychiatric distress and reduced quality of life linked to VSS cannot be solely explained by the impact of living with symptoms, and are likely to be influenced by the pathophysiological changes underlying VSS.

In the following sections, potential pathophysiological explanations for these findings will be explored, followed by a discussion of the implications of this research for the utility of OM measures in VSS and the clinical management of patients.

8.2 Pathophysiological explanations

8.2.1 Cortical hyperexcitability

Increased cortical hyperexcitability, or hyperresponsiveness of the visual cortex, might explain the changes to ocular motor behaviour exhibited by VSS participants. Evidence from neurophysiological, neuroimaging, and behavioural studies in VSS are consistent with

heightened cortical excitability (O. Eren et al., 2018; Fraser, 2022; McKendrick et al., 2017; Yildiz et al., 2019).

Hyperresponsiveness of visual networks in the cortex might underlie the perception of normally sub-threshold visual stimuli in VSS, resulting in the accelerated detection of visual targets and the consequent speeded generation of ocular motor responses (Fraser, 2022). In support of this explanation, there is evidence to suggest that lower visual thresholds in the general population are associated with faster saccade latencies (Warren, Thurtell, Carroll, & Wall, 2013). The higher number of inhibitory errors generated by VSS participants is likely to reflect a speed/accuracy trade-off, with faster visual orienting resulting in a greater difficulty inhibiting unwanted eye movements (Li et al., 2012).

8.2.2 Brain network dysfunction

Widespread alterations in functional connectivity have been identified in VSS, both within and extending beyond the visual cortex, and implicating large scale brain networks (Aldusary et al., 2020; F. Puledda et al., 2021). Notably, the frontal eye fields (FEF) have been found to show increased connectivity with the primary visual cortex in VSS (F. Puledda et al., 2021). Given the key role of the FEF in control of visual attention and saccade generation (Pierrot-Deseilligny et al., 2004), altered FEF function is likely to be related to altered saccadic behaviour. Increased regional cerebral blood flow has also been revealed in the FEF (Francesca Puledda, Christoph J. Schankin, et al., 2021).

Functional imaging studies in VSS have shown evidence of disruption to various brain networks including pre-cortical visual pathways, the dorsal and ventral attentional networks, the default mode network, and in particular the salience network (Fraser, 2022; F. Puledda et al., 2021). The functions of the salience network are varied, but a primary role is the identification of relevant stimuli to guide goal-directed behaviour, and coordination of

behavioural responses to stimuli (Menon & Uddin, 2010; Peters, Dunlop, & Downar, 2016). Hence, disruption to the salience network may have perceptual consequences (visual symptoms), and behavioural consequences (ocular motor differences). Reduced or inadequate filtering by the salience network might be associated with a speeded saccadic response.

The main cortical nodes of the salience network are the anterior cingulate cortex and anterior insula (Menon & Uddin, 2010; Peters et al., 2016; Uddin, 2015). Altered grey matter volume and functional changes have been reported in each of these areas in VSS (F. Puledda et al., 2021; Francesca Puledda, Christoph J. Schankin, et al., 2021; Schankin, Maniyar, et al., 2020).

Salience network dysfunction might also underlie psychiatric symptom risk in VSS. The salience network integrates and prioritises both external stimuli (sensory information), and internal stimuli relating to cognitive processes, emotional responses, and interceptive awareness (Peters et al., 2016). Impaired functioning of the salience network has been proposed as a transdiagnostic risk factor across a number of common psychiatric and neurological diagnoses including depression, anxiety, chronic pain, insomnia, and epilepsy (McTeague, Goodkind, & Etkin, 2016; Menon & Uddin, 2010; Peters et al., 2016).

Disturbances in salience network function may underly various cognitive and affective symptoms. Overactivity of the insula, for example, has been linked to anxiety and neuroticism, which could reflect an over-attribution of emotional salience to mundane stimuli or events (Menon & Uddin, 2010; Schimmelpfennig, Topczewski, Zajkowski, & Jankowiak-Siuda, 2023). As the salience network is integral for both bodily perception and the emotional valence of stimuli, dysfunction may also be linked to experiences of depersonalization and derealization, which often involve feelings of disconnection from the body and attenuation of emotional responses (Medford et al., 2016; Salami, Andreu-Perez, & Gillmeister, 2020).

8.2.3 Thalamic dysfunction

As discussed throughout this thesis VSS may involve pathological changes to thalamic function, or in networks connecting the thalamus and cortex (J. L. Hepschke et al., 2021; Jenny L. Hepschke et al., 2021a; Lauschke et al., 2016). This hypothesis is compelling given the critical role of thalamocortical networks in sensory processing and attentional control, and the influence of thalamocortical projections on cortical function (McAlonan et al., 2008; Usrey & Alitto, 2015; Zobeiri et al., 2019).

The thalamus acts as a 'gateway' to the cortex, filtering and regulating the flow of incoming sensory information (McAlonan et al., 2008; Usrey & Alitto, 2015). Neuroimaging studies have reported evidence of thalamic dysfunction in VSS, specifically alterations in connectivity between the pulvinar and cortex (F. Puledda et al., 2021). Abnormalities within pre-cortical visual pathways at the level of the thalamus might drive dysfunction in later cortical visual processing networks (Fraser, 2022; F. Puledda et al., 2021). Ocular motor behavioural differences in VSS would therefore be a direct consequence of altered visual information transmission in early thalamic pathways.

Networks connecting the thalamus and cortex feature resonant oscillatory activity. A pathological type of oscillatory activity referred to as thalamocortical dysrhythmia (TCD) has been associated with a number of neuropsychiatric disorders, including depression, as well as migraine and tinnitus, and is speculated to be present in VSS (De Ridder et al., 2015; Jenny L. Hepschke et al., 2021b; Lauschke et al., 2016; Zobeiri et al., 2019). A diverse range of symptoms may be attributed to TCD based on the localisation of dysfunction within thalamocortical networks (J. L. Hepschke et al., 2021; Schulman et al., 2011).

Abnormal thalamocortical function might therefore underlie the perceptual symptoms of VSS, as well as impaired attentional control and changes to saccadic behaviour (Stitt, Zhou, Radtke-Schuller, & Fröhlich, 2018; Zobeiri et al., 2019). Finally, the thalamus plays

an important role in regulation of arousal and the sleep-wake cycle (Zobeiri et al., 2019). Consequently, impairment in thalamic function might result in sleep disturbances, as well as fatigue and concentration difficulties related to difficulty maintaining an appropriate arousal level (Gent, Bassetti, & Adamantidis, 2018; Ward, 2013).

In VSS, it has been proposed that TCD may be triggered by neuronal excitability, or by abnormal functioning of the koniocellular visual pathway (J. L. Hepschke et al., 2021; Lauschke et al., 2016).

8.2.4 Neurotransmitter involvement

Neurotransmitter imbalances have been proposed in VSS pathophysiology, albeit infrequently (Lauschke et al., 2016; F. Puledda, D. Ffytche, et al., 2020). Lauschke et al. (2016) noted that migraine and hallucinogen persisting perception disorder (HPDD), both of which overlap significantly in terms of symptomology with VSS, involve heightened excitation of serotonergic receptors. They proposed that this mechanism could be shared among the disorders. Serotonergic involvement was also proposed by Ozan E. Eren, Schöberl, Schankin, and Straube (2021). It has also been suggested that the risk for developing VSS may be associated with a genetic predisposition towards heightened neuronal excitability, potentially involving genes that regulate glutamatergic excitation. (Lauschke et al., 2016).

The possible involvement of dopamine dysfunction in VSS pathophysiology has not been discussed previously. However, the high prevalence of inattentive and hyperactive/impulsive symptoms reported by VSS participants is arguably consistent with dopaminergic dysfunction (T. R. Mehta et al., 2019; Mogavero et al., 2018). Dopamine is a catecholamine neurotransmitter that plays an integral role in motivation and salience, as well as aspects of cognitive control and sensory processing (Conio et al., 2020; M. O. Klein et al.,

2019; Menon & Uddin, 2010; Ott & Nieder, 2019; Thiele & Bellgrove, 2018). ADHD symptoms (inattentive and hyperactive/impulsive) are often assumed to originate from dopaminergic processes (T. R. Mehta et al., 2019; Mogavero et al., 2018).

Disturbances to dopaminergic signalling in VSS might contribute to alterations in cortical excitability and brain network function outlined previously. Dopamine signalling is reported to strongly influence the activity of large-scale brain networks including the salience network (Conio et al., 2020; McCutcheon et al., 2019), and may modulate the excitability of sensory cortices (M. F. K. Happel, 2016; Zaldivar et al., 2018).

Interestingly, dopaminergic dysfunction might also impact the koniocellular visual pathway, which has been speculated to drive thalamocortical dysfunction in VSS (J. L. Hepschke et al., 2021; Lauschke et al., 2016). The koniocellular pathway derives input from S-cone cells in the retina, which are relatively few in number and appear to be sensitive to alterations in retinal dopamine (Tannock, Banaschewski, & Gold, 2006). Altered S-cone function as a consequence of abnormal retinal dopamine might affect the functioning of the koniocellular visual pathway, with downstream effects on thalamocortical networks (Fraser, 2022; J. L. Hepschke et al., 2021).

Abnormal retinal dopamine transmission has also been associated with reduced contrast sensitivity, i.e. the capacity to differentiate between different light intensities, which is a feature of both VSS and ADHD (Bartgis, Lefler, Hartung, & Thomas, 2009; Brooks et al., 2022; Ozan E. Eren, Straube, et al., 2021; Korshunov, Blakemore, & Trombley, 2020; Ulucan Atas, Ceylan, Dönmez, & Ozel Ozcan, 2020). An interesting finding from Chapter 7, which was not discussed within the chapter due to journal word count constraints, is that VSS participants with significantly high inattentive and hyperactive/impulsive symptoms were more likely to report experiencing nyctalopia (poor night vision), despite no other differences in the prevalence of sensory symptoms. The cause of nyctalopia in VSS is unknown (White et

al., 2018). Hypothetically, reduced contrast sensitivity related to dopaminergic dysfunction could contribute to night vision difficulties.

There has been little research conducted on the association between contrast sensitivity and night vision, but measures of contrast sensitivity have been shown to predict visual acuity in low-light conditions, and night driving performance (Wood & Owens, 2005). Reductions in contrast sensitivity linked to dopamine transmission might have more severe ramifications for night vision in people with VSS than in people with normal vision, as people with VSS are dealing with the additional visual challenge of constant visual static, which is generally described as more intense and intrusive in the dark. In addition, transmission in the retina is also reported to play a direct role in facilitating low-light vision (Herrmann & Arshavsky, 2014; Herrmann et al., 2011).

8.2.5 Pathophysiology summary

The eye movement characteristics and psychiatric symptom profiles of VSS participants are consistent with existing theories of VSS pathophysiology. Importantly, the mechanisms outlined above are not mutually exclusive. Altered functioning of cortical structures and brain networks in VSS may either trigger or represent a consequence of abnormal thalamocortical dynamics, and cortical and subcortical dysfunction may be associated with imbalances in neurotransmitter activity.

8.3 The utility of ocular motor assessment in VSS

The results presented in this thesis are highly promising for the utility of OM assessment in VSS. The differences in OM behaviour exhibited by VSS participants were both consistent across tasks (faster reflexive saccade latencies and more inhibitory errors), and logically consistent with the current knowledge base of VSS pathophysiology. In

addition, OM results were not significantly influenced by co-occurring psychiatric sequalae, with the sole exception of extremely severe depression. Collectively, these findings demonstrate that OM measures are able to detect dysfunction in visual and attentional networks in VSS, that are not a consequence of psychiatric influences on attention.

While the OM behavioural signature of VSS identified in this thesis is not specific enough to function as a diagnostic tool, its potential utility is in assessing the degree of visual processing dysfunction, and in monitoring the progression or improvement of symptom severity over time. If refined, OM assessment could be highly valuable for future investigations of therapeutic strategies. Further research is required to confirm whether OM assessment is able to detect change in symptom severity over time.

Although OM measures offer a number of advantages- namely that they are highly sensitive to neural pathology, brief to administer, and well-tolerated by participants (Broerse, Crawford, & den Boer, 2001)- a possible barrier to their use is access to the equipment and resources needed to record eye movement characteristics and analyse and interpret output.

8.4 Psychiatric sequalae in VSS: implications for patient management

The characterisation of psychiatric symptoms in VSS has important implications for the treatment of patients. Firstly, the high prevalence of all psychiatric symptoms assessed (depression, anxiety, stress, depersonalization and derealization, fatigue, and sleep difficulties), and their association with reduced quality of life, emphasises the importance of a holistic approach to VSS patient management, and of screening for psychological distress. These findings also highlight the severe impact that VSS can have on patient quality of life: social, academic, and occupation functioning can be profoundly affected.

Some psychiatric symptoms (specifically: depersonalization/derealization, anxiety, and fatigue) were found to be associated with poorer self-ratings of visual snow, suggesting

that they are associated with either the severity of visual symptoms, and/or individual tolerance of sensory dysfunction. When asked what factors helped or worsened their symptoms, a number of participants stated that improving their sleep and/or mental and physical health resulted in an improved perception of visual disturbances. Given that many VSS patients find pharmacological treatments intolerable or ineffective, treating psychiatric symptoms therefore offers an avenue through which to improve patient quality of life and coping ability with minimal risk of harm.

The high percentage of VSS participants exhibiting impairing levels of inattentive and hyperactive/impulsive symptomology is consistent with a previous report of elevated ADD and ADHD diagnoses in VSS patients (D. G. Mehta et al., 2021). Screening for and diagnosing ADHD when appropriate can help patients receive adequate and appropriate psychiatric support. However, the results of the follow-up interview in Chapter 7 indicate that caution should be taken if screening for ADHD in the immediate months following VSS onset. Most participants reported an apparently permanent worsening of distractibility and concentration problems following VSS onset. However, two participants described a distinct course of attentional dysfunction, where unusually severe inattentive symptoms were experienced immediately following VSS onset, which then gradually alleviated over a period of months and returning to a nearly 'normal' level.

If suggesting psychiatric treatment as an option to patients, health professionals should be careful not to imply that visual snow is caused by psychiatric dysfunction, which may cause distress and frustration. Negative experiences of having symptoms dismissed as psychological were often related by patients, and are frequently discussed in online VSS forums (lifeoverstuff, 2022). It can be emphasised to patients that psychiatric assessment and treatment are important for coping and general wellbeing: there is no evidence that VSS is psychogenic, or that sensory symptoms can be resolved with psychiatric treatment. Indeed,

the fact that lifelong and later onset VSS participants exhibit equal psychiatric symptom levels suggests the opposite. Increased psychiatric vulnerability appears to be related to VSS pathophysiology.

8.4.5 Sensory dysfunction and psychiatric sequalae

The findings of this thesis support an increased prevalence of various psychiatric symptoms in VSS, but the nature of this association is not clear. In Chapter 5, two main possibilities were raised: first, that psychiatric symptoms could be a consequence of distress related to sensory dysfunction, and second, that psychiatric symptoms and sensory dysfunction might share underlying risk factors and/or pathophysiological mechanisms. However, a third possibility is that sensory processing dysfunction could directly contribute to or cause psychiatric symptoms, and this possibility could have relevance to the psychiatric management of patients.

It should first be acknowledged that limited evidence of an association between sensory and psychiatric symptom severity was found. Some psychiatric measures were found to correlate with self-ratings of VSS and the number of reported visual symptoms (Chapter 5), but these correlations could be due to the influence of psychiatric symptoms on individual's ability to tolerate or 'tune out' symptoms. No correlations were identified between the ocular motor variables in VSS and psychiatric measures (Chapter 6). However, a lack of correlations does not necessarily preclude a causal relationship (Nogueira, Pugnana, Ruggieri, Pedreschi, & Gama, 2022). The absence of correlations could be due to the inadequacy of measures representing VSS severity, as mentioned previously. Previous research on sensory processing patterns and psychiatric symptoms has indicated that sensory dysfunction could causally influence psychiatric symptoms.

In the general population, sensory modulation dysfunction (i.e., an impaired ability to appropriately regulate the experience of sensory information) is linked to difficulties with

sleep initiation, which may be a direct consequence of difficulty filtering out sensory stimuli while attempting to sleep (B. Engel-Yeger et al., 2017; B. Engel-Yeger & Shochat, 2012; Keating, Gaffney, Bramham, & Downes, 2022). Heightened sensory sensitivity and lower registration of sensory stimuli have also been found to be predictive of depression and anxiety (Batya Engel-Yeger et al., 2016; Paquet, Calvet, Lacroix, & Girard, 2022). Although these findings are correlational, a recent review examining sensory processing difficulties and anxiety in participants with autism spectrum disorder concluded the existing evidence is indicative of a causal relationship (Amos, Byrne, Chouinard, & Godber, 2019). Sensory processing difficulties are also linked with experiences of depersonalization/derealization (Jauregui-Renaud et al., 2008; Lopez, 2013), and impaired attentional control (Dellapiazza et al., 2021).

Taking into account how sensory dysfunction might directly contribute to the expression of psychiatric symptoms, and impact life activities, should be an important consideration during treatment (B. Engel-Yeger et al., 2017). Practical strategies and interventions aimed at adjusting aversive or overwhelming sensory experiences to improve a patient's home or work environment might be useful for some individuals. For example, installing dimmer lighting if photophobia is a prominent symptom. One participant involved in this research described how she printed anything she needed to read on coloured paper, as screen use aggravated her visual snow, and the high contrast of black text on a white page caused visual strain.

8.5 Limitations

The main limitations of the research presented in this thesis relate to the recruitment and screening of participants with VSS, and the reliance on self-report measures. Some of the recruitment methods utilised (specifically, public advertising of the study online and over the

television and radio) are likely to result in a bias towards patients with higher levels of concern about their symptoms. VSS participants with a more recent onset of the disorder, and/or higher levels of distress regarding it, may be more likely to search for and volunteer for VSS research. Additionally, not all participants who were recruited remotely had been diagnosed with VSS by a neurologist. While participants were carefully screened using detailed questionnaires to ensure that they met the criteria for VSS, with their responses reviewed by a neurologist, this approach is imperfect and may have resulted in the inclusion of participants who were not appropriate. Migraine diagnoses were also affected by this limitation.

Relying on self-report methodology for assessment of psychiatric symptom levels is inherently limited by participant self-awareness, memory, and willingness to disclose personal information. It is therefore likely that participants may have over- or under-reported various symptoms. There is also the potential that asking participants to indicate symptoms from a list could result in over-reporting. Finally, Chapter 5 would have been strengthened with the inclusion of a large and representative control group to provide normative data, instead of relying on previous large-scale population studies to compare the prevalence of symptoms.

8.6 Conclusion

The research presented in this thesis provides clear evidence that OM assessment can be utilised in VSS as an objective behavioural marker of visual and attentional dysfunction. With further investigation, this OM signature of VSS may represent a method of tracking symptom severity and change over time, potentially as a means of monitoring treatment response.

These results also extend our understanding of attentional changes in VSS, demonstrating a faster and more difficult to control orienting of attention at a behavioural level. While the pathophysiological underpinnings of these changes are not clear, they are consistent with theories of VSS pathophysiology proposing a hyper-responsive cortex, thalamocortical network dysfunction, and/or impaired functioning of the salience network.

Of equal importance, this research illustrates the profound impact that living with VSS can have on an individual's quality of life. The participants in this study exhibited significantly reduced physical and mental health, and a high prevalence of common psychiatric symptoms. This highlights the importance of psychiatric screening and support in the management of VSS patients. Until effective and reliable treatments for sensory symptoms are identified, treating psychiatric symptoms offers an avenue to improve patient quality of life for these often disenfranchised individuals.

Chapter Nine: References

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Appendix A. Visual Snow Syndrome questionnaire and Migraine questionnaire

The following questions are presented below how they appeared to participants in the online survey.

○ = only one response could be selected

□ = multiple responses could be selected

___ = short or long answer, open-ended question

Visual Snow Syndrome questionnaire

Have you ever been diagnosed with visual snow syndrome by a medical professional?

- o Yes
- o No
- o Maybe

Age of onset

___

Please describe your visual snow

___

Below are a list of frequently used words to describe the experience of visual snow. Please select all that apply:

	Yes	**No**
Black and white	○	○
Colourful	○	○
Transparent	○	○
Flashing	○	○
Entire visual field	○	○
Present with eyes open	○	○
Present with eyes closed	○	○

Worse at night/in the dark	○	○

Are there any other words you would use to describe your visual snow?

___

Below are a list of visual symptoms experienced alongside visual snow. Please select all that apply.

	Yes	**No**
Afterimages	○	○
Trailing after moving objects	○	○
Nyctalopia (poor night vision)	○	○
Light is painful/too bright	○	○
Floaters	○	○
Blue field entoptic phenomenon (appearance of tiny bright dots moving quickly along squiggly lines in the visual field, especially when looking into bright blue light such as the sky)	○	○
Self-light of the eyes (sudden bright flashes)	○	○
Halos	○	○

Below are a list of other symptoms commonly experienced alongside visual snow. Please select all that apply.

	Yes	**No**
Tinnitus (Ringing in the ears)	○	○
Tingling in the fingers or toes	○	○
Tremors	○	○

Irritability	○	○
Concentration problems	○	○
Distractibility	○	○
Fatigue/lethargy	○	○
Depersonalisation (detachment within the self, regarding one's mind or body, or being a detached observer of oneself)	○	○
Derealisation (alteration in the perception or experience of the external world so that it seems unreal)	○	○
Problems sleeping	○	○
Neck pain	○	○
Dizziness	○	○

Are there any other symptoms you experience that you associate with your visual snow?

___

Please list any medications you are currently taking, and if they have resulted in any improvements.

___

Select any tests or procedures you have undergone in relation to your visual snow.

	Yes	**No**
MRI	○	○
CT	○	○
EEG	○	○
ERG	○	○

VEP	○	○
Ophthalmic examinations	○	○

Did any of these tests yield significant results?

___

Have you used illicit drugs in the past?

- Yes
- No
- Prefer not to answer

If yes, what drugs?

___

Did you take drugs before or after the onset of visual snow?

- Before visual snow onset
- After visual snow onset
- Not applicable

If you took drugs before the onset of visual snow, how long after taking the drugs did your visual snow start?

- Within hours of taking the drug
- Within a day of taking the drug
- Within 2-3 days of taking the drug
- Within a week of taking the drug
- Within 2-3 weeks of taking the drug
- Within a month of taking the drug
- More than a month after taking the drug
- Not applicable

Do you suffer from migraines?

- o Yes – migraine with aura
- o Yes – migraine without aura
- o No

Did you suffer from migraines before the onset of visual snow?

- o Yes
- o No
- o Not applicable

Do you have a family history of any of the following? (Please select all that apply)

- □ Visual snow
- □ Migraine
- □ Migraine with aura
- □ None of the above

Whom in your family suffered from any of these conditions (e.g. maternal grandmother suffered from migraine)

___

Has your visual snow worsened since onset?

- o Yes
- o No
- o Maybe

How would you describe it getting worse?

- o Stepwise worsening – e.g. woke up one morning and visual snow was noticeably worse
- o Progressive worsening – e.g. gradual increase in visual snow
- o Combination of both
- o Not sure

- Not applicable; visual snow has been constant since onset

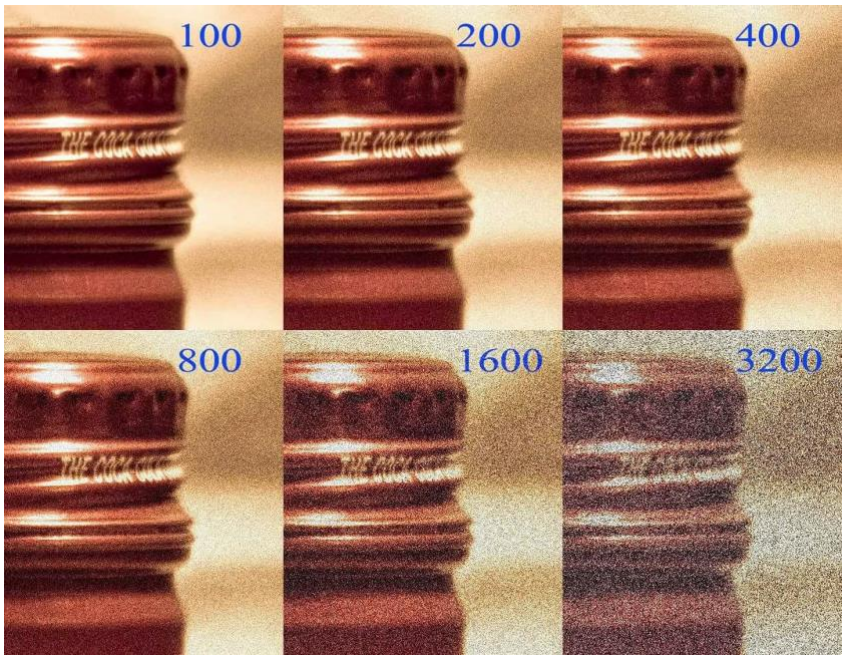
Has anything improved your visual snow? If so, was this improvement permanent or temporary

___

Are there any activities that are impacted due to your visual snow? If so, what do you do as a result (e.g. avoid activity or do it less often)

___

On a scale of 1 to 6, how intense would you describe your visual snow? (Please refer to picture as a guide)



	1	2	3	4	5	6	
Low intensity (Snow is not very dense or noticeable)	○	○	○	○	○	○	Extreme intensity (Snow is very dense and highly noticeable)

On a scale of 1-7, how disruptive is your visual snow?

On a scale of 1 to 7, how has your visual snow impacted your quality of life?

Are there any other comments you would like to make in regards to your visual snow?

___

Migraine questionnaire

How frequently do you experience migraines?

- More than once a week
- Once a week
- Once a fortnight
- Once a month
- Once every few months
- Less often than once every few months

How long does a migraine typically last?

- Less than an hour
- 1-3 hours
- Less than a day
- 1-2 days
- Less than a week
- More than a week

Do you take any ongoing medication for migraines (e.g. preventative medication)? If so, what medication?

___

What medication do you take when experience migraines and are they helpful?

___

Do you experience visual area along with migraines?

- Yes
- No
- Maybe

Please describe what you see when you experience an aura

___

How frequently do you experience aura along with migraine?

- Always
- Most of the time
- Some of the time
- Rarely
- Never
- Not applicable

In relation to a migraine, when do you experience aura?

- More than an hour before a migraine
- Hour before a migraine
- Beginning of a migraine
- During a migraine
- After a migraine
- Not applicable

How long do the auras typically last?

- Less than 5 minutes
- 5-30 minutes
- 30-60 minutes
- 1-2 hours
- More than 2 hours but less than a day
- A day
- More than a day
- Not applicable

Have you ever experienced an aura without a migraine?

- Yes
- No

- Maybe

Below are a list of symptoms commonly experienced alongside migraine. Please select all that apply.

	Yes	**No**
Sensitivity to light	○	○
Sensitivity to noise	○	○
Vomiting	○	○
Nausea	○	○
Blurred vision	○	○
Dizziness	○	○

Do you experience any other symptoms with your migraine?

___