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Visual contrast perception in visual snow syndrome reveals abnormal neural gain but not neural noise

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Abstract

Visual snow syndrome is a neurological condition characterised by a persistent visual disturbance, visual snow, in conjunction with additional visual symptoms. Cortical hyperexcitability is a potential pathophysiological mechanism, which could be explained by increased gain in neural responses to visual input. Alternatively, neural noise in the visual pathway could be abnormally elevated. We assessed these two potential competing neural mechanisms in our studies of visual contrast perception. Cortical hyperexcitation also occurs in migraine, which commonly co-occurs with visual snow syndrome. Therefore, to determine whether the effect of visual snow syndrome can be distinguished from interictal migraine, we recruited four participant groups: controls, migraine alone, visual snow syndrome alone, visual snow syndrome with migraine. In the first experiment, we estimated internal noise in 20 controls, 21 migraine participants, 32 visual snow syndrome participants (16 with migraine) using a luminance increment detection task. In the second experiment, we estimated neural contrast gain in 21 controls, 22 migraine participants, 35 visual snow syndrome participants (16 with migraine) using tasks assessing sensitivity to changes in contrast from a reference. Contrast gain and sensitivity were measured for the putative parvocellular and ON and OFF magnocellular pathways, respectively. We found that luminance increment thresholds and internal noise estimates were normal in both visual snow syndrome and migraine. Contrast gain measures for putative parvocellular processing and contrast sensitivity for putative OFF magnocellular processing were abnormally increased in visual snow syndrome, regardless of migraine status. Therefore, our results indicate that visual snow syndrome is characterised by increased neural contrast gain but not abnormal neural noise within the targeted pathways.

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Abbreviations: VSS=visual snow syndrome

Introduction

Visual snow syndrome (VSS) is a relatively newly described neurological condition. The defining symptom of VSS is visual snow, a continuous visual disturbance that consists of tiny, dynamic dots filling the entire visual field.[1] A diagnosis of VSS requires at least two additional visual symptoms of palinopsia, enhanced entoptic phenomena, nyctalopia or photophobia. [1] VSS is also associated with increased visual discomfort and distortions elicited by aversive stimuli such as patterns and flicker.[2] The neural basis of this pattern of symptoms is unknown. One proposal is that the visual cortex is hyperexcitable due to an imbalance in cortical excitation and inhibition.[3, 4]

Theoretically, the increased neural responses of a hyperexcitable visual cortex could indicate either elevated neural noise or increased neural gain.[5] The visual snow percept potentially corresponds to spontaneous neural activity in the visual system (neural noise).[6-8] Neural noise is typically subliminal but perceptible visual snow could arise from elevated levels of neural noise. Elevated neural noise could also contribute to a heightened awareness of the usually subliminal stimuli, through stochastic resonance,[9] giving rise to perceptible entoptic phenomena.[10] Additionally, symptoms of visual discomfort suggest a hypersensitivity to visual stimuli, which could result from increased neural responses due to elevated neural noise. An alternate explanation is increased neural gain, which describes the situation where a given visual input elicits a stronger neural response. By amplifying responses to external stimuli, increased neural gain could lead to visual hypersensitivity and enhanced entoptic phenomena. Therefore, we propose that increased neural noise and increased neural gain are competing hypotheses regarding the neural basis of symptoms in VSS.

Here we perform a novel investigation with the primary aim of distinguishing between these two competing mechanisms of cortical hyperexcitability, increased neural noise and increased neural gain. We specifically examined visual contrast perception, since preliminary research indicates that it is abnormal in VSS.[4] To achieve our aim, we used well-established psychophysical methods to estimate neural noise and neural gain. Additionally, we included a questionnaire on visual discomfort[11] to assess whether self-reported visual hypersensitivity in VSS was associated with either increased neural noise or neural gain.

Our secondary aim was to distinguish the effects of VSS from that of migraine. Migraine is a common comorbid condition in people with VSS.[1, 12] Comorbid migraine is associated with a higher prevalence of additional visual symptoms in VSS.[12, 13] Significantly, cortical hyperexcitability or hyperresponsivity is also implicated in migraine pathophysiology,[14, 15] and photophobia[16-18] and visual discomfort[11, 18-20] occur in interictal migraine. Therefore,

neural mechanisms present in interictal migraine likely overlap with and influence VSS pathophysiology. However, studies have typically not considered healthy controls, people with migraine alone, people with VSS alone and people with both VSS and migraine as four distinct groups. In this study, we investigated how VSS, migraine and the co-occurrence of both conditions affected neural noise and neural gain.

Firstly, we hypothesised that cortical hyperexcitability in VSS could reflect elevated spontaneous neural activity. We tested this hypothesis by evaluating how contrast perception in VSS is limited by internal noise in the visual system, which acts like random fluctuations in physical luminance.[21, 22] Internal noise consists of a baseline level that reflects spontaneous neural activity (additive noise) and an additional component that increases in amplitude with the level of visual input (multiplicative noise).[23] Elevated thresholds arise from increased noise, whether internal to the visual system or created externally by randomly varying the luminance of a display.[23] Our previous research found elevated luminance increment thresholds in VSS in both low and high external noise.[4] An increase in thresholds independent of the external noise level potentially indicates an increase in the baseline level of internal noise (i.e., additive noise). However, interictal migraine is associated with increased multiplicative noise, which produces larger increases in internal noise and thresholds in high external noise.[24, 25] Consequently, comorbid migraine may have contributed to our previous finding of elevated thresholds in VSS in high external noise. Here, we explore luminance increment detection in more detail by a) measuring thresholds over a wider external noise range b) directly estimating internal noise and c) considering the effect of comorbid migraine.

Alternatively, we hypothesised that cortical hyperexcitability in VSS could indicate increased neural gain. Correspondingly, in our second experiment, we investigated whether neural gain was increased for the detection of visual contrast. We used established methods that relate

behavioural contrast discrimination thresholds to the contrast gain of the parvocellular (P) and magnocellular (M) visual pathways.[26] These are the main pathways transmitting information about different visual attributes from the retina to the primary visual cortex.[27] We propose that VSS symptomatology could indicate neural hyperexcitability in either pathway. VSS may primarly affect the P pathway, which has superior spatial resolution,[28] since visual snow consists of fine-grained static. Alternatively, the dynamic nature of visual snow may reflect greater involvement of the M pathway, which is the predominant pathway for encoding rapid temporal information.[28, 29] Neurophysiologically, the M and P pathways are further subdivided into ON and OFF sub-pathways that are sensitive to increments (targets that are lighter than their background) and decrements (targets that are darker than their background), respectively.[30] Visual snow may affect both subdivisions, since the static is commonly perceived as white on black backgrounds and black on white backgrounds.[12] Hence, our experiment was designed to assess neural gain in each of these neural visual pathways.

In summary, this study implemented a structured approach to investigating VSS pathophysiology, guided by the nature of its symptoms and controlling for comorbid migraine. Our experiments tested the following hypotheses: (H1) neural noise is increased in VSS or (H2) neural gain is increased in VSS. We hypothesised that neural gain could be increased in either the P pathway (H2a), M pathway (H2b) or its ON (H2c) or OFF (H2d) subdivisions.

Materials and methods

Participants

We recruited participants with migraine alone (migraine without VSS), VSS alone (VSS without migraine), both VSS and migraine (VSS with migraine) and neither condition (controls). In this cross-sectional study, participants were recruited from a database of previous study participants and via advertisement within the University of Melbourne from November 2018 to February 2020. A sample size of 15 to 20 participants per group was chosen based on previous studies that identified perceptual differences between controls and VSS[4] and controls and migraneurs.[24, 31] The relevant diagnostic criteria were used to classify participants with VSS[1] and migraine.[32] Supplementary Table 1 provides the clinical history of VSS participants. Controls were excluded if they reported unexplained headaches, headaches with any clinical features of migraine or more than four headaches a year. Controls and participants with migraine alone were excluded if they consumed medications known to affect visual or cognitive function, including medication for migraine prophylaxis. VSS participants were not excluded if taking neuroactive medications (see Supplementary Table 1). Participants with migraine were tested at least three days post migraine and follow up noted if a migraine occurred within 48 hours of testing.

As this study investigated the visual pathways, ophthalmic inclusion criteria were emphasised. All participants were required to have best corrected visual acuity of 6/7.5 or better, refractive error no more than ± 5.00 D sphere and 2.00 D astigmatism and no history of ocular or health conditions known to affect vision. Normal ocular health was determined by clinical examination (pupil responses, ocular motility, slit lamp biomicroscopy, ophthalmoscopy) and optical coherence tomography of the disc and macula (Spectralis, Heidelberg Engineering, Heidelberg, Germany). If participants failed a suprathreshold

screening of the visual field using the Glaucoma Screening Test[33] on the Octopus 600 perimeter (Haag-Streit Diagnostics, Koeniz, Switzerland), 24-2 full threshold visual fields were performed (Humphrey Field Analyser, Carl Zeiss Meditec, Dublin, CA). Minor visual field defects are known to occur between migraine attacks[34-37] but visual field loss indicative of ophthalmic or neurologic disease was a basis for exclusion. We excluded six potential participants (five controls, one migraine) who did not meet ophthalmic inclusion criteria upon the screening eye examination.

All protocols were approved by the University of Melbourne Human Research Ethics Committee and participants provided written informed consent in accordance with the Declaration of Helsinki prior to any formal testing. Participants completed two experiments, one to test neural noise and one to test neural contrast gain, over two experimental sessions. Participants were invited to participate in both experimental sessions, but due to logistical constraints some participants only attended one session (see below). Each session was approximately two hours long. Participants were reimbursed with a $20 gift voucher for each session to assist with travel costs incurred.

Visual discomfort questionnaire

To assess self-reported hypersensitivity to visual stimuli, all participants completed a questionnaire that assessed the frequency of discomfort, headache and migraine induced by viewing nine aversive visual stimuli (encompassing bright lights, glare, flicker, colour and contrasting patterns, see He et al.[11]). For each questionnaire category (discomfort, headache, migraine) responses were summed to calculate a discomfort trigger score, headache trigger score and migraine trigger score.[11]

General set up

Two experiments were conducted (described in detail below) that involved participants viewing visual stimuli on a calibrated monitor and responding via button press to indicate what they had seen. Stimuli were generated on the ViSaGe system (Cambridge Research Systems, Cambridge, UK) using software custom written in MatLab R2008a (Mathworks, Natick, MA) running on a Paragon computer. Stimuli were displayed on a Sony Trinitron G520 monitor (Sony, Tokyo, Japan) which was regularly calibrated using an OptiCal luminance meter (Cambridge Research Systems, Cambridge, UK). Participants viewed the monitor binocularly from a distance of 65 cm with appropriate refractive correction. Head position was maintained using a chin rest. The experiment was conducted in a dim room. A button box (CB6, Cambridge Research Systems) was used to collect responses.

Internal noise task

This experiment tested the hypothesis that neural noise is elevated in VSS. Twenty control (mean age 26, 19-45 years), 21 migraine without VSS (mean age 29, 18-42 years; 11 with aura), 16 VSS without migraine (mean age 28, 19-42 years) and 16 VSS with migraine (mean age 30, 20-43; 11 with aura) participants completed the task. Data derived from one additional migraine participant was excluded due to poor quality. One migraine participant did not complete the no noise condition (see below) as they did not attend all sessions.

Stimuli and procedure

The task consisted of multiple trials in which participants chose which of two squares contained a luminance increment. We measured two aspects of performance – response accuracy (whether correct or incorrect for that presentation) and response consistency (whether the choice varied across multiple presentations of the same stimulus). We used response accuracy to determine thresholds (the minimum luminance increment required for

reliable detection) and response consistency to estimate internal noise (see task analysis below), since inconsistent responses to identical stimuli reflect internal noise.[38]

Experimental stimuli were displayed on a monitor with a resolution of 1024 x 768 pixels, frame rate of 100 Hz and maximum luminance of 112 cd/m^2. The 4° x 4° squares were presented side by side for 1 second with a centre-to-centre separation of 6.9°. On each trial, either the left or right square contained a 1.4° diameter circular disc (the luminance increment). Both squares contained the same background, which varied with experimental condition (Fig. 1A). In the no external noise condition, the squares were filled with a uniform grey background with a luminance of 35 cd/m^2. In the low and high external noise conditions, the squares were filled with static luminance noise with a pixel size of 5.7' x 5.7'. Left and right squares contained identical luminance noise, which we varied on each trial by randomly drawing the luminance of each pixel from a Gaussian distribution with a mean of 0 and standard deviation of 4.375 cd/m^2 (0.125 of the background luminance) and 17.5 cd/m^2 (0.5 of the background luminance) for the low and high noise conditions, respectively.

The task was performed for each experimental condition separately using the same procedure, which was based on the study by Webster et al.[24] This procedure entailed first obtaining a preliminary estimate of each participant's threshold, since thresholds can vary markedly between individuals. We used a 3-1 staircase procedure, in which luminance was decreased upon three consecutive correct responses and increased upon one incorrect response. For each staircase, the threshold was calculated as the mean of the last eight out of twelve reversals in staircase direction. The preliminary threshold estimate was the average of two repeats of the staircase.

Subsequently, we formally measured thresholds using a method of constant stimuli in which the luminance increment was presented at four different stimulus levels. The levels were

individually tailored for each participant, with two below (0.7406 and 0.8516 times) and two above (1.189 and 1.413 times) their preliminary threshold estimate from the staircase procedure. There were 40 presentations per stimulus level, resulting in a total of 160 stimuli (40 presentations x 4 levels). The participant's response was recorded for each presentation.

We assessed response consistency using an N-pass procedure,[39] in which the method of constant stimuli was repeated three times using identical stimuli. For each participant, the stimuli (the 160 combinations of luminance increment and randomly generated external noise) used in the first run were saved and presented in subsequent repeats but in a different order.

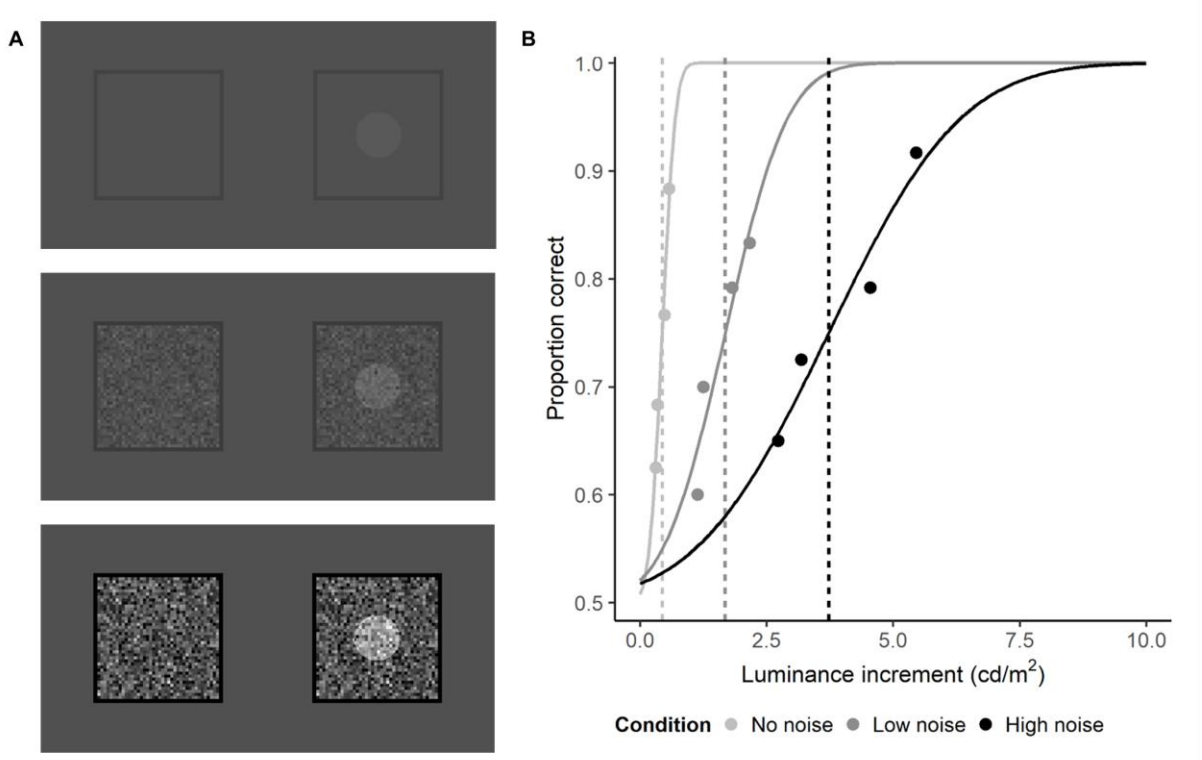


Figure 1. Internal noise task. (A) Illustration of stimuli for the no noise condition (top), low noise condition (middle), high noise condition (bottom). Participants chose the square with the circular luminance increment. In these examples, the right square contains the luminance increment. **(B)** Data (circles) and fitted psychometric functions

(lines) for an example control participant for the luminance increment detection task under no noise (light grey), low noise (dark grey) and high noise (black) conditions. The dashed lines indicate the thresholds.

Task analysis

For each condition, we calculated the final luminance increment thresholds by combining the data on response accuracy from the three repeats of the method of constant stimuli and fitting a psychometric function[40]:

$$\Psi(x) = \gamma + (1 - \gamma - \lambda)G(x, \mu, \sigma) \qquad (1)$$

which describes the well-known sigmoidal change in performance (proportion correct responses) as a function of stimulus level (x). $G(x, \mu, \sigma)$ is a cumulative Gaussian with mean μ and standard deviation σ. The guess rate (γ) and lapse rate (λ) were 0.5 and 0, respectively, as performance runs from 0.5 to 1 on this task.[24] Psychometric functions were fit using the R package quickpsy[41] and R (Version 3.5.1, 2018, the R Foundation, Vienna, Austria) and RStudio (Version 1.1.463, 2018, RStudio Inc, Boston, MA) software. The threshold was taken as the mean of the psychometric function, which equates to the luminance increment (the difference in luminance between the circular disc and the average luminance of the background) required for 75% correct performance (see Fig. 1B).

Next, for each condition, we assessed response consistency separately for each participant. The N-pass procedure provides information on response consistency across the three task repeats that can be used to estimate internal noise (see Levi et al.[39] for a detailed formal explanation). Briefly, the variability in a participant's responses is defined as the sum of consistent sources (determined by a stimulus dependent response to the combination of the specific external noise and signal in a particular trial) and random sources (i.e., internal noise). The ratio of consistent to total response variance, q^2, may be estimated by correlating

the observer's responses for each pair of task repeats (repeat 1 with repeat 2, repeat 1 with repeat 3 and repeat 2 with repeat 3) and taking the average of the Pearson correlation coefficient.[39] This allows derivation of an internal noise estimate, expressed as the ratio of random to total noise, 1-q.

Contrast gain task

This experiment tested the hypothesis that neural gain is elevated in VSS. Twenty-one control (mean age 26, 19-45 years), 22 migraine without VSS (mean age 30, 18-45 years; 10 with aura), 19 VSS without migraine (mean age 27, 19-42 years) and 16 VSS with migraine (mean age 30, 20-43; 11 with aura) participants completed this experiment. Of these participants, 14 control, 20 migraine without VSS, 16 VSS without migraine and 15 VSS with migraine also took part in the internal noise task. A complete set of data for all three contrast gain tasks (see below) was not obtained for some participants, either due to difficulty completing the requirements of the task (pedestal-delta-pedestal paradigm: one migraine without VSS (increment and decrement), one VSS with migraine (decrement), pulsed pedestal paradigm: one control) or non-attendance of a testing session (one VSS without migraine and one VSS with migraine, see Supplementary Table 1).

Stimuli and procedure

We measured contrast discrimination thresholds, that is the ability to detect a change in contrast from a reference, by asking participants to choose the square with a different brightness in an array of four squares. We were interested in how steeply contrast discrimination thresholds increased with increasing reference contrast, which is determined by contrast gain. Pokorny and Smith[26] designed contrast discrimination paradigms that selectively target the M and P pathways, revealing the underlying neural contrast responses of each pathway though modelling (see model fitting below).

Experimental stimuli were displayed on a monitor with a resolution of 1264 x 947 pixels, a frame rate of 75 Hz and a maximum luminance of 112 cd/m^2. The four-square array was presented in central vision on a background of 30 cd/m^2, with each square subtending 1° and separated by 9' (Fig. 2A). In all tasks, participants viewed an adaption stimulus for 1 minute, followed by a series of 27 ms trial stimuli. In each trial, one square in the array (the test square) was randomly selected to differ from the fixed luminance of the others (the reference).

The first task used the pulsed pedestal paradigm, which assesses the gradual rise in thresholds with increasing reference contrast that is characteristic of the P pathway with its low contrast gain.[26] Participants first adapted to the background luminance. In each trial, three squares of the array were presented at the reference luminance (the pedestal) and the luminance of the test square equalled the pedestal plus a variable luminance increment (Fig. 2A). Participants were instructed to choose the brighter square. Contrast discrimination thresholds were measured for four widely spaced pedestals of 38, 44.3, 51.5 and 60 cd/m^2 (corresponding to pedestal contrasts 0.27, 0.48, 0.72 and 1).

We also used the pedestal-delta-pedestal paradigm, which assesses the steep rise in thresholds with increasing reference contrast that is characteristic of the M pathway with its high contrast gain.[26] There were two tasks, as thresholds were measured separately for discrimination of increments and decrements (Fig. 2A), which reflect processing in the ON and OFF pathways, respectively.[42, 43] Participants first adapted to a four-square array with a pedestal luminance of 38 cd/m^2. In each trial, three squares briefly increased in luminance by a fixed amount (the delta-pedestal) and the luminance of the test square briefly changed by a different amount. When measuring increment thresholds, the test square increased in luminance from the delta-pedestal by a variable increment. Participants identified the brightest square. When measuring decrement thresholds, the test square decreased in

luminance from the delta-pedestal by a variable decrement. Participants identified the darkest square. Contrast discrimination thresholds were measured for four closely spaced pedestal-delta-pedestals of 38.9, 39.8, 40.7 and 41.7 cd/m^2 (corresponding to contrasts 0.024, 0.047, 0.071 and 0.097).

For all tasks, thresholds were measured by systematically varying the luminance of the test square according to the participant's responses using two interleaved 3-1 staircases that converged on 79% correct performance.[44] The increment or decrement was decreased by 25% upon three consecutive correct responses and increased by 25% upon one incorrect response. The threshold was calculated as the mean of the last four out of six reversals for each staircase, and then averaged for the two staircases.

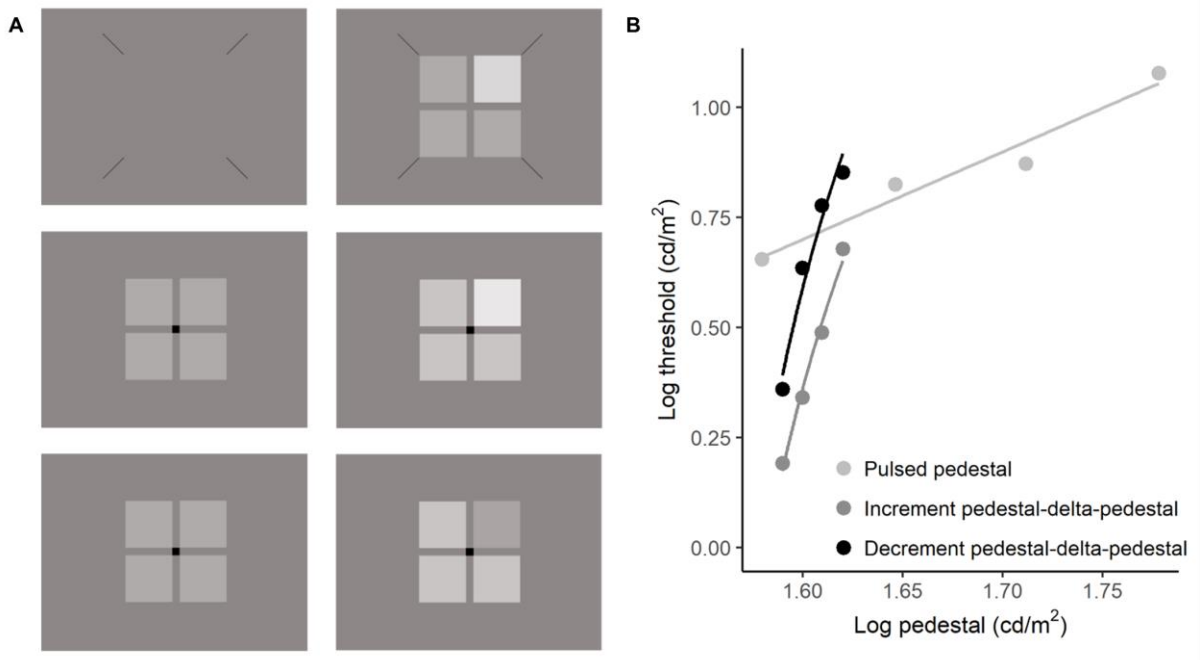


Figure 2. Contrast gain task. (A) Illustration of the adaptation stimulus (left) and an example trial stimulus (right) for the pulsed pedestal paradigm (top), increment pedestal-delta-pedestal paradigm (middle) and decrement pedestal-delta-pedestal paradigm (bottom). In these examples, the top right square differs in luminance from the other three squares in the array. Participants were instructed to choose the

location of either the brightest square or the darkest square. **(B)** Data (circles) and fitted models (lines) for an example control participant for the pulsed pedestal (light grey), increment (dark grey) and decrement (black) pedestal-delta-pedestal tasks.

Model fitting

The pedestal paradigms provide a measure of neural contrast gain by assessing, within each individual, how steeply contrast discrimination thresholds rise with increasing reference contrast. As we were interested in inferring group differences in neural processing, group mean contrast discrimination thresholds were not the focus of our analysis but are provided in Supplementary Fig. 1-3 for completeness.

We hypothesised that contrast gain is increased in VSS, which would manifest as a steeper rise in thresholds with increasing pedestal contrast. We evaluated our hypothesis by relating contrast discrimination thresholds, expressed as the difference in luminance ΔL, to neuronal contrast responses with a model[26, 45] simplified to include fewer free parameters as recommended when fitting to a limited number of data points[46]:

$$\log \Delta L = K + \log[(C_{sat} + C)^2] - \log[C_{sat}] \qquad (2)$$

where C is the reference contrast, K is a vertical scaling parameter and C_{sat} is the semisaturation constant, the contrast for which the neural response is half the maximum.

For each participant, we fit the model to their contrast discrimination thresholds separately for the three tasks (pulsed pedestal, increment and decrement pedestal-delta-pedestal paradigms) using a least-squares criterion (see Fig. 2B). Fitting the model separately for each participant, rather than fitting a single model to group mean thresholds, accounts for inter-individual threshold variability.

To evaluate our hypothesis of altered contrast gain in VSS, the model parameter of interest was C_{sat}. Smaller C_{sat} values indicate a steeper rise in contrast discrimination thresholds with reference contrast and therefore higher contrast gain. Of secondary interest, the model parameter K provided a measure of contrast sensitivity. Lower K values indicate lower contrast discrimination thresholds and therefore greater contrast sensitivity.

Statistical analysis

Statistical analyses were conducted in SPSS Statistics 26 (IBM, Armonk, NY, US). For the contrast gain and internal noise tasks, the four participant groups were accounted for by two factors: migraine (present or absent) and VSS (present or absent). Luminance increment thresholds (cd/m^2) were log transformed for analysis because the variance differed with external noise level. Log thresholds and internal noise estimates were analysed separately by fitting a linear mixed model with fixed effects of condition (the three external noise levels), migraine and VSS and a random intercept for each participant. Models were fit using restricted maximum likelihood estimation with Kenward-Roger approximation for degrees of freedom. For each of the three tasks (pulsed pedestal, increment and decrement pedestal-delta-pedestal paradigms), contrast gain (C_{sat}) and sensitivity (K) were analysed separately using a two-way ANOVA with VSS and migraine as factors. Simple effect analysis was performed if the interaction between migraine and VSS was statistically significant. Visual discomfort questionnaire scores were compared between groups as follows: discomfort trigger scores and headache trigger scores were analysed using the Kruskal-Wallis test and migraine trigger scores were analysed using the Mann-Whitney U test. Discomfort trigger scores were correlated with the main experimental measures, internal noise estimates and C_{sat}, using Spearman rank correlation. A migraine within 48 hours of testing was reported by one VSS participant on both tasks, one VSS participant on the contrast gain task alone, one

migraine participant on the contrast gain task alone and one migraine participant on the internal noise task alone. Reported analyses include the data from these participants, as their exclusion from the analysis did not affect the results (see Supplementary Tables 2-3).

Data availability

Data available upon reasonable request.

Results

Internal noise task

Luminance increment thresholds are normal in VSS

Log thresholds were analysed using a linear mixed model, which revealed that thresholds increased with external noise level ($F(2,137.19)=2201.65$, $P<0.001$; Fig. 3). However, there was no effect of VSS ($F(1,69)=0.086$, $P=0.77$). Additionally, comorbid migraine did not influence the performance of participants with VSS. There was no overall effect of migraine ($F(1,69)=0.39$, $P=0.53$) or interaction between VSS and migraine ($F(1,69)=2.69$, $P=0.11$). Thresholds were not selectively affected at a particular external noise level due to VSS (no VSS x condition interaction: $F(2,137.19)=2.14$, $P=0.12$; Fig. 3A), migraine (no migraine x condition interaction: $F(2,137.19)=0.78$, $P=0.46$) or an interaction between diagnoses (no migraine x VSS x condition interaction: $F(2,137.19)=2.27$, $P=0.11$; Fig. 3B-D).

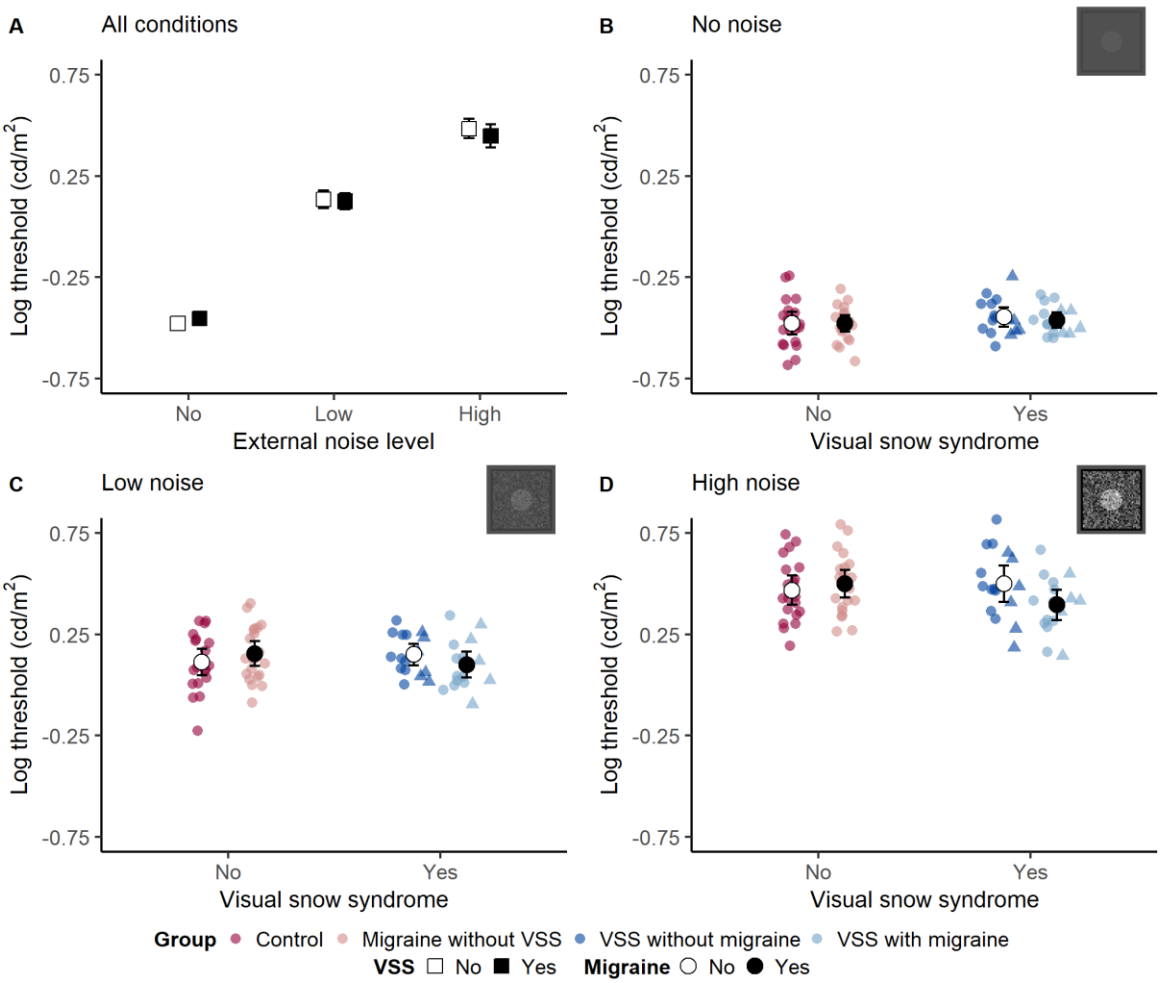


Figure 3. Luminance increment thresholds. (A) All conditions **(B)** No noise condition **(C)** Low noise condition **(D)** High noise condition. Mean (large open and closed symbols) and 95% confidence intervals (error bars) of log thresholds are shown. Panel A compares those with VSS (filled squares) and without VSS (open squares), regardless of migraine. Panels B-D show the same data, illustrating the interaction between VSS (indicated on the x axis) and migraine (large open circles indicate groups without migraine, filled circles groups with migraine) for each condition. Small circles are individual data coloured according to group as either controls (red), migraine without VSS (pink), VSS without migraine (dark blue) or VSS with migraine (light blue). Participants taking neuroactive medication are shown as triangles.

Internal noise estimates are normal in VSS

Contrary to our hypothesis (H1), the linear mixed model analysing internal noise estimates indicated that neural noise is normal in VSS. Firstly, VSS was not associated with a generalised increase in internal noise ($F(1, 67.40)=0.097$, $P=0.76$; see Fig. 4A), contrary to our expectation that additive noise would be increased. There was also no effect of migraine ($F(1,67.40)=0.78$, $P=0.38$) or interaction between migraine and VSS ($F(1,67.40)=0.002$, $P=0.97$), indicating that additive noise in VSS was unaffected by comorbid migraine.

Secondly, our results indicated that multiplicative noise levels were normal in individuals with VSS, including individuals with both VSS and migraine. Multiplicative noise results in an increase in internal noise estimates with external noise level, revealed here as a significant effect of condition ($F(2,135.89)=6.18$, $P=0.003$). Bonferroni corrected pairwise comparisons showed a small increase in internal noise estimates in high compared to no external noise ($M_D=0.041$ [0.013-0.069], $P=0.002$). However, the level of multiplicative noise was not affected by VSS (no VSS x condition interaction: $F(2,135.89)=1.30$, $P=0.28$; Fig. 4A), migraine (no migraine x condition interaction: $F(2,135.89)=2.63$, $P=0.076$) or an interaction between diagnoses (no migraine x VSS x condition interaction: $F(2,135.89)=1.15$, $P=0.32$; Fig. 4B-D).

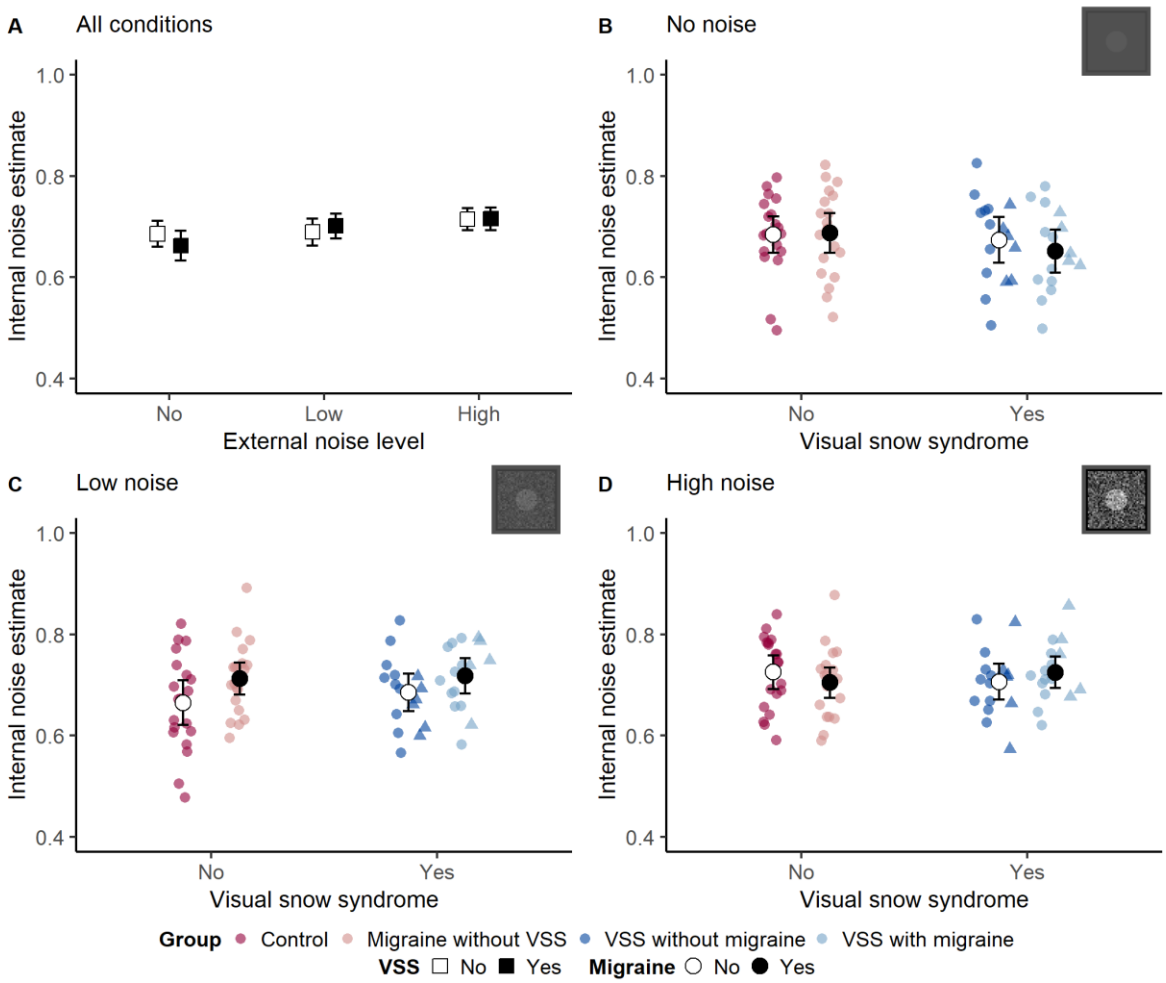


Figure 4. Internal noise estimates. (A) All conditions **(B)** No noise condition **(C)** Low noise condition **(D)** High noise condition. Mean (large open and closed symbols) and 95% confidence intervals (error bars) of internal noise estimates are shown, along with individual data (small, coloured circles). Participants taking neuroactive medication are shown as triangles. As in Fig. 3 (see previous caption), Panel A compares participants with VSS and without VSS regardless of migraine and panels B-D show the same data, examining the interaction between VSS and migraine for each condition. Internal noise estimates are the ratio of random noise to total noise and are expressed in arbitrary units.

Contrast gain task

Contrast gain is increased in the parvocellular (P) but not the magnocellular (M) pathway in VSS

To test our hypothesis (H2) that neural contrast gain is increased in VSS, we assessed whether the semisaturation constant (C_{sat}) was smaller. C_{sat} values were larger for the pulsed pedestal task (Figure 5A-B) than for the pedestal-delta-pedestal tasks (Figure 5C-F), consistent with the lower contrast gain of the P pathway. The different task configurations (pulsed pedestal, increment and decrement pedestal-delta-pedestal paradigms) were analysed separately, each with a two-way ANOVA, to evaluate if VSS predominately affected a particular retinogeniculate pathway.

Firstly, we hypothesised that the fine spatial grain of the visual noise in VSS might indicate dysfunction in the P pathway (H2a). In agreement with our hypothesis, contrast gain for increments processed in the inferred P pathway (pulsed pedestal paradigm) was increased in participants with VSS ($F(1,73)=5.34$, $P=0.024$, $\eta_p^2=0.068$; Fig. 5A) regardless of whether they had migraine (no migraine x VSS interaction: $F(1,73)=1.40$, $P=0.24$; Fig. 5B). Migraine was not associated with altered contrast gain on the pulsed pedestal task ($F(1,73)=0.31$, $P=0.58$).

Secondly, we hypothesised that the dynamic, flickering nature of visual snow could signal M pathway involvement (H2b). However, contrast gain for increments processed in the inferred M pathway (increment pedestal-delta-pedestal paradigm) was unaffected by VSS ($F(1,71)=0.30$, $P=0.59$; Fig. 5C) and migraine ($F(1,71)=0.75$, $P=0.39$) and there was no interaction between the diagnoses ($F(1,71)=0.17$, $P=0.68$; Fig. 5D). Therefore, contrast gain was not increased in the ON subdivision of the inferred M pathway in VSS (H2c).

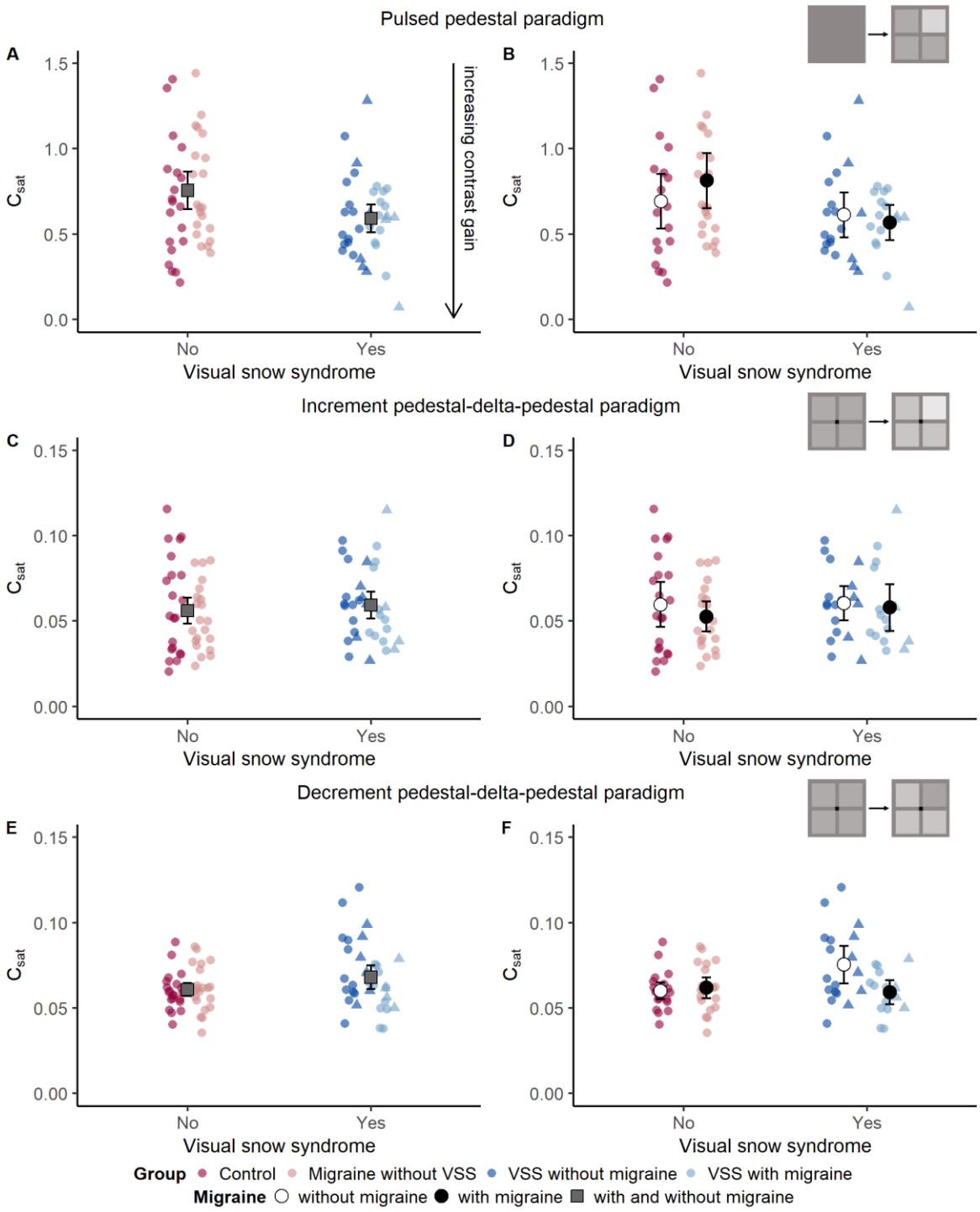


Figure 5. Contrast gain. (A & B) Pulsed pedestal paradigm **(C & D)** Increment pedestal-delta-pedestal paradigm **(E & F)** Decrement pedestal-delta-pedestal paradigm. Group differences in C_{sat} signify differences in contrast gain, with smaller C_{sat} values indicating higher contrast gain. Large symbols with error bars indicate mean and 95% confidence intervals for C_{sat} in groups without and with VSS (indicated on the x axis),

either regardless of migraine status (grey filled squares) in left panels or grouped into those without migraine (open circles) and those with migraine (black filled circles) in right panels. Small circles are individual data coloured according to group. Participants taking neuroactive medication are shown as triangles. Lower C_{sat} values indicate higher contrast gain.

Using the decrement version of the pedestal-delta-pedestal paradigm, we investigated our hypothesis that VSS may also affect the OFF subdivision of the inferred M pathway (H2d). There was no overall effect of VSS on contrast gain ($F(1,71)=3.23$, $P=0.077$; Fig. 5E). However, there was an effect of migraine ($F(1,71)=4.07$, $P=0.047$, $\eta p^2=0.054$) and an interaction between diagnoses ($F(1,71)=6.36$, $P=0.014$, $\eta p^2=0.082$; Fig. 5F), indicating that migraine pathophysiology influenced decrement processing in VSS. Specifically, there was a simple effect of VSS in participants without migraine ($F(1,71)=9.83$, $P=0.002$, $\eta_p^2=0.12$) but not those with migraine ($F(1,71)=0.25$, $P=0.62$). There was a simple effect of migraine in participants with VSS ($F(1,71)=9.17$, $P=0.003$, $\eta_p^2=0.11$) but not those without VSS ($F(1,71)=0.14$, $P=0.71$). Therefore, simple effect analyses suggested that contrast gain was selectively reduced in VSS without migraine for the OFF pathway (Fig. 5F). There were no apparent differences in the clinical history of VSS between groups with and without migraine, in terms of syndrome duration ($t(31)=-0.91$, $P=0.34$) or the presence of additional symptoms considered separately (afterimages ($P=0.73$), trailing ($P=0.73$), floaters ($P=0.61$), blue field entoptic phenomenon ($P=0.30$), self-light of the eye ($P=0.73$), photopsia ($P=0.73$), photophobia ($P=0.72$), nyctalopia ($P=0.35$); Fisher's exact test).

Contrast sensitivity is increased for decrements but not increments in VSS

While the main purpose of the experiment was to investigate neural gain for visual contrast, the pedestal paradigms also provide data on contrast sensitivity. Thresholds were higher for the pulsed pedestal task (Supplementary Fig. 1) compared to the pedestal-delta-pedestal tasks

(Supplementary Fig. 2-3), consistent with the poorer contrast sensitivity of the P pathway. Within a task, group differences in model parameter K indicate differences in contrast sensitivity. Therefore, in a secondary analysis, we evaluated K values for each task separately using a two-way ANOVA.

Sensitivity for the pulsed pedestal paradigm was unaffected by VSS ($F(1,73)=1.30$, $P=0.26$; Fig. 6A) or migraine ($F(1,73)=0.40$, $P=0.53$) but there was a statistically significant interaction between the two diagnoses ($F(1,73)=7.22$, $P=0.009$, $\eta_p^2=0.090$; Fig. 6B). There was a simple effect of VSS in participants with migraine ($F(1,73)=7.15$, $P=0.009$, $\eta_p^2=0.089$) but not without migraine ($F(1,73)=1.22$, $P=0.27$), and a simple effect of migraine in participants without VSS ($F(1,73)=6.08$, $P=0.016$, $\eta_p^2=0.077$) but not with VSS ($F(1,73)=1.93$, $P=0.17$). Altogether, this suggests that sensitivity is selectively decreased in participants with migraine who do not have VSS (Fig. 6B).

For the pedestal-delta-pedestal paradigm, sensitivity for increment discrimination was unaffected by VSS ($F(1,71)=0.48$, $P=0.49$; Fig. 6C) and migraine ($F(1,71)=0.014$, $P=0.91$) with no interaction between the diagnoses ($F(1,71)=1.59$, $P=0.21$; Fig. 6D). However, sensitivity for decrement discrimination was increased in VSS ($F(1,71)=4.72$, $P=0.033$, $\eta_p^2=0.062$; Fig. 6E), suggestive of OFF pathway dysfunction. There was no effect of migraine ($F(1,71)=0.45$, $P=0.50$) and no interaction between diagnoses ($F(1,71)=0.017$, $P=0.90$; Fig. 6F), indicating that the presence of comorbid migraine did not influence decrement sensitivity in VSS.

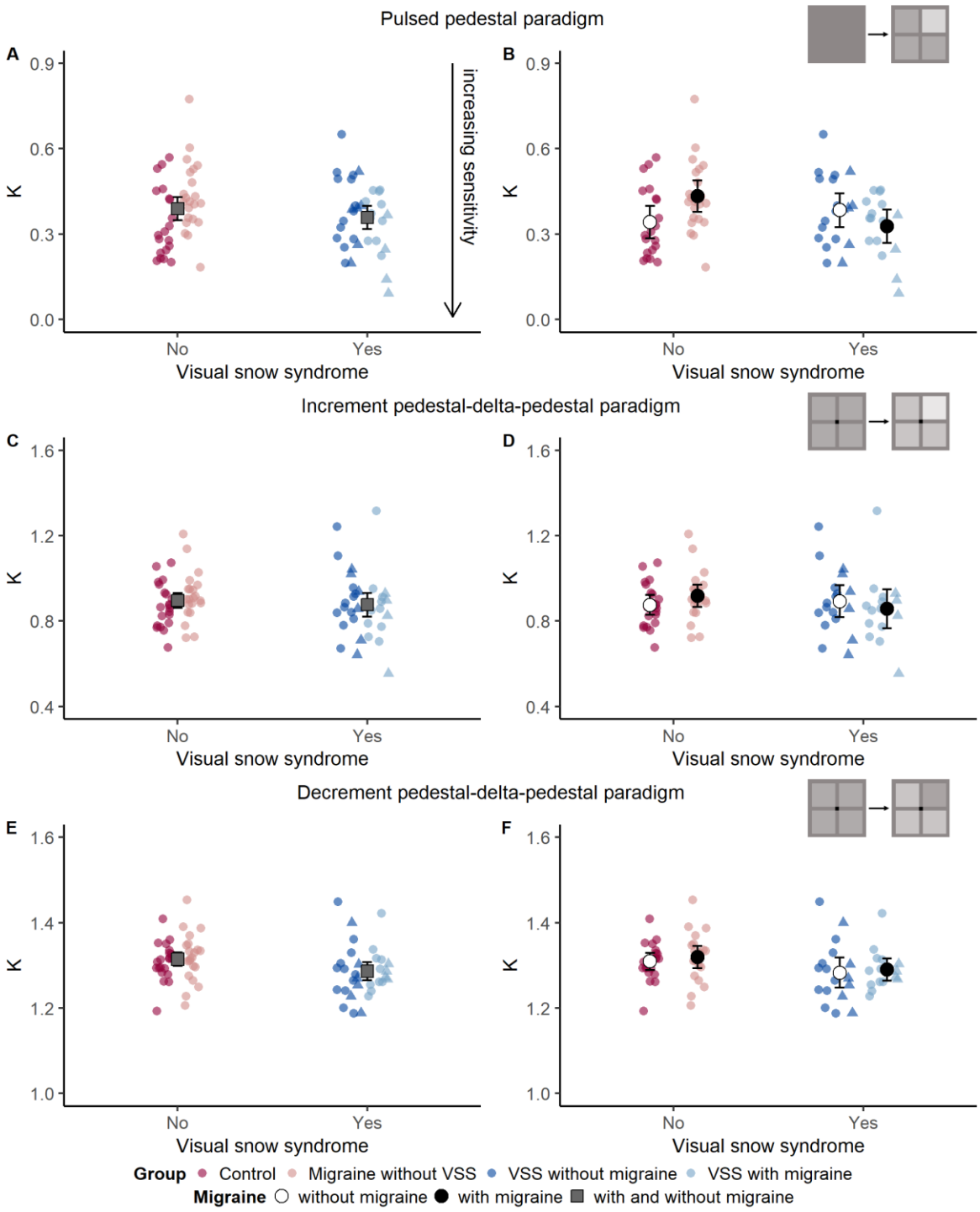


Figure 6. Contrast sensitivity. (A & B) Pulsed pedestal paradigm **(C & D)** Increment pedestal-delta-pedestal paradigm **(E & F)** Decrement pedestal-delta-pedestal paradigm. Within a task, group differences in model parameter K indicate differences in contrast sensitivity, with lower values signifying higher sensitivity. Large symbols with error bars indicate mean and 95% confidence intervals for K in groups without

and with VSS (indicated on the x axis), either regardless of migraine status (grey filled squares) in left panels or grouped into those without migraine (open circles) and those with migraine (black filled circles) in right panels. Small circles are individual data coloured according to group. Participants taking neuroactive medication are shown as triangles. Lower K values indicate higher sensitivity.

Visual discomfort questionnaire

General visual discomfort is heightened in migraine and VSS

We investigated whether increased internal noise and increased contrast gain were associated with greater self-reported visual discomfort. Scores for the control and migraine without VSS groups on the visual discomfort questionnaire (Fig. 7) were comparable to previously published results.[11] The discomfort trigger score differed between groups (Kruskal-Wallis test: $H(3)=42.31$, $P<0.001$; Fig. 7A). Bonferroni corrected pairwise comparisons revealed that the following groups all had greater discomfort trigger scores than controls: migraine without VSS ($z=-4.05$, $P<0.001$), VSS without migraine ($z=-4.62$, $P<0.001$) and VSS with migraine ($z=-5.95$, $P<0.001$). However, there was no difference in discomfort trigger scores between migraine without VSS and VSS groups with ($z=-2.17$, $P=0.18$) and without migraine ($z=-0.76$, $P=1.0$) or between the two VSS groups ($z=-1.38$, $P=1.0$). Altogether, this indicates that migraine without VSS, VSS without migraine and VSS with migraine groups experience discomfort from aversive stimuli with greater frequency than controls but with similar frequency to each other. Excluding controls, the headache trigger score was similar across groups (Kruskal-Wallis test: $H(2)=5.37$, $P=0.068$; Fig. 7B). The migraine trigger score was also comparable in migraine without VSS and VSS with migraine groups (Mann-Whitney U test: $U=193$, $P=0.94$; Fig. 7C).

Discomfort trigger scores were not correlated with internal noise estimates in the no noise (r_s=-0.005, *P*=0.96), low noise (r_s=0.17, *P*=0.16) or high noise (r_s=0.034, *P*=0.78) condition. Discomfort trigger scores were also not correlated with C_{sat} values for the pulsed pedestal (r_s=-0.12, *P*=0.29), increment (r_s=0.028, *P*=0.81) or decrement (r_s=0.020, *P*=0.87) pedestal-delta-pedestal paradigms. Therefore, we found no link between our estimates of neural noise and neural gain and our self-reported measure of generalised visual discomfort.

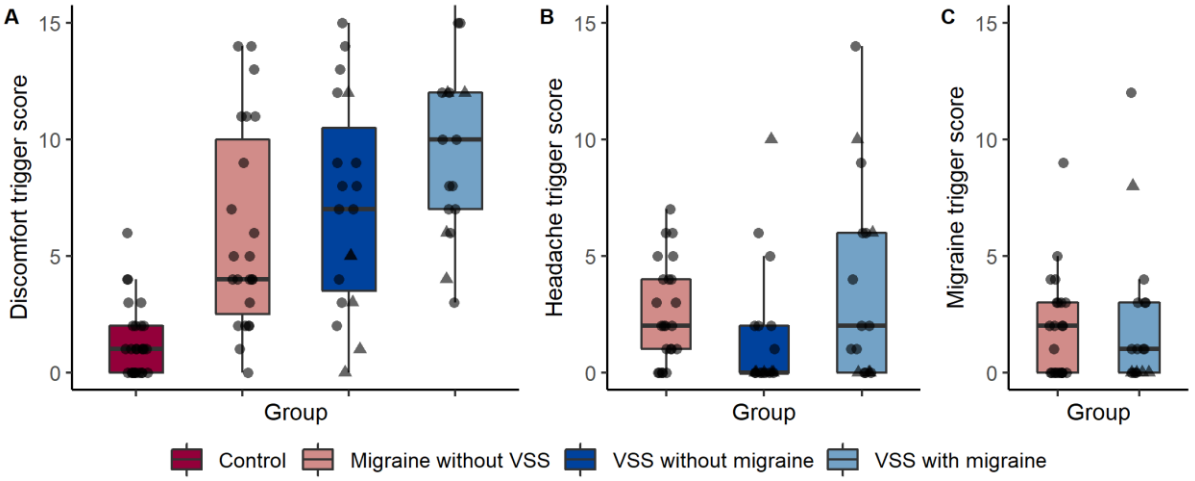


Figure 7. Visual discomfort questionnaire scores. (A) Discomfort trigger score. **(B)** Headache trigger score. **(C)** Migraine trigger score. Box plots indicate the median (line), interquartile range (box) and whiskers (extending to values within 1.5 times the interquartile range). Individual data is shown as circles (no neuroactive medication) or triangles (taking neuroactive medication).

Discussion

We conducted a novel investigation of visual contrast perception in VSS that evaluated two potential competing neural mechanisms of cortical hyperexcitability, neural noise and neural gain. Our study is the first report to examine decrement contrast perception in VSS and compare behavioural visual performance between individuals with migraine alone, VSS alone and VSS with migraine. The first experiment indicated that neural noise levels are

normal in VSS regardless of migraine status. However, the second experiment supported the alternative hypothesis that neural gain is increased in VSS, specifically finding that contrast gain was increased in the P pathway.

The first experiment showed that additive noise was not increased in VSS, suggesting that spontaneous neural activity is not significantly elevated. Our study extends the previous report of normal internal noise levels for a small group of patients with visual snow[7] to a larger group of participants meeting the proposed diagnostic criteria for VSS. We hypothesised that luminance increment thresholds would be raised in VSS due to elevated internal noise. However, we found that luminance increment thresholds were normal in VSS, contrary to our hypothesis but consistent with the normal internal noise levels. Therefore, this study did not replicate the previous report of elevated luminance increment thresholds in VSS compared to controls by McKendrick et al.[4] using similar methods. However, our current study had a significantly increased sample size and a study design that controlled for co-occurring migraine and VSS. Studies investigating luminance increment thresholds in migraine have also yielded conflicting results, ranging from decreased thresholds[31] to unaltered thresholds (present study) to elevated thresholds in high external noise.[24, 25] Therefore, abnormal luminance increment detection may not be a reliable marker of group differences in cortical excitability.

Our second experiment revealed increased contrast gain (as indicated by lower C_{sat} values) for increments processed in the putative P pathway in VSS regardless of migraine status. The pedestal paradigms are influenced by abnormalities in the visual pathway from the retina to the brain.[47] The experimental indicator of contrast gain, C_{sat}, is not simply inherited from the retina as it progressively decreases along the visual pathway.[48-50] This decrease is thought to reflect increasing neural convergence[49, 50] and rapid normalisation by local intracortical recurrent activity upon visual stimulation.[51] Consequently, it is unclear whether

hyperexcitability is intrinsic to the visual cortex or inherited from earlier in this visual pathway, as our study cannot specifically localise the neural stage of processing (from eye to brain) that results in the abnormal parvocellular contrast gain in VSS. Conversely, contrast gain for increments processed in the M pathway was unaffected by VSS. This pattern of results is consistent with our proposal that the symptomatic reports of the fine spatial scale of visual snow suggest predominant P pathway dysfunction.

As visual snow commonly consists of black and white static,[12] we explored whether a feature of VSS is anomalous neural responsiveness to contrast decrements. We found that contrast gain in the OFF subdivision of the magnocellular pathway was decreased, counter to the proposal of cortical hyperexcitability. This was an unexpected finding, since decreased contrast gain occurs in healthy aging[52] and some ocular diseases,[53-54] conditions that, unlike VSS, are associated with reduced visual performance. Only the VSS without migraine group was affected, suggesting an interaction between migraine and VSS pathophysiology. However, we cannot exclude differences between VSS groups unrelated to migraine as a factor, given that contrast gain was normal in individuals with migraine alone. Though our VSS subgroups with and without migraine had comparable VSS clinical histories, the observed difference could be driven by differences in visual snow features such as colour or severity. Future research could examine whether increment and decrement processing in VSS is related to visual snow appearance within individuals.

Conversely, we found that decrement contrast sensitivity was increased in VSS, suggestive of an increase in signal to noise ratio irrespective of the delta-pedestal contrast. The experimental measure of sensitivity (model parameter K) scales predicted thresholds to incorporate the effects of cortical summation as behavioural performance reflects the pooled activity of multiple neurons rather than the sensitivity of a single neuron.[26, 45, 55] Neurophysiological work in primates indicates that OFF responses are amplified in the

primary visual cortex.[56, 57] Therefore, heightened decrement sensitivity in VSS could reflect abnormal cortical summation or amplification of the neural response to decrements, indicative of increased neural responsiveness.

Our questionnaire results indicate that VSS is associated with significant self-reported visual discomfort, comparable in frequency to episodic migraine. However, we did not find more frequent discomfort in VSS with migraine compared to migraine alone. Previous research found more severe light and pattern glare in people with both diagnoses when comparing to migraine subgroups with or without aura using the Leiden Visual Sensitivity Scale.[2] The high prevalence of palinopsia in VSS[1, 12] may contribute to elevated scores on the Leiden Visual Sensitivity Scale, which includes two questions assessing afterimages.[58] Alternatively, comorbid migraine may affect the severity of visual discomfort in VSS but not the frequency.

The visual discomfort questionnaire also provides a more comprehensive assessment of visual hypersensitivity in VSS than the Leiden Visual Sensitivity Scale. It includes a broader range of aversive visual stimuli and distinguishes their tendency to elicit discomfort, headache and migraine. Increased visual hypersensitivity in VSS could plausibly manifest as headaches or migraines triggered by aversive stimuli. Headache history in VSS is not just limited to migraine,[1] and people with migraine can distinguish between headache subtypes, as their headache and migraine trigger scores are not identical on the visual discomfort questionnaire.[11] However, our results indicate that VSS does not affect the frequency of self-reported headache or migraine elicited by aversive visual stimuli.

Increased parvocellular contrast gain may contribute to visual hypersensitivity in VSS, since visual discomfort is hypothesised to result from elevated cortical excitation.[59] However, we did not find an association between higher discomfort trigger scores, which indicate more frequent visual discomfort, and increased parvocellular contrast gain. As the questionnaire

included a broad range of aversive stimuli beyond contrasting patterns, it likely indexed multiple pathophysiological processes contributing to visual discomfort. A more tailored questionnaire, or a specific assessment of discomfort to a standardised set of stimuli, may be more likely to reveal relationships between our measures and subjective report, if present.

VSS pathophysiology likely involves multiple mechanisms. However, our experiments were motivated by the proposal that the visual cortex is hyperexcitable in VSS,[3, 4] which could potentially be explained by an increase in neural gain or neural noise[5] that would be compatible with VSS symptoms of abnormal positive visual phenomena and subjective hypersensitivity. Behavioural vision tests are a helpful research tool for investigating VSS pathophysiology and identifying objective measures of visual dysfunction. Our first experiment demonstrated that neural noise is not significantly elevated in VSS and that psychophysical measures of internal noise are unlikely to be useful in the assessment of VSS. Our second experiment, however, revealed subtle changes in visual processing in VSS. As the observed group difference in C_{sat} was small in magnitude, tests of parvocellular contrast gain would not be suitable for VSS diagnosis due to individual variability but changes in an individual could possibly be a marker for monitoring response to treatment. Lastly, our finding of increased decrement contrast sensitivity in VSS suggests that visual tasks comparing increment and decrement perception may be a useful avenue for future research.

Another area for future research is the link between VSS and tinnitus. Tinnitus could be considered the auditory analogue to visual snow and it is highly prevalent in VSS, which suggests a common pathophysiology.[1, 12] Indeed, tinnitus was self-reported by most VSS participants completing the internal noise task (26 out of 32). As we only investigated internal noise in the visual system, our study was not designed to investigate whether these symptoms co-occur due to a generalised increase in internal noise in both auditory and visual systems. However, we did not find increased internal noise in the visual system and the

common link between visual snow and tinnitus could be disordered processing of sensory input affecting both systems.[1, 12, 60]

VSS research is complicated by the high prevalence of migraine,[1, 12] anxiety and depression.[61, 62] Consequently, a subset of our VSS participants were taking neuroactive medication (see Supplementary Table 1). While this is a potential limitation of our study, inclusion of these participants ensures that our study population is a fair representation of the VSS clinical population. Anxiety and depression are severe in a significant proportion of patients and may be partially inherent to the syndrome as well as a consequence of symptom-related distress.[61] While VSS onset is possibly associated with medication use in some cases,[12] in our study those participants taking neuroactive medication either had lifelong symptoms or reported no association between their medications and symptom onset. Blurred vision was also not an issue for our participants, who reported good quality vision in a clinical history and had distance visual acuity ranging from 6/3.8 to 6/6. Deficits in accommodation, if present, could have potentially blurred the fine spatial detail of the external noise (5.7' x 5.7' pixels) but not the larger critical stimulus features (the 1.4° disc and the 1° squares). Critically, inspection of data for the individuals taking such medications did not reveal any difference from the larger group (see Fig. 3-6). The possibility of prodromal effects on our experimental measures is another potential limitation, though research suggests that luminance increment thresholds are stable across the migraine cycle. [31] However, our results are unlikely to be influenced by prodromal effects since exclusion of the few participants reporting a migraine within 48 hours of testing from the analysis did not alter our findings (see Supplementary Tables 2-3).

In conclusion, an abnormally high level of neural noise does not seem to be a key factor in VSS pathophysiology. However, there was an abnormal increase in neural contrast gain (increments, inferred P pathway) and contrast sensitivity (decrements, inferred M pathway) in

VSS, indicating abnormalities in the processing of luminance contrast. Unlike VSS, migraine was not associated with neural hyperresponsiveness to contrast, signifying differences in the pathophysiology of the two neurological conditions despite superficial similarities in subjective hypersensitivity.

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Competing interests

JF & OBW receive philanthropic support from VSI

Supplementary material

Supplementary material is available at *Brain* online.

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