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RESEARCH REPORT

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Effect of temporal frequency on habituation in migraine

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Abstract

Individuals with migraine tend to experience discomfort when viewing flickering stimuli. It has been suggested that one of the characteristics of migraine is a lack of habituation to repetitive visual stimuli, although findings can be mixed. Previous work has typically used similar visual stimuli (chequerboard) and only one temporal frequency. This study systematically varied the spatial and temporal characteristics of the visual stimulus, using steady-state visual evoked potentials to assess the differences in amplitude between migraine and control group over consecutive blocks of stimulation. Twenty individuals with migraine and 18 control observers were asked to rate their visual discomfort after viewing sequences of flickering Gabor patches with a frequency of either 3 or 9 Hz across three different spatial frequencies (low 0.5 cpd; mid-range 3 cpd; high 12 cpd). Compared to the control group, the migraine group showed a reduction in SSVEP responses with increased exposure, suggesting habituation processes are intact at 3-Hz stimulation. However, at 9-Hz stimulation, there was evidence of increased responses with increasing exposure in the migraine group in particular, which might suggest a build-up of the response over repetitive presentations. Visual discomfort varied with spatial frequency, for both 3- and 9-Hz stimuli, the highest spatial frequencies were the least uncomfortable compared to the low- and mid-range spatial frequencies in both groups. This difference in SSVEP response behaviour, dependent on temporal frequency, is important to consider when researching the effects of repetitive visual stimulation in migraine and could give some indication of build-up of effects leading to aversion to visual stimuli.

KEYWORDS
flicker, habituation, migraine, potentiation, SSVEP

1 | INTRODUCTION

Migraine is a disabling neurological disorder affecting around 10% of the population, and prevalence rates are thought to be rising (Woldeamanuel & Cowan, 2017). Migraine has been ranked amongst the top five causes of disability (Vos et al., 2017), causing a considerable burden on the individual, the economy and society (Saylor &

Abbreviations: MA, migraine with aura; MO, migraine without aura; SSVEP, steady-state visual evoked potentials.

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Steiner, 2018). The International Classification of Headache Disorders (International Headache Society [IHS], 2018) states that migraine consists of five or more attacks, lasting around 4 to 72 h if left untreated. The attacks have two or more of the following qualities, a unilateral (one-sided) headache, pulsating sensation, a strong urge to avoid light (photophobia), sound (phonophobia) and physical activity, as well as being accompanied by nausea or vomiting (IHS, 2018). The causes of migraine are debated amongst the literature (e.g. Aurora & Wilkinson, 2007; Coppola et al., 2007, 2009), and it is vital that more work is done to determine the exact causes of migraine to guide effective treatments, so the disabling qualities associated with the disorder can be reduced.

There is a strong association between migraine and sensory disturbances (O'Hare & Hibbard, 2016). One of the key features of migraine is photophobia/phonophobia during an attack (IHS, 2018). It has been argued that migraine can also be triggered by visual stimuli (Harle et al., 2006; Shepherd & Joly-Mascheroni, 2017). Photophobia (aversion to light) is associated with increased activity in the visual areas of the brain (Maniyar et al., 2014). In-between attacks, individuals with migraine tend to experience increased sensitivity to visual stimuli that are also found uncomfortable by others, for example, striped patterns (Marcus & Soso, 1989). Aversion to striped patterns is also known as pattern glare (Evans & Stevenson, 2008), and individuals with migraine tend to report more illusory sensations and discomfort from the Pattern Glare Test (IOO Sales Ltd) compared to control groups (e.g., Harle et al., 2006; Shepherd, 2000), as well as to other striped patterns (e.g., Huang et al., 2011; Shepherd et al., 2013). There is evidence of increased discomfort judgements with increased fMRI BOLD responses in those with migraine in response to striped stimuli (Huang et al., 2011). As well as spatially periodic stimuli, temporally periodic stimuli (e.g., flicker) can cause discomfort in those with migraine (Karanovic et al., 2011; McKendrick & Badcock, 2004).

Several theories of visual discomfort in migraineurs have been suggested, including hyperexcitability (Aurora & Wilkinson, 2007), hyperresponsiveness (Coppola et al., 2007) and a lack of habituation (Coppola et al., 2009). In the case of hyperexcitability, it is thought that the brain responds excessively to any stimulation (Aurora & Wilkinson, 2007). This theory is supported through phosphene induction (illusory flashes of light, Cowey & Walsh, 2000) using transcranial magnetic stimulation (TMS) (Aurora et al., 1998). TMS stimulation was applied over the occipital cortex with increasing intensity until the observer reported phosphenes, finding that participants with migraine required lower stimulation intensities than controls (Aurora et al., 1998). This suggests that the visual areas may be overexcited due to a lower threshold (Mulleners et al., 2001).

It has been argued that because repetitive stimulation results in increased responses in individuals with migraine, it may be more accurate to describe the migraine brain as hyperresponsive instead of hyperexcitable (Coppola et al., 2007). Habituation is the normal reduction in response to repeated stimulation (Rankin et al., 2009), and a lack of habituation has been suggested to be a reliable indicator of migraine (Coppola et al., 2009). However, the mechanisms for the habituation deficit are poorly understood (de Tommaso et al., 2014; Shahaf et al., 2018), and the findings in the literature can be mixed (e.g., Áfra et al., 1998; Oelkers et al., 1999). Table 1 displays some of these differences, regarding varying spatial frequencies, temporal frequencies and contrasts chosen for visual stimulation. It must be noted that this is in the time scale of minutes (e.g., Áfra et al., 1998), please see Table 1 for the duration of habituation time scales used in previous studies. It should be noted that comparable adaptation effects, such as the motion after-effect, show adaptation after time scales as short as 25 ms (Glasser et al., 2011), although more usually, this is adaptation on the scale of minutes (Anstis et al., 1998). In the current study, we will restrict to similar time scales as in previous research on migraine.

There appears to be a slightly lower contrast for the studies supporting the idea of habituation deficit in migraine, compared to those who do not. This may be a factor affecting the findings because a weaker stimulus may cause the habituation response to be more pronounced (Thompson & Spencer, 1966). Therefore, stronger stimuli (presented at higher contrasts) tend to make differences between groups harder to observe as the response is less pronounced (Nguyen et al., 2016). Also, supporting evidence uses frequencies no less than 2 Hz (e.g., Bednář et al., 2014) and mainly 3.1 Hz (e.g., Áfra et al., 1998), whereas opposing evidence used frequencies as slow as 1 Hz (e.g., Oelkers et al., 1999). This may be affecting the findings because it has been suggested that increased number of repetitions (possibly as a result of increased temporal frequencies) lead to more pronounced habituation (Bonetti & Massimo, 2019).

The different findings amongst the literature are potentially due to differences between the methodology (Ambrosini et al., 2003; Ambrosini & Schoenen, 2006). Some authors have instead argued that the discrepancies between findings have come from researchers being aware of each observers' diagnosis (Omland et al., 2013). However, other authors have found habituation deficits

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TABLE 1 Table showing studies supporting and opposing habituation deficit in migraine compared to controls, listing stimulus (all chequerboard), approximate spatial frequency in cycles per degree (SF, in cpd), temporal frequency (TF, in Hz) and contrast level. Important to note, Oelkers-Ax et al., (2005) observers were children; Sand et al. (2009) showed no habituation in control group or the migraine group.

		Stimulus type	SF (cpd)	TF (Hz)	Contrast (%)	Duration
Supporting	Áfra et al. (1998)	chequerboard	3.7	3.1	80	15 blocks of 100 responses, total duration of 15 min
	Áfra et al. (2000)	chequerboard	3.7	3.1	8	5 blocks of 50 responses (calculated to be 1.3 min)
	Ambrosini et al. (2017)	chequerboard	2	3.1	80	10 min adaptation, then 6 blocks of 100 sweeps lasting 3 mins 20 s
	Bednář et al. (2014)	chequerboard	2.3	2	85	5 blocks of 60 responses (estimated to be 2.5 min)
	Bohotin et al. (2002)	chequerboard	3.7	3.1	Unknown	6 blocks of 100 responses (194 s total)
	Coppola et al. (2010)	chequerboard	2	3.1	80	6 blocks of 100, 600 sweeps lasting 200 ms each (2 min total)
	Di Clemente et al. (2005)	chequerboard	3.7	3.1	80	600 stimuli, 6 blocks of 100 responses (calculated to be 194 s)
	Fumal et al. (2006)	chequerboard	3.7	3.1	Unknown	6 blocks of 100 responses (3 min total)
	Judit et al. (2000)	chequerboard	3.7	3.1	80	5 blocks of 50 responses, (2 min total)
	Kalita et al. (2018)	chequerboard	2.5, 1.9	3	80	5 blocks of 100 sweeps, each lasting 500 ms (calculated to be 4.2 min)
	Lisicki et al. (2017)	chequerboard	2.1	3.1	Unknown	6 blocks of 100 sweeps, each lasting 200 ms (calculated to be 2 min)
	Ozkul and Bozlar (2002)	chequerboard	3.7	3.1	80	5 blocks of 50 responses, total 1.5 min
	Schoenen et al. (1995)	chequerboard	3.7	3.1	80	5 blocks of 50 responses (calculated to be 1.3 min)
	Wang et al., (1999)	chequerboard	3.7	3	80	5 blocks of 50 responses (calculated to be 1.3 min)
opposing	Oelkers et al. (1999)	chequerboard	0.5, 1, 2 & 4	1	>99	5 blocks of 50 responses, 450 ms epoch (calculated to be 1.9 min)
	Oelkers-Ax et al. (2005)	chequerboard	4	1	30	5 blocks of 50 responses of 640 ms epoch (calculated to be 2.7 min)
	Omland et al. (2013)	chequerboard	0.5, 3.7	3	93	6 blocks of 100 responses (calculated to be 3.3 min)
	Omland et al. (2016)	chequerboard	1.9	3	93	6 blocks of 100 responses (calculated to be 3.3 min)
	Sand and Vingen (2000)	chequerboard	3.7, 0.9	3.7	97	2 blocks of 100 sweeps (calculated to be 0.9 min)
	Sand et al. (2008)	chequerboard	1, 0.5	1.9	>90	4 blocks of 50 responses (calculated to be 1.75 min)
	Sand et al. (2009)	chequerboard	1, 0.5	1.9	>90	4 blocks of 50 responses (calculated to be 1.75 min)

even when the researchers were blind to the diagnosis (Ambrosini et al., 2017). It may instead be that supporting (Áfra et al., 1998, 2000; Ambrosini et al., 2017; Bohotin et al., 2002; Coppola et al., 2010; Judit et al., 2000; Lisicki et al., 2017; Schoenen et al., 1995) and opposing (Omland et al., 2013, 2016; Sand & Vingen, 2000) research tends to come from the same group of collaborating authors. Despite this, both arguments have been independently confirmed by few authors (Bednář et al., 2014; Kalita et al., 2018; Oelkers

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et al., 1999). The vast amount of discrepancies between the literature on habituation research using VEPs causes concern for understanding the causes of migraine because a habituation deficit can arguably no longer be considered a reliable indicator (Omland et al., 2013, 2016). It is vital that these discrepancies are resolved because treatments for this deficit have been suggested (Ozkul & Bozlar, 2002).

Based on the above literature, it may be that differences between the spatial and temporal frequencies (Ambrosini et al., 2003; Ambrosini & Schoenen, 2006) of stimuli are causing the different results (e.g., Oelkers et al., 1999). Specifically, the size of chequers makes a difference to the VEP magnitude (Harter & White, 1970). Therefore, the aim of the current study is to vary both spatial and temporal frequencies. Visual discomfort shows spatial frequency tuning (e.g., Fernandez & Wilkins, 2008; Juricevic et al., 2010; O'Hare & Hibbard, 2011; Wilkins et al., 1984). The visual system is more sensitive to mid-range spatial frequencies, peaking at 3 cpd (Campbell & Robson, 1968), and there are increased SSVEP responses to these mid-range (3–4 cpd) spatial frequencies (Plant, 1983);, therefore, it is expected that both SSVEP response amplitude, and discomfort judgements, would vary with spatial frequency. In the current study, we use the term 'mid-range' to refer to 3 cpd, 'high' to refer to 12 cpd and 'low' to refer to 0.5 cpd to facilitate comparison with previous researchers who have used the term 'mid-range' to refer to approximately 3 cpd (Campbell & Robson, 1968; Plant, 1983; Fernandez & Wilkins, 2008). The terminology for 'high' and 'low' spatial frequencies relates to the terms used when referring to pattern glare (Evans & Stevenson, 2008). Researchers in previous studies on habituation in migraine have typically used slower reversal rates than the 9 Hz in the current study (less than 4 Hz, see Table 1) and also higher contrasts, typically between 80% and 90% contrast, compared to 12.5% contrast in the current study. Both the higher temporal frequency (Bonetti & Massimo, 2019) and the lower contrast (Thompson & Spencer, 1966) would be expected to lead to more pronounced habituation effects compared to previous research, therefore increasing the chances that effects will be seen.

Additionally, a different analysis method will be used. It has been suggested that if the EEG response to repeated trials overlaps in time, the estimation of transient components such as the P100 may not be valid (Heinrich, 2010). It has been suggested that the effects of a stimulus last for a minimum of 1 s (Woodman, 2010), and so there should be sufficient baseline shown on figures to demonstrate that there is no contamination from the response to the previous trial. One way of avoiding distortion from stimulus overlap is the SSVEP technique (Woldorff, 1993). SSVEPs have been shown to have the advantage of increased signal-to-noise ratio and simplified analysis protocols in the form of spectral analysis (Norcia et al., 2015; Vialatte et al., 2010). Additionally, analysis of peaks and troughs of the pattern-reversal waveform has been argued to be subjective and requiring specially trained expertise in interpretation of waveforms, which can be remedied by using frequency analysis, for example, Fourier analysis (Zemon & Gordon, 2018). Although SSVEP responses tend to be in the higher frequency bands, spectral analysis has been used for stimulation frequencies as low as 1 (Norcia et al., 2002) and 2.5 Hz (Eizenman et al., 1999). Therefore, this technique will be used in the current study.

There are four hypotheses in the current study; the first two relating to migraine and the remaining two relating to visual discomfort, which is greater in those with migraine. First, if the theory of lack of habituation characterising migraine is correct, it is proposed that (a) SSVEP amplitudes will decrease over time (in this case, over the four experimental blocks, please see Section 2) (indicative of habituation); (b) SSVEP amplitudes will be significantly different between migraine and control groups, specifically showing less of a decline over time (in this case experimental block, please see Section 2) in the migraine group (lack of habituation). Second, if visual discomfort is related to increased neural responses, it is predicted that (c) spatial characteristics of the stimuli will affect SSVEP amplitudes; (d) SSVEP amplitudes will be related to discomfort judgements.

2 | MATERIALS AND METHODS

2.1 | Observers

The study adhered to the British Psychological Society ethical guidelines for human research and was scrutinised by the School of Psychology Ethics Committee (approval number PSY181910). Written informed consent was obtained from all observers prior to taking part in the study. The migraine group consisted of 20 individuals (three males, mean age 25.25, SD = 12.09), the control group consisted of 18 individuals (five males, mean age 21.05, SD = 4.42). The final sample was estimated based on the programme G*Power (Faul et al., 2007, 2009) to estimate sample size for repeated measures ANOVA for the within-between interaction with two groups and four measurements of block. Assuming power of 0.8 then a minimum sample of 24 in total (12 per group) is required to be able to detect a medium effect of f = 0.25 at the 0.05 alpha criterion level. It should be noted that ANOVA is

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not the same analysis as the linear mixed effect model included in the results section here. One of the main differences is that the linear mixed effects model includes the observer as a random effect, whereas the ANOVA regresses each individual to their own mean value. In the ideal situation, pilot data would have been used to simulate a linear mixed effect model with realistic estimates of the effect sizes (in this case the unstandardised coefficients) and the residual variance. Unfortunately, in the absence of pilot data, or anything suitable in the literature, we were unable to make these estimates for the linear mixed effect model prior to starting the study. However, both the linear mixed effect model and the ANOVA are both from the same linear model, with similar assumptions of the data. Therefore, as an approximation, the effect sizes for ANOVA were used for the a priori sample size estimation; however, the reader should note this is not ideal. Additionally, midway through the data collection for the current study, the sample size estimation for a linear mixed effect model was able to be simulated using the package 'simr' (Green & MacLeod, 2016) in the programme R (R Core Team, 2019). This simulation confirmed the effect size estimation of approximately 24 observers as the required sample size assuming power of 0.8 and alpha of 0.05. The details and results of this simulation can be seen in the Supporting Information. The R script for the simulations can be found in the Open Science Framework, alongside the data and analysis scripts for the overall study (https://osf.io/8fw5g/). Individuals fulfilling the International Headache Society Classification Criteria (IHS, 2018) for migraine with aura (MA) and for migraine without aura (MO) were included in the migraine group. MA and MO participants were included together as previous research into habituation has shown no differences between the two groups (for a discussion, see Omland et al., 2013; Bednář et al., 2014). As the study is of interictal migraine, individuals with a headache attack less than 2 days before the experiment were excluded from the analysis (observer numbers 37 and 49). Only seven of the individuals taking part in the study reported a diagnosis of migraine by a medical professional (observer number 8, 23, 30, 37, 45, 46 and 49); however, many individuals experiencing migraine do not seek professional help; around half of individuals meeting IHS criteria reported a physician diagnosis (Lipton et al., 2001; MacGregor et al., 2003; Song et al., 2019; Vetvik & MacGregor, 2017), although there is evidence that the headache disability is the same in diagnosed and undiagnosed individuals (Oliveria et al., 2011). All of the individuals in the migraine sample were female, which is likely as migraine is more common in women compared to men (e.g., 8.6% males, 17.5% females, Victor et al., 2010). Ten of the migraine group fulfilled the IHS criteria for MA; however, many (15, please see Table 2) reported visual or sensory disturbances around the time of the attack. Typically, these did not fulfil the criteria for part 1.2 MA part C, relating to the qualities of the visual disturbances. A table of clinical characteristics of the migraine group can be seen in Table 2.

For ethical and safety reasons, all potential participants with a history of seizures and epilepsy were excluded from the study. In addition, all of the control participants were recruited as being free from regular headaches and without a known family history of migraine.

2.2 | Apparatus

Stimuli were presented using an Asus prime computer with an Intel i7 core and NVidia GEForce graphics card, running Ubuntu 14 on a 22 'Iiyama Vision Master Pro 514 monitor set to a resolution of 1024 × 768 with a refresh rate of 85 Hz. The viewable size of the display was 20.4', meaning the viewable width was 40.6 cm and the viewable height was 30.4 cm. This resulted in the viewable width of the display being 22.10° of visual angle. The display was calibrated using a Minolta CS-LS110 photometer, the maximum luminance of the display was 148.33 cd/m^2, and the minimum was 0.19 cd/m^2. Stimuli were created and presented using MATLAB 2013b (The Mathworks, Natick) and the Psychtoolbox (Brainard, 1997; Kleiner et al., 2007; Pelli, 1997).

2.3 | Stimuli

Stimuli were vertical sine gratings presented in a soft-edged Gaussian window with a central visual radius of 150 pixels and a sigma of 10 pixels. The stimulus therefore subtended approximately 7° visual angle before fading to the background mid-grey. There were nine stimulus conditions, stimuli had spatial frequencies of either 0.5 (low), 3 (mid) or 12 (high) cycles per degree and were presented at temporal frequencies of either 1, 3 or 9 Hz. Figure 1a shows a diagram of the 0.5-cpd stimulus, Figure 1b shows the 3-cpd stimulus and Figure 1c shows the 12-cpd stimulus. As spatial frequency depends on the size of the image and the viewing distance, these diagrams will be appropriate for spatial frequency content when enlarged to occupy a width of 40.6 cm (maintaining aspect ratio) and viewed at a distance of 100 cm.

Temporal frequency modulation was achieved by varying in contrast from the mid-grey pedestal (0%) to maximum contrast (12.5%) and back again as a sine-wave

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TABLE 2 Migraine characteristics of the individuals experiencing migraine, including attack frequency (number of attacks per month), whether the individual experiences visual disturbances prior to an attack, whether the individual experiences speech disturbances prior to the attack, the time since the last attack and whether the individual uses prophylactic medication. U = unanswered. Observers 8, 23, 30, 37, 45, 46 and 49 reported diagnosis by a medical professional. Participants 37 and 49 were excluded as they experienced a migraine attack too close to the time of testing.

Obs	Type	Sex	Age	Frequency (months)	Visual disturbances	Other sensory disturbances	Time since last attack	Prophylactic medication
2	MO	F	20	1–3	Y	N	3 days	N
4	MO	F	44	1–3	Y	N	3 weeks	N
8	MO	F	18	<1	N	N	6 days	N
10	MO	F	21	<1	N	N	6 moths	N
12	MO	F	25	1–3	N	N	U	N
16	MO	F	20	<1	Y	N	2 weeks	N
18	MO	F	21	<1	Y	N	2 moths	N
22	MA	F	18	<1	Y	N	2–3 moths	N
23	MA	F	19	1–3	Y	Y	2 weeks	Y
24	MO	F	20	<1	N	Y	5 days	Y
28	MA	F	20	<1	Y	N	1 moth	N
30	MA	F	21	1–3	Y	Y	10 days	N
37	MA	F	20	1–3	Y	N	1 day	N
38	MA	M	20	3–10	Y	N	U	N
41	MA	M	20	<1	Y	N	2 weeks	N
42	MO	M	20	<1	Y	N	2 months	N
44	MO	F	21	<1	N	N	1 year	N
45	MA	F	60	1–3	Y	N	4 days	N
46	MA	F	53	>10	Y	Y	3 days	Y
49	MA	F	19	>10	Y	Y	1 day	Y

modulation. In effect, the striped stimulus smoothly increased and decreased in contrast, appearing/disappearing from mid-grey. Norcia et al. (2015) highlight that the main difference between a square-wave modulation and that of a sine-wave modulation is that the former contains the higher harmonics and the latter does not. As the visual system itself is non-linear, it is likely that there will be higher harmonics in the response; however, for simplicity, these were not introduced at the level of the signal. Figure 1d shows a schematic diagram of the temporal profile of the stimulus.

For ethical, comfort and safety reasons high-contrast stimuli were not included in this experiment as people who have migraine tend to report particular aversion to flicker and high-contrast stimuli. In addition, as it has been reported that visual stimuli can elicit migraine (Harle et al., 2006), it was considered prudent to keep the overall contrast low to avoid such an outcome. The luminance in cd/m^2 was measured to be 0.19, 21.93 and 148.33 for black, mid-grey and white, respectively, prior to gamma correction. After gamma correction, the display values would have been linearised, and so mid-grey was defined as half the maximum luminance value for the display, approximately 74.17 cd/m^2. This was the average luminance of the display and would remain constant during the presentation of stimuli.

2.4 | Procedure

Observers were seated in a sound-attenuated, darkened room, 100 cm from the display. Head movements were restricted using a chinrest. There were four blocks of stimuli containing three repetitions of each of the nine stimulus conditions (three spatial frequencies and three temporal frequencies), a total of 27 trials per block. At the start of each trial, a black fixation cross was displayed against a mid-grey background in the centre of the screen. Stimuli appeared for 20 s, after which time, the stimulus was replaced with a screen asking the observer to rate the stimulus for discomfort on a scale from 1 to 7. The exact phrasing appeared on the screen as 'How

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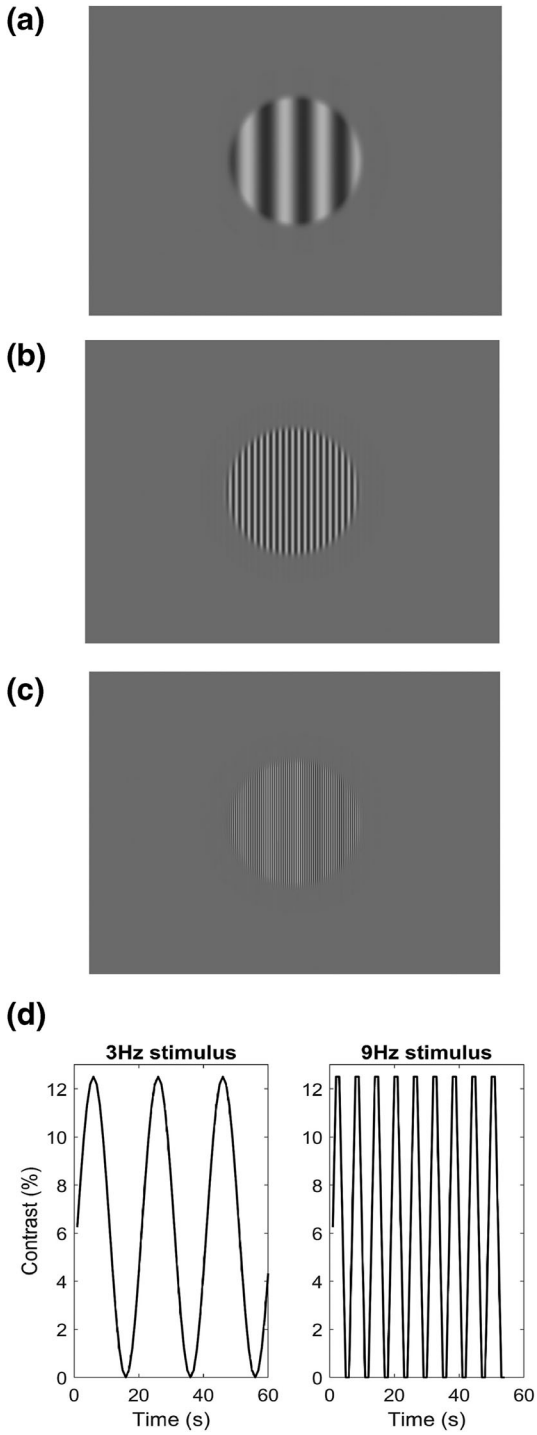

FIGURE 1 Stimulus diagram: (a,b,c). This figure consists of a diagram of the stimuli that were displayed to participants. This will be to scale if the diagram is enlarged on screen to be 40.5 cm in width and viewed at a distance of 100 cm. Spatial frequencies used were 0.5, 3 and 12 cpd, viewed on a CRT display at a distance of 1 m. As spatial frequency is dependent on viewing distance, the spatial frequency content of the stimuli cannot be accurately represented here, unless the presentation instructions are followed. The lowest spatial frequency would correspond to wider stripes and the higher spatial frequency to thinner stripes. Gratings were modulated in contrast from maximum contrast (12.5% of the maximum available range of the display) to mid-grey (appears blank) for 20 s for each trial. (a) This shows the lowest spatial frequency (0.5 cpd) stimulus that will be to scale when enlarged to occupy 40.6 cm in width and viewed at a distance of 100 cm. (b) This shows the mid-range spatial frequency stimulus (3 cpd) that will be to scale when enlarged to occupy 40.6 cm in width and viewed at a distance of 100 cm. (c) This is the highest spatial frequency (12 cpd) stimulus that will be to scale when enlarged to occupy 40.6 cm in width and viewed at a distance of 100 cm. (d) Schematic diagram of the time course of the presentation. This shows the temporal profile for 1 s of the 3-Hz stimulation (stimuli were displayed for 20 s). The contrast varied with time, at 0 contrast there was a mid-grey stimulus only, indistinguishable from the background. At maximum contrast, there was 12.5% contrast of black and white sine grating shown in Figure 1a. Right shows 1 s of the 9-Hz stimulation (stimuli were displayed for 20 s).

uncomfortable is this to look at? 1-7)'. There were no additional instructions given to participants as to how to interpret 'discomfort'. The experimenter was not in the EEG cubicle during the blocks. The next stimulus appeared after a short variable time delay (random time interval between 1 and 1.5 s). Stimuli appeared three times each (total of 60-s display time per stimulus), and the order was randomised within each block. This results in nine data points per block, with 60 s of data in total per data point. After each block observers were invited to rest for a few minutes between each block, during which time, they could blink freely and move their eyes around the room, before commencing the next block in order to mitigate fatigue effects. Head movements were restricted during this rest period due to the EEG setup, and the lights were switched on to enable the experimenter to check on the observer's well-being. Observers were asked to keep as still as possible and to refrain from blinking during stimulus presentation. After the experiment, observers were asked to complete the Pattern Glare Test (IOO Sales Ltd).

2.5 | EEG data acquisition

Data were recorded using a 64-channel Biosemi Active-Two system with 10–20 electrode placement. There were eight additional facial electrodes, placed on the mastoids, outer canthi, suborbital and supraorbital locations. The impedance was reduced using Signa Gel (conductive electrode gel). The Active-Two system uses a common mode sense and a driven right leg feedback loop to further reduce the effective impedance; please see https://www.biosemi.com/faq/cms&drl.htm for details. Data were

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initially recorded at 2048 Hz but decimated offline to 256 Hz. Data were converted to EDF files and transferred for further analysis using MATLAB 2017b (The Mathworks, Natick) and the EEGLAB extensions (Delorme & Makeig, 2004).

Data were referenced to the linked mastoid channels, and band-pass finite impulse response (FIR) filtered between 0.1 and 40 Hz. The FIR filter used had zero phase and a Hamming window, with a roll-off (transition bandwidth)of 25% of the minimum value defined as 2 Hz. The 100 ms before the start of each 20-second stimulus presentation was defined as the baseline, and this was removed by subtraction. Each 20-second "trial" period was then divided into four epochs of five seconds each. As there were 3 repetitions of each "trial" this resulted in a total of 12 epochs for each stimulus type. This epoch length was retained to be long enough for sufficient resolution in the frequency analysis. Bad channels were identified using three methods, probability, spectrum and kurtosis, with a threshold of 5 for each, any channel exceeding these would be removed from the analysis. Finally, Gratton-Coles correction (Gratton et al., 1983) was applied, with a threshold of 200 mV in a window of 20 ms. The Gratton-Coles correction allows for eye movement artefacts such as blinks to be identified and corrected for, by calculating propagation factors for the correction of the other channels. This has the benefit of reducing the impact of eye movement artefacts, without necessarily removing large sections of data from analysis.

Based on previous work, the electrodes of interest were defined a priori as early occipital areas, and so data for early occipital channels O1, O2, Oz, Iz, were averaged. Scalp topography (averaged over channels of interest) can be seen in Figure 2a for 3 Hz, and Figure 2b for 9 Hz, respectively. It should be noted that there is apparently a slight lateralisation to the SSVEP responses for these stimuli. It is unclear why this is the case, as stimuli were presented binocularly, and displayed centrally on the screen.

Spectral analysis was conducted using the EEGLAB toolboxes, which use the MATLAB *pwelch()* function. This uses a Hamming window to segment the data, compute the power spectral density function and then average the segments. The trade-off for this is a low-pass signal but much improved noise reduction compared to a standard Fourier transform. The units of this output are in dB (10*log10), normalised by the frequency (Hz). The peak of the signal (that was previously averaged over the channels of interest) can be seen in Figures 3a and 6a, showing the spectra for 3 and 9 Hz, respectively. Previous work has been using the time domain (e.g., Ambrosini et al., 2017; Lisicki et al., 2017; Oelkers-Ax et al., 2005),

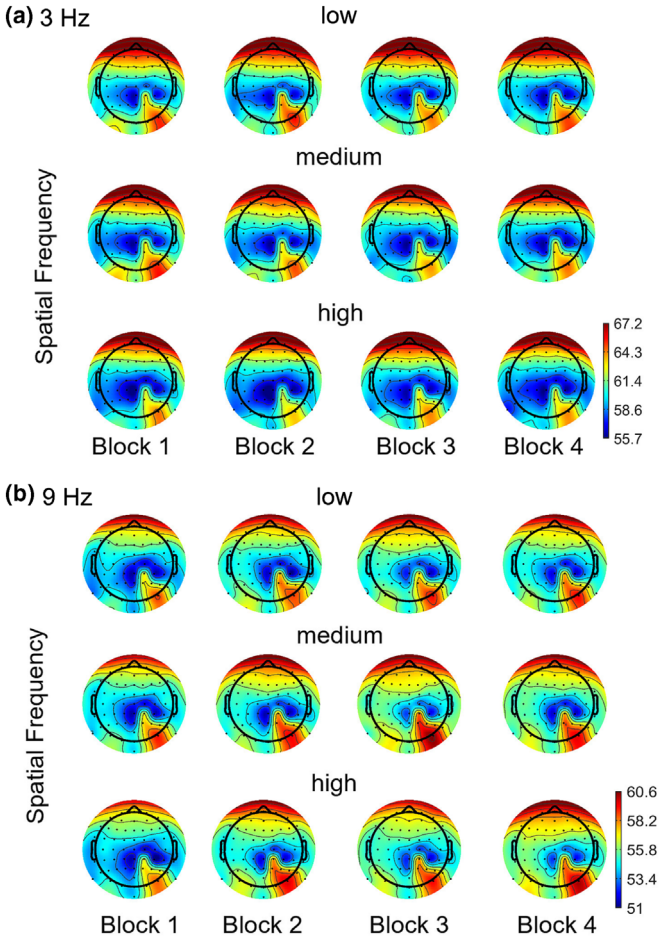

FIGURE 2 Scalp topography of SSVEP responses. (a) Scalp topography of the 3-Hz stimuli, for each block and spatial frequency condition, showing occipital activity. (b) Scalp topography of the 9-Hz stimuli, for each block and spatial frequency condition, showing occipital activity.

but for periodic stimulation, it is more appropriate to analyse the data in the frequency domain (Norcia et al., 2015).

In summary, after data cleaning procedures, SSVEP responses for the four channels of interest (O1, O2, Oz and Iz) were first averaged. Then the peak of the response to the fundamental frequency of stimulation (either 3 or 9 Hz) was extracted. No further averaging took place before entering into the linear mixed effect model, which requires trial-by-trial data (please see Section 2.6).

2.6 | Analysis

Although it has been shown that there is no difference between blinded and unblinded analysis in the past (e.g., Ambrosini et al., 2017), analysis was conducted

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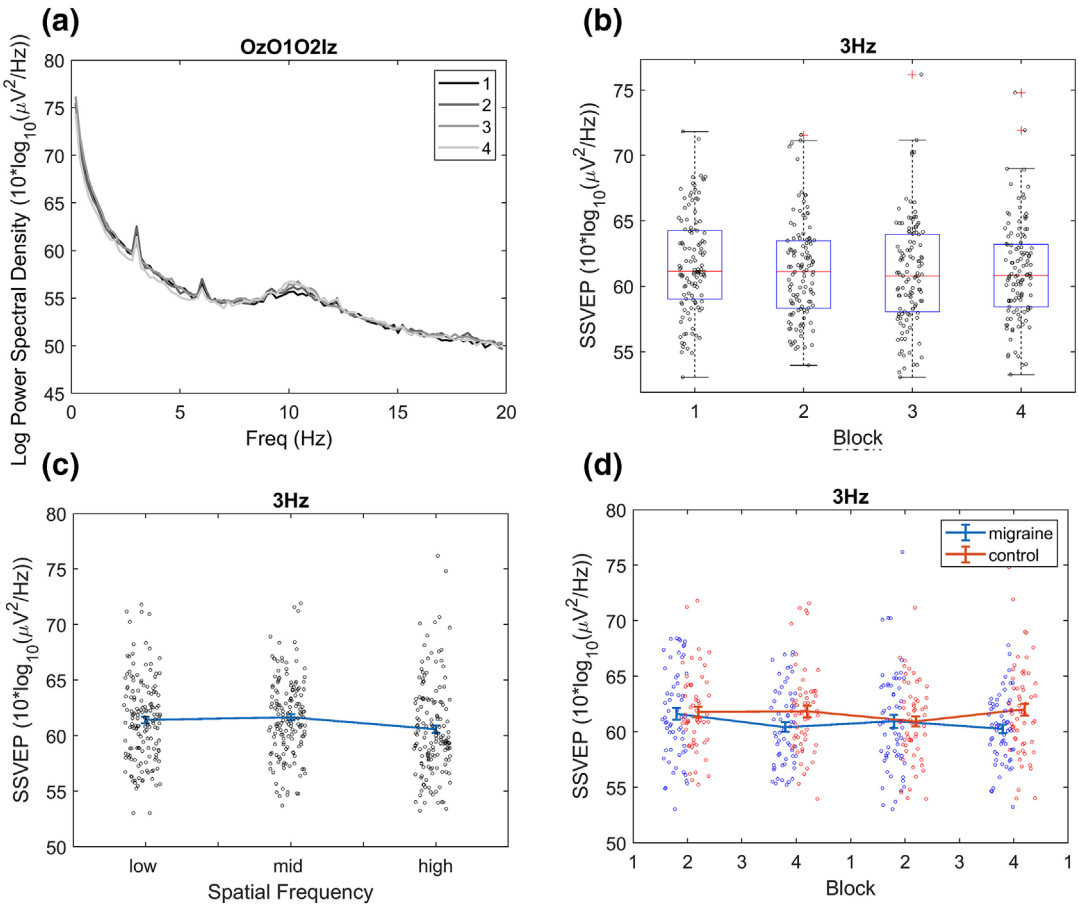

FIGURE 3 SSVEP responses for 3-Hz stimuli. (a) Power spectrum from electrodes O1, O2, Oz and Iz in response to stimulation at 3 Hz, averaged over spatial frequency. Responses were averaged over the four channels. Blocks 1 to 4 represented as individual lines. Peaks can be seen at the fundamental (3 Hz) and the harmonic (6 Hz). (b) Boxplot showing distribution of SSVEP responses for each block, averaged over spatial frequency, for the 3-Hz stimuli. Centre line shows the median, the box outline shows the 25th and 75th percentile. The lower whisker shows 1.5× the interquartile range from the first quartile, and the upper whisker shows 1.5× the interquartile range from the third quarter. Outliers are marked as individual points (crosses). The black scatterplot is overlaid to show the individual data points making up the boxplot. These have been jittered by a small amount for visibility purposes. (c) Mean SSVEP response plotted against spatial frequency for the 3 Hz stimuli. Stimuli are averaged over block and group (migraine or control). Error bars show 1 SE of the mean. The black scatterplot is overlaid to show the individual data points making up the summary statistics. These have been jittered by a small amount for visibility purposes. (d) Mean SSVEP response plotted against block for the migraine and control groups for the 3-Hz stimuli. Responses are averaged over spatial frequency. Error bars show 1 SE of the mean. The black scatterplot is overlaid to show the individual data points making up the summary statistics. These have been jittered by a small amount for visibility purposes.

using a fully automated procedure for reliability. Although it is common to use visual inspection for data cleaning in EEG research, analysis was fully automated in order to minimise the potential for bias in the analysis. Additionally, raw data (EDF files) and analysis scripts (MATLAB and R) can be found at the Open Science Framework (https://osf.io/8fw5g/). Statistical analysis was conducted in R. Linear mixed models were conducted using the package 'lme4' (Bates et al., 2015) to estimate the predictive effect of fixed factors group, spatial frequency and block on first SSVEP response amplitude and also on subjective discomfort judgements, including observer as a random factor. Importantly, temporal frequency was not included as a factor in a single omnibus model, as there is an approximately 1/f spectrum, where f refers to frequency, for the EEG signal (Buzsáki, 2006), and so comparisons across temporal frequency would not be fair. This 1/f spectrum can be seen in Figures 3a and 6a for 3 and 9-Hz stimulation, respectively. As a result, the analysis was completely split by temporal frequency. Linear mixed models can account for nonindependence of clusters of data points (e.g., multiple observations from one observer), by accounting for variance between cluster means (random effects). Linear mixed models have advantages over general linear models in terms of handling small samples

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and missing data points (Arnau et al., 2009; Muth et al., 2016). Likelihood ratio tests were used to estimate statistical significance, and the Satterthwaite approximation will be used to adjust the degrees of freedom for violations of sphericity (Satterthwaite, 1946), which has been suggested to be appropriate for linear mixed models (Luke, 2017). The distribution of the raw data has been demonstrated as boxplots (see Figures 3b, 4a, 6b and 7a, please see Section 3). The reader is referred to the Supporting Information for figures demonstrating the residual plots to test the assumptions of the linear mixed effect model. In most cases, the assumption of homoscedasticity was met; however, the linear mixed effect model is relatively robust to minor violations of this assumption (Grajeda et al., 2016; Jacqmin-Gadda et al., 2007). The Akaike Information Criterion (AIC) was used to estimate the information lost by the model, trading off the number of parameters fitted and the goodness of fit. The AIC is a way of testing how good a model fit is. It is based on the maximum likelihood estimation of the model, and it penalises the number of parameters needed to fit the model. It is useful when comparing between models and selecting the best one. In the current study case, a full model was defined, with all parameters included. This was compared to a reduced model, without the variable of interest, as the 'null' model. The model with the lower AIC gives the best fit. If the null model has a better explanation of the data compared to the full model, then this is an indication that although the model may have a statistically significant *p*-value, one should not put too much emphasis on this finding, as actually the null model gives the better account of the variation in the data. There are published guidelines about cut-offs for strong, middling and weak evidence in favour of the alternative compared to null model, for example, a full model with a difference in AIC of less than two relative to the minimum AIC (in our case, the null model) is considered to represent substantial supporting evidence (Burnham, 2002). The AICc is a special case of the AIC that is corrected for small sample sizes (Hurvich & Tsai, 1989), which was estimated using the 'MuMIn' package in R (Barton, 2019). The alternative model (including all terms) was compared to a null model without the factor of interest. The difference in AICc (ΔAICc) between the alternative and null models gives an estimation of strength of evidence in favour of the model with the lower AICc (least information lost). This difference in AICc can be converted into Akaike weights, using the following formula (Equation 1), which gives an estimation of how many times more likely one model is over the other (Wagenmakers & Farrell, 2004).

$$wi(AIC) = \frac{exp\left(-\frac{1}{2}\Delta i\,(AIC)\right)}{\sum_{k=1}^{k} exp\left(-\frac{1}{2}\Delta k\,(AIC)\right)} \quad (1)$$

where *i* is the model in question. The weights are normalised by the sum of the weights of all models (*k*). In this case, only one model is being compared to the null model at a time.

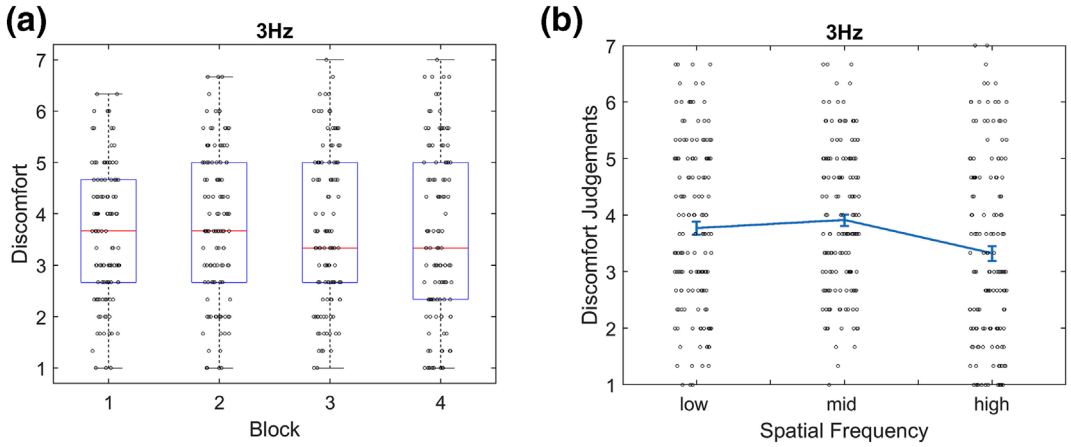

FIGURE 4 Discomfort judgements for 3-Hz stimuli. (a) Boxplot showing distribution of discomfort judgements for each block, averaged over spatial frequency for the 3-Hz stimuli. Centre line shows the median, the box outline shows the 25th and 75th percentile. The lower whisker shows 1.5× the interquartile range from the first quartile, and the upper whisker shows 1.5× the interquartile range from the third quarter. The black scatterplot is overlaid to show the individual data points making up the boxplot. These have been jittered by a small amount for visibility purposes. (b) Mean discomfort judgements plotted against spatial frequency for the 3-Hz stimuli. Stimuli are averaged over block and group (migraine or control). Error bars show 1 SE of the mean. The black scatterplot is overlaid to show the individual data points making up the summary statistics. These have been jittered by a small amount for visibility purposes.

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The weights can be compared using a ratio (Equation 2).

$$\frac{w(AIC)\,model\,1}{w(AIC)\,model\,2} \quad (2)$$

Although the AIC has been criticised for being too liberal compared to other measures of information, for example, Bayes Information Criterion (Kass & Raftery, 1995), however, the AIC does not assume the presence of a 'true' model and also has a correction for small sample sizes, the AICc, therefore in this case, will be used. Figures showing the linear mixed model effects were created using the package 'visreg' (Breheny & Burchett, 2017).

As spatial frequency was a factor, it was possible to conduct post hoc tests using estimated marginal means of the *emmeans()* package in R (Length, 2021) using the method suggested by Searle et al. (Searle et al., 1980).

It should be noted that the use of frequentist statistics can lead to incorrect interpretations of the data presented, with overreliance on *p*-values for interpreting whether effects are present or not. It may be the case that effects are present, but as statistics relies on probability then they are undetected due to small samples, large variability or just by chance (Amrhein et al., 2019; Vasishth & Gelman, 2021). Therefore, as data are presented using *p*-values as a guide, the scientific interpretation of the results should bear the limitations of the *p*-values in mind.

3 | RESULTS

3.1 | 1-Hz stimulation

The signal from the 1-Hz stimulation was rather weak and did not demonstrate a good signal-to-noise ratio; therefore, this was not analysed further.

3.2 | 3-Hz stimulation

3.2.1 | 3-Hz SSVEP responses

Figure 3a shows the spectrum at 3 Hz, averaged over observers, for channels O1, O2, Oz and Iz. Data are averaged over spatial frequency, and the four blocks are shown in the legend.

Boxplots showing the distribution of the SSVEP data (peak response to the fundamental frequencies of the stimulus) for each block can be seen in Figure 3b.

A linear mixed model was used to predict the SSVEP response at 3 Hz, including group, block, spatial frequency and their interactions as fixed factors and observer as a random factor. With the current sample, we found statistical evidence to suggest a main effect of spatial frequency ($F(2407 = 7.98$, $p < 0.001$), $\Delta AICc = 11.45$, wAICc ratio = 93,780), this can be seen in Figure 3c. Post hoc tests using estimated marginal means showed statistical evidence to suggest that the SSVEP response to the high spatial frequencies to be lower compared to the mid-range ($p = 0.0005$) and low spatial frequencies ($p = 0.013$), but there was no statistical evidence to support a difference between the low- and mid-range spatial frequencies ($p = 0.59$).

We were unable to find statistical evidence to suggest a difference between the migraine and control group (as a main effect) given the current sample ($F[1,37] = 1.14$, $p = 0.29$). Additionally, with the current sample, we found no statistical support to suggest that there was a main effect of block ($F[3407] = 1.88$, $p = 0.13$). However, with the current sample size, there is some statistical evidence to support a block × migraine interaction ($F[3407] = 3.94$, $p = 0.008$), with $\Delta AICc = 5.32$, wAICc ratio = 206.07 times the null. This can be seen in Figure 3d. Separate linear mixed models for the migraine and control groups were created to explore this interaction further. For the current observers in the migraine group, there was statistical evidence to suggest an effect of block ($F[3198] = 2.89$, $p = 0.037$), and for the current observers in the control group, there was also statistical evidence to suggest an effect of block ($F[2209] = 2.96$, $p = 0.033$). From Figure 3c, there appears to be a downward trend for the migraine group, although the pairwise comparisons did not survive correction for multiple comparisons using the Tukey method. For the control group, there appears to be an upward trend, Block 4 was higher than Block 3 ($p = 0.04$), although none of the other comparisons were survived correction for multiple comparisons using the Tukey method.

A boxplot showing the distribution of discomfort judgements can be seen in Figure 4a.

3.2.2 | 3-Hz discomfort ratings

A linear mixed model was created to predict discomfort judgements using group, block and spatial frequency and their interactions as fixed effects and observer as a random effect. Considering the current sample, there was statistical evidence to support a significant effect of spatial frequency, ($F[2407] = 12.81$, $p < 0.001$) $\Delta AICc = 20.63$, wAICc ratio = 9.1×10^8, which can be seen in Figure 4b. Post hoc pairwise comparisons showed

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high spatial frequencies to be judged as more comfortable compared to low ($p = 0.01$) and mid-range ($p < 0.001$) spatial frequencies. With the current sample, there was no statistically significant difference between low- and mid-range spatial frequencies ($p = 0.59$).

With the current sample, we found no statistical evidence to suggest a main effect of block (F[3407] = 0.20, $p = 0.89$) and also no statistical evidence to suggest different between the migraine and control groups (as a main effect) with the current sample (F[1,37] = 0.35, $p = 0.56$). We were also unable to find any evidence of an interaction effect between migraine and block for the current sample (F[3407] = 0.32, $p = 0.81$).

It was possible that there may be a predictive effect of SSVEP response on discomfort judgements at 3 Hz. A linear mixed model was created, including SSVEP, migraine, block and spatial frequency and their interactions as fixed factors and observer as a random factor. SSVEP showed a nonsignificant trend towards predicting judgements at 3 Hz (F[2400.70] = 3.55, $p = 0.06$) ΔAICc = 1.39, wAICc ratio = 4.00, and this can be seen in Figure 5, which shows the discomfort judgements plotted against SSVEP. Each symbol represents a different spatial frequency. Although a nonsignificant trend, the discomfort judgements decreased with increasing SSVEP (coefficient = −0.04, ±0.02 standard error).

To summarise, at 3 Hz, SSVEP responses for the migraine group showed a downward trend with increasing block, whereas for the control group, they showed an upward trend. Discomfort judgements for both groups showed that high spatial frequencies were more comfortable compared to low- and mid-range spatial frequencies.

3.3 | 9-Hz stimulation

3.3.1 | 9-Hz SSVEP responses

Figure 6a shows the spectrum at 9 Hz, averaged over observers, for channels O1, O2, Oz and Iz. Data are averaged over spatial frequency, and the four blocks are shown in the legend.

Figure 6b shows the distribution of the SSVEP data for the four blocks for the migraine and control groups prior to any outlier removal procedures.

A linear mixed model was used to predict SSVEP response at 9 Hz, including group, block and spatial frequency and the interaction between migraine and block as fixed factors and observer as a random factor. With the current sample, we found statistical evidence to suggest a main effect of spatial frequency (F[2407] = 3.80, $p = 0.02$), ΔAICc = 3.14, wAICc ratio = 27.59, which can be seen in Figure 6c. Post hoc pairwise comparisons with the current sample using estimated marginal means shows the low spatial frequencies result in a lower SSVEP compared to the mid-range spatial frequencies ($p = 0.018$), but there was no statistically significant difference between the low and the high ($p = 0.31$) and the mid-range and the high spatial frequencies ($p = 0.41$) with the current sample.

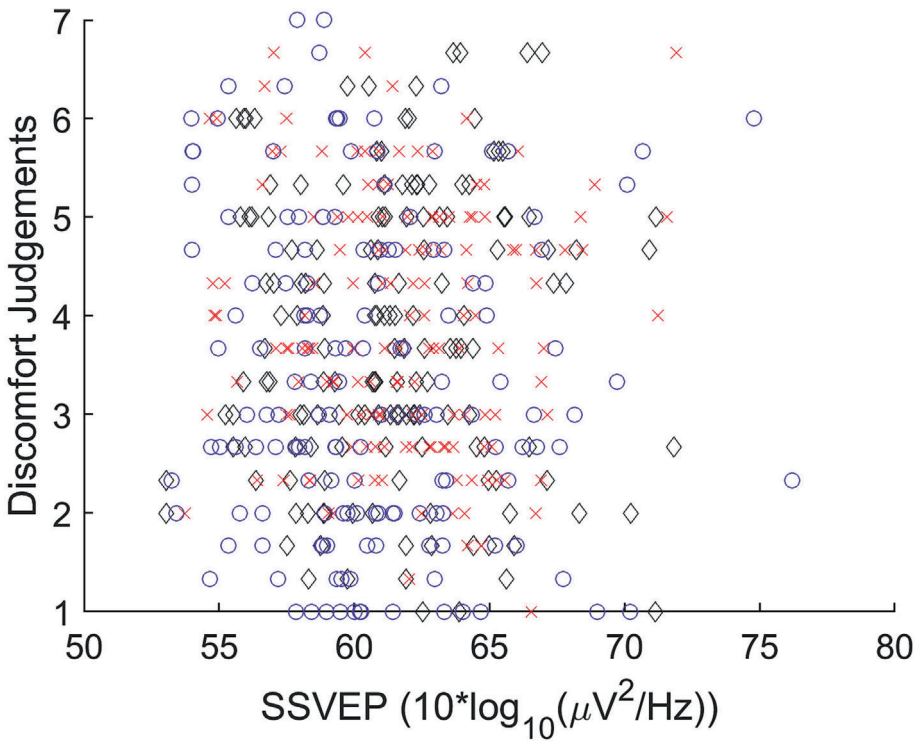

FIGURE 5 SSVEP response plotted against discomfort judgements for the 3-Hz stimuli. Symbols represent the different spatial frequencies.

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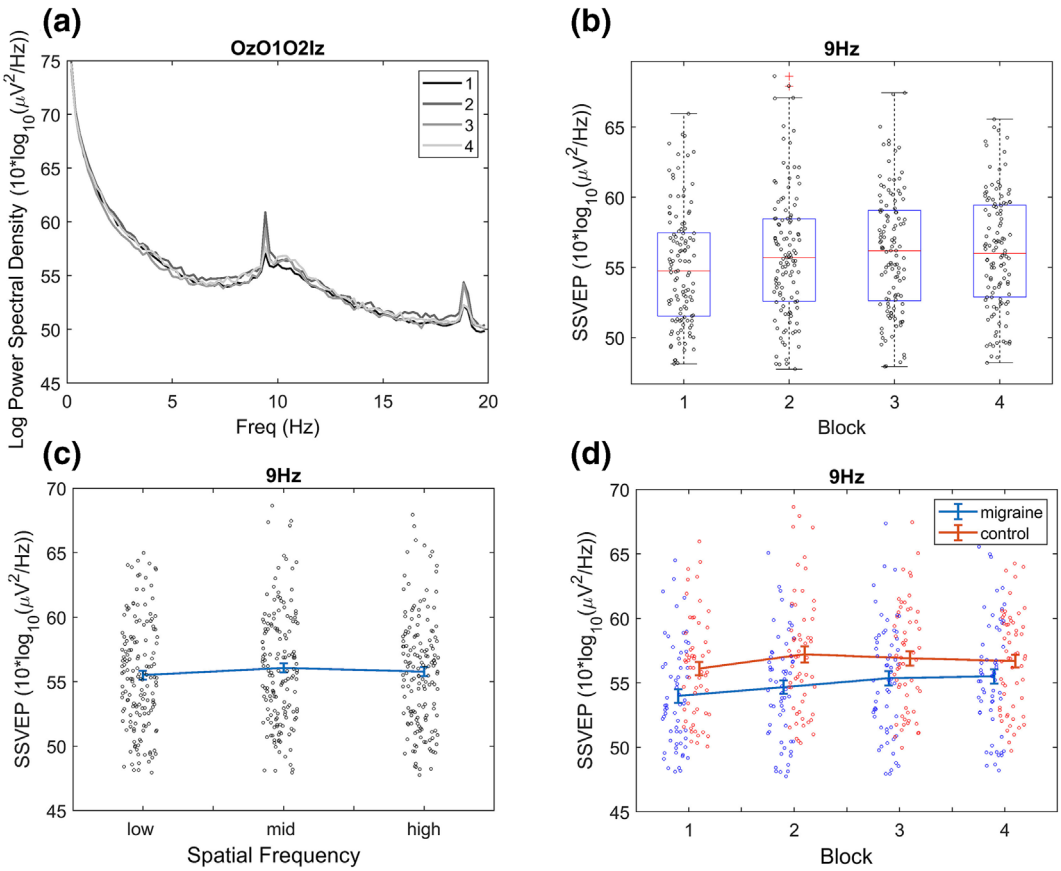

FIGURE 6 SSVEP responses for 9-Hz stimuli: (a) Power spectrum from electrodes O1, O2, Oz and Iz in response to stimulation at 9 Hz, averaged over spatial frequency. Responses were averaged over the four channels. Blocks 1 to 4 represented as individual lines. Peaks can be seen at the fundamental (9 Hz) and the harmonic (18 Hz). (b) Boxplot showing distribution of SSVEP responses for each block, averaged over spatial frequency, for the 9-Hz stimuli. Centre line shows the median, the box outline shows the 25th and 75th percentile. The lower whisker shows 1.5× the interquartile range from the first quartile, and the upper whisker shows 1.5× the interquartile range from the third quarter. Outliers are marked as individual points (crosses). The black scatterplot is overlaid to show the individual data points making up the boxplot. These have been jittered by a small amount for visibility purposes (c) Mean SSVEP response plotted against spatial frequency for the 9-Hz stimuli. Stimuli are averaged over block and group (migraine or control). Error bars show 1 SE of the mean. The black scatterplot is overlaid to show the individual data points making up the summary statistics. These have been jittered by a small amount for visibility purposes. (d) Mean SSVEP response plotted against block for the migraine and control groups for the 9-Hz stimuli. Responses are averaged over spatial frequency. Error bars show 1 SE of the mean. The black scatterplot is overlaid to show the individual data points making up the summary statistics. These have been jittered by a small amount for visibility purposes.

We were unable to find any statistical evidence to suggest a difference between the migraine and control groups (main effect) with the current sample ($F[1,37] = 2.53$, $p = 0.12$). However, with the current sample, we found statistical evidence to suggest a main effect of block ($F[3.407] = 9.75$, $p > 0.001$), $\Delta AICc = 23.75$, wAICc ratio $= 2.0 \times 10^{10}$ and a block × migraine interaction ($F[3407] = 3.01$, $p = 0.03$), $\Delta AICc = 4.22$, wAICc ratio $= 67.75$. This can be seen in Figure 6d. This relationship was explored by creating two models: one for migraine and one for the control group. For the current observers in the migraine group, there was a statistical evidence that there was an effect of block ($F[3198] = 9.57$, $p = 6.25 \times 10^{-6}$), and for the current observers in the control group, there was statistical evidence to suggest a significant effect of block ($F[3209] = 3.79$, $p = 0.01$). For the observers in the migraine group, post hoc pairwise comparisons showed the SSVEP response in Block 1 to be lower than Block 3 ($p < 0.001$) and Block 4 ($p < 0.001$). The other comparisons did not survive correction for multiple comparisons using the Tukey method. For the observers in the control group, the response for Block 1 is lower compared to Block 2, but none of the other comparisons survived the correction for multiple comparisons using the Tukey method. Figure 6d shows the block against SSVEP for the migraine and control groups.

Figure 7a shows the distribution of the discomfort data for the 9-Hz stimulation.

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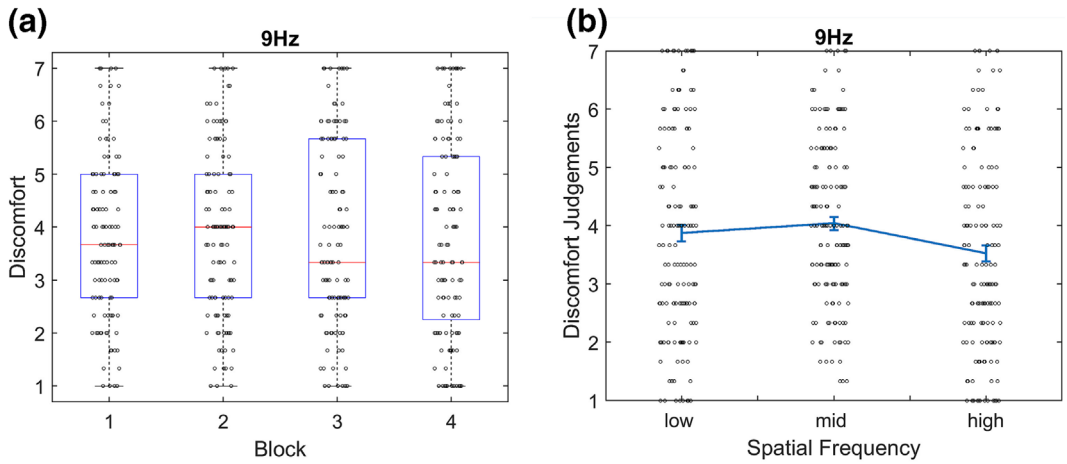

FIGURE 7 Discomfort judgements for 9-Hz stimuli. (a) Boxplot showing distribution of discomfort judgements for each block, averaged over spatial frequency for the 9-Hz stimuli. Centre line shows the median, the box outline shows the 25th and 75th percentile. The lower whisker shows 1.5× the interquartile range from the first quartile, and the upper whisker shows 1.5× the interquartile range from the third quarter. The black scatterplot is overlaid to show the individual data points making up the boxplot. These have been jittered by a small amount for visibility purposes. (b) Mean discomfort judgements plotted against spatial frequency for the 9-Hz stimuli. Stimuli are averaged over block and group (migraine or control). Error bars show 1 SE of the mean. The black scatterplot is overlaid to show the individual data points making up the summary statistics. These have been jittered by a small amount for visibility purposes.

3.3.2 | 9-Hz discomfort ratings

A linear mixed model was created to predict discomfort judgements using group, block and spatial frequency and their interaction as fixed effects and observer as a random effect. With the current sample, there was statistical evidence to suggest a main effect of spatial frequency ($F[2407] = 8.48$, $p < 0.001$), $\Delta AICc = 12.39$, wAICc ratio 2.4×10^5 times more likely than the null. Post hoc comparisons using estimated marginal means the high spatial frequencies to have lower discomfort judgements compared to the low ($p = 0.01$) and mid-range spatial frequencies ($p < 0.001$) but no statistically significant difference between the low- and mid-range ($p = 0.57$) spatial frequencies with the current sample. Discomfort judgements against spatial frequency can be seen in Figure 7b.

Considering the current sample, we were unable to find statistical evidence to suggest there was a difference between the migraine and control groups (main effect of migraine) ($F[1,37] = 0.38$, $p = 0.54$), and similarly, we were also unable to find statistical evidence to suggest that there was an effect of block on discomfort judgements ($F[3407] = 0.28$, $p = 0.84$). Finally, with the current sample and analysis method, we were unable to find evidence of an interaction between migraine and block ($F[3407] = 0.06$, $p = 0.98$).

A linear mixed model was created to see if there was a predictive effect of SSVEP response amplitude at 9 Hz on discomfort judgements. SSVEP, spatial frequency, migraine and the interaction between spatial frequency and migraine were included as fixed effects and observer as a random effect. With the current sample, we were unable to find statistical evidence to suggest that there was an effect of SSVEP response amplitude in predicting discomfort judgements ($F[1290.23] = 0.04$, $p = 0.83$).

To summarise, for the migraine group, SSVEP responses at 9-Hz stimulation showed an increase with block, whereas for the control group, the first block only showed lower SSVEP responses compared to subsequent blocks, as this appears to plateau. High spatial frequency stimuli were judged to be more comfortable compared to mid-range or low spatial frequencies.

3.4 | Auxiliary measures

3.4.1 | Pattern sensitivity

Pattern sensitivity to gratings was estimated using the method of Evans and Stevenson (2008); the total number of positive responses to 3-cpd stimuli, those with scores higher than three, was deemed to experience pattern glare. With the current sample, we were unable to find statistical evidence to suggest a difference between the control group reporting visual discomfort from the 3-cpd pattern compared to the migraine group (Fisher's exact test, $p = 0.76$).

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3.4.2 | Time to last migraine attack

Linear mixed model was created to estimate the effect of days since last migraine attack (included as a fixed factor) on SSVEP response, with observer as a random factor. Control subjects were coded as 'nan'. With the current sample, we did not find any statistical evidence to suggest that time since last attack predicts SSVEP response at 3 Hz ($F[1,18] = 0.04$, $p = 0.84$), or at 9 Hz ($F[1,18] = 3.08$, $p = 0.10$).

4 | DISCUSSION

There were four main hypotheses for the current study, the first two related to habituation: (a) SSVEP amplitudes will decrease over block (indicative of habituation); (b) SSVEP amplitudes will be significantly different between migraine and control groups, specifically showing less of a decline over block in the migraine group (lack of habituation). Previous literature suggests a lack of habituation in migraine (Áfra et al., 1998, 2000; Ambrosini et al., 2017; Bohotin et al., 2002; Bednář et al., 2014; Coppola et al., 2010; Judit et al., 2000; Lisicki et al., 2017; Kalita et al., 2018; Schoenen et al., 1995); however, this is not conclusive. The main aim of this study was to investigate the possibility of habituation in migraine for different spatial and temporal frequencies, as the previous literature has tended to focus on similar stimuli. There was a lower signal-to-noise at 1-Hz stimulation compared to the other conditions, as there are fewer reversals at 1 Hz; therefore, this was no included in the analysis. At 3-Hz stimulation, there was a downward trend in SSVEP responses in the migraine group suggesting intact habituation processes. For the 9-Hz stimulation, there was an effect of block and importantly an interaction between migraine and control groups. The control group showed an increase in SSVEP responses from Block 1 to the later Blocks (2, 3 and 4), but this appeared to plateau in the remaining blocks. However, the migraine group did show a change in SSVEP responses, in the form of *increasing* SSVEP responses with increasing block, which may be an indication of increased cortical *responsiveness* in migraine (Coppola et al., 2007), which is an increase in activity after an initial lower baseline response. This is in contrast to the theory of *hyperexcitability* (Aurora & Wilkinson, 2007), which suggests that individuals who experience migraine have overall higher levels of neural activity compared to controls. As in the current study, those with migraine appeared to have lower initial levels, this seems to support the idea of hyperresponsiveness (Coppola et al., 2007) rather than hyperexcitation (Aurora & Wilkinson, 2007).

This complex pattern of results appears to be dependent on temporal frequency. Although behavioural habituation effects, for example, oculomotor capture, may be increased with a greater number of stimuli (Bonetti & Massimo, 2019), it is possible that SSVEP responses may not follow the same pattern. Although these studies were not studies of habituation processes, previous researchers found different SSVEP effects depending on stimulation frequency—for frequencies of 3, 4 and 8.57 Hz, there was an increase in SSVEP response to visual stimuli, but for 6 Hz frequencies, there was a reduction (Bekhtereva & Müller, 2015; correction 2017; Bekhtereva et al., 2018). It has been suggested that the SSVEP response is a linear supposition of transient ERP responses (Capilla et al., 2011), and so these waveforms can potentially have destructive interference effects (Heinrich, 2010; Capilla et al., 2011; Bekhtereva et al., 2018). From Table 1, it can be seen that previous research into the effects of repetitive visual stimulation in migraine has typically used a single stimulation frequency, which may result in a narrow view of the effects of repetitive visual stimulation on those with migraine.

There are some limitations of the way the stimuli were presented during the study. The visual system is thought to consist of different spatial frequency channels, which may influence each other (Wilson and Wilkinson, 1997). Whilst the overall exposure to each of the spatial and temporal frequency stimuli as equal for observers, and equal within each block, there may be issues with this method. For example, a particular channel responding to 3-cpd stimulus may have the opportunity to recover during the presentation of the 12-cpd stimuli, for example. This presents a potential issue in interpreting the results in this experiment. How much of an issue this is depends on the timescale for habituation and recovery from this habituation. If recovery is within a block, then this will serve to reduce any habituation/potentiation effects. Additionally, there are well-known interaction effects between spatial frequency channels, for example, cross-channel suppression (Foley, 1994). It is possible that by exposure to 9-cpd stimuli, then the cross-channel inhibition will have acted to sharpen the response to 3-cpd stimulus, for example. Adaptation to a particular spatial frequency will affect the sensitivity to neighbouring frequencies (cross-channel suppression), although the range for this is thought to be limited to relatively close neighbouring frequencies. For example, Blakemore and Campbell (1969) showed there to be much reduced threshold elevation after adapting to 3.5-cpd stimuli in response to 9-cpd stimuli, and this response would have extrapolated to the baseline at the 12-cpd stimuli. Although some researchers have failed to find evidence

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of cross-channel suppression effects, these seem to be pronounced for superimposed low spatial frequency stimuli, similar to the 0.5 cpd used in the current study (for a discussion, see Meese & Hess, 2004). Additionally, the time needed to recover from adaptation is related to the initial adaptation period, for example, adapting to a stimulus for 60 s led to a 60-s period for recovery (Blakemore & Campbell, 1969). However, there may be longer periods for adaptation to gratings, for example, it has been shown that the effects of the adaptation did not revert to baseline levels even after the posttest period of 270 s but had reverted to baseline after 1 h of rest in the normal visual environment (Mei et al., 2017). As the stimuli in the current experiment were presented for several seconds, it might be suggested that any influence of cross-channel suppression may be limited. However, this possibility cannot be ruled out. Therefore, it is difficult to predict the potential impact of cross-channel suppression in the current study, and therefore, this is a limitation. An alternative method for future research would be to present stimuli of one type (e.g., 3 cpd at 3 Hz) within its own block and compare the SSVEP responses at the beginning to those at the end. This would involve counterbalancing to counteract any potential order effects.

Additionally, during the time between blocks, the visual stimulus was the room in which the EEG recording took place. Observers could blink freely and look around the room although head movements were restricted by the EEG recording equipment. The lights were turned on to allow the experimenter to check on the observers for ethical reasons. The time was self-paced, but all participants completed the experiment in approximately the same overall time; therefore, it is unlikely that there are substantial differences between observers during the rest periods; however, this cannot be ruled out. Unfortunately, we did not record during the rest periods in-between blocks, and so we cannot analyse these rest periods for each observer. This is a limitation of the current study.

Low-contrast levels were used in the current study to limit the likelihood of causing extreme visual discomfort and also the possibility of eliciting a migraine attack itself. As much of the previous literature showing reduced habituation in migraine used high-contrast stimuli (see Table 1), this creates an issue for direct comparison. It has been noted that the effects of habituation have been greater at low-contrast levels compared to high-contrast levels (Rankin et al., 2009; Thompson & Spencer, 1966); therefore, it was expected that we would still be able to see habituation effects even at low contrasts. There are a limited number of studies using low-contrast stimuli investigating habituation in migraine. Using relatively low-contrast stimuli (30%), which would have been expected to result in increased habituation, Oelkers-Ax et al., (2005) showed no habituation deficit in those with migraine compared to controls. Bednář et al. (2014) found the habituation deficit in migraine compared to control groups at 85% but not at low contrasts 14%. The interpretation of these results is complex. Although habituation processes may be greater at lower contrast levels, VEP signals to low-contrast stimuli are simply smaller. It could be that either the habituation deficit is only found for high-contrast stimuli because lower contrast increases habituation in general and so the group difference disappears, or it could be that smaller VEPs to low-contrast stimuli have a lower signal-to-noise ratio compared to high-contrast stimuli. It would be fruitful in future research to investigate the role of contrast on habituation in migraine systematically, perhaps using the SSVEP approach which has better signal-to-noise ratios in general.

It has been suggested that repetitive visual stimuli can drive neural oscillations, dependent on the stimulation frequency and the particular individual's frequency for their ongoing oscillations (e.g., individual alpha frequency), which has been shown for visual (e.g., De Graaf et al., 2013) and multimodal stimuli (e.g., Cecere et al., 2015). By increasing and decreasing the speed of ongoing alpha-band oscillations using neurostimulation techniques, Cecere et al. (2015) were able to demonstrate changes in the temporal window of integration for visual and sound information using the flash-beep illusion. Specifically, there have been demonstrable effects of the importance of the phase of the ongoing alpha-band oscillations at the time of stimulus onset for perception (e.g., Dugué et al., 2011; Ergenoglu et al., 2004; Hanslmayr et al., 2005; Hanslmayr et al., 2007). There is evidence to suggest that neural oscillations in migraine may be different from control groups (Mehnert et al., 2019; O'Hare et al., 2018), and so the interaction between stimulation frequency and ongoing oscillations is something to consider.

The heterogeneity of the sample is an issue throughout migraine research. The current study did not discriminate between MO and MA, as previous research has shown no difference in habituation between these migraine subgroups (e.g., Bednář et al., 2014; Omland et al., 2013). By using linear mixed models for the analysis, this provides a more sophisticated way of handling individual differences that are ubiquitous in migraine research, through statistical modelling, rather than relying on averaging. The use of *p*-values in research has been criticised (e.g., Nuzzo, 2014); therefore, this is used as a rule of thumb here and estimates of the strength of the evidence (ΔAICc) was calculated in addition.

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There is evidence that the habituation deficit increases between attacks (interictally) and disappears during the attack (Coppola et al., 2013; de Tommaso et al., 2014; Judit et al., 2000). There is fMRI evidence for differences in neural activity throughout the migraine cycle (Schulte & May, 2016), and MRI evidence for structural changes throughout the migraine cycle (Coppola et al., 2015). Cycle effects have been suggested as a reason for the mixed findings in research into habituation in migraine (Magis et al., 2016). Cycle effects were not addressed in the current study, as if habituation deficits are a reliable biomarker for migraine, it would be needed to be demonstrable interictally, as patients do not always present at the medical professional clinic at the time of their choosing, and it would be expensive and time consuming for medical professionals to administer EEG throughout the migraine cycle on a diagnostic basis. However, there was tentative evidence of a relationship between time to last attack and SSVEP response magnitude for 9-Hz stimulation, with longer time since the last attack increasing SSVEP responses. From previous research, it might be expected that the longer the time, the greater the response would be; however, in the current study, this is based on one self-reported time estimate, it is not valid to compare to studies measuring effects over the migraine cycle using migraine diaries (e.g., de Tommaso et al., 2014; Judit et al., 2000).

To summarise, previous researchers showed a lack of habituation in those with migraine; however, the current study did not show this. Instead, for 9-Hz stimulation, there was an increase in SSVEP responses with increasing block. This might be indicative of a build-up of brain activity over successive presentations for the migraine compared to the control group.

5 | DISCOMFORT JUDGEMENTS

The second two hypotheses for the current study related to discomfort judgements, it was predicted that (c) spatial characteristics of the stimuli will affect SSVEP amplitudes; and (d) SSVEP amplitudes will be related to discomfort judgements. There were lower discomfort judgements for the higher spatial frequency stimuli for both the 3- and 9-Hz stimuli in both groups. One possible reason for this is that the peak of the spatial contrast sensitivity function shifts with increasing temporal frequency (Kelly, 1977). A shift in the peak of the contrast sensitivity function might mean that the perceived contrast is lower at certain temporal frequencies. This is speculative, as it was not estimated in the current study. Additionally, the temporal contrast sensitivity function (e.g., Kelly, 1977) shows that stimuli presented at higher temporal frequencies (e.g., 9 Hz in the current study) stimuli may require less contrast to be perceived compared to slower 3-Hz stimuli. As a result, it must be noted that stimuli may not be matched for perceived contrast (visibility) across temporal frequencies. There is a mixed literature about differences in overall contrast sensitivity in those with migraine compared to controls, with some authors finding deficits in contrast sensitivity (e.g., Shepherd et al., 2012) and others finding no deficits, possibly even superior contrast sensitivity (Asher et al., 2018). We are unaware of any study specifically exploring the temporal contrast sensitivity function in those with migraine and therefore have no predictions based on this. Therefore, temporal frequencies were analysed separately. Future research might investigate differences in contrast sensitivity at different temporal frequencies in migraine compared to control groups.

We failed to find evidence for any statistically significant difference in discomfort judgements between migraine and control groups in the current study. This result was unexpected as those with migraine tend to report greater visual discomfort compared to those without (e.g., Marcus & Soso, 1989). However, for ethical reasons, stimuli were not very intense in the current study; specifically, contrast was rather low, and exposure time was limited to 20 s at a time. This may have the result that the stimuli were simply too weak to result in pronounced group differences for discomfort judgements. Additionally, as individuals tended to choose values from the middle of the scale, rather than the extreme, one could imagine that these stimuli were not particularly uncomfortable. It is possible that there may be other methods of measuring visual discomfort that avoid the issues of rating scales. One option is to increase the contrast of the stimulus until it is considered unbearable to look at (e.g., Haigh et al., 2012; Karanovic et al., 2011; Thabet et al., 2013). This could be explored with contrast sweep techniques for measuring SSVEP; however, this may have the issue that those with migraine may abort the stimulus earlier and have therefore less data compared to the control participants. The different techniques for addressing the issues inherent to measuring subjective responses could be explored in future research.

Alternatively, it has been suggested that visual discomfort in migraine may be unrelated to the image-forming pathways but is due to the photosensitive retinal ganglion cells (Noseda et al., 2010). Previous work by Thabet et al. (2013) also failed to find correspondence between task performance and visual discomfort in migraine, and therefore, it is possible that visual discomfort is separate, and therefore, there would not be a

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relationship between discomfort and SSVEP response in the image-forming pathways in the current study. This is speculative and beyond the scope of the current study.

Unusually, there was no difference in pattern sensitivity for the migraine and control group in the current sample, unlike previous studies (e.g., Harle et al., 2006; Shepherd, 2000, 2006). However, previous studies have shown differences between migraine and high visual discomfort groups (Conlon & Humphreys, 2001), suggesting that despite an overall tendency for those with migraine to be more susceptible to visual discomfort, migraine and visual discomfort are separate. In the current study, both individuals with and without aura were included. It is also possible that those with MO simply do not experience the same visual sensitivity compared to those with aura. Although there was a similar pattern of spatial frequency tuning for both SSVEP responses and discomfort judgements in the case of the 3-Hz stimuli, SSVEP responses did not predict discomfort judgements at either 3 or 9 Hz. This is contrary to the idea that increased neural responses result in increased discomfort judgements. However, it could be the case that due to the low overall contrast of the images, stimuli were simply not strong enough to cause visual discomfort from excessive neural responses. This decision was made on ethical grounds, as high-contrast flicker might be particularly aversive to those with migraine and may have the effect of triggering an attack (Harle et al., 2006).

In summary, in previous research using static stimuli, mid-range spatial frequencies have been shown to be more uncomfortable compared to high and low spatial frequencies (Wilkins et al., 1984). In the current study (using similar spatial frequency ranges), results showed the higher spatial frequency stimuli were shown to be the least uncomfortable, possibly due to poorer visibility at the faster levels of flicker. It was also expected that the migraine group would show increased discomfort on the Pattern Glare Test compared to control group; however, in the current study, this was not the case.

6 | CONCLUSION

There was a trend to reduced SSVEP responses to repetitive stimulation at 3 Hz, indicating intact habituation processes in the migraine group. However, at 9-Hz stimulation, there was an increase in SSVEP responses in the migraine group, whilst this effect plateaued in the control group. This might be suggestive of a build-up of brain activity in the migraine group that may speculatively result in increased aversion to flicker at 9 Hz. From these results, the effects of temporal frequency need to be accounted for in terms of investigating habituation in migraine. Higher spatial frequencies were judged to be less uncomfortable, in line with previous research; however, this did not relate to the magnitude of SSVEP responses, suggesting efficient coding may not account for the findings here.

AUTHOR CONTRIBUTIONS

Alex Sharp: Conceptualisation, methodology, investigation—data collection, writing the manuscript, writing the manuscript—original draft and review and editing.

Julia Föcker: Investigation—data collection, training and supervision, writing—review and editing.

Louise O'Hare: Conceptualisation, methodology, software, training and supervision, data analysis, writing the manuscript—original draft and review and editing.

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CONFLICT OF INTEREST STATEMENT

There are no conflicts of interest to report.

DATA AVAILABILITY STATEMENT

Raw data and analysis scripts can be found on the Open Science Framework: https://osf.io/8fw5g/?view_only=c69382aed8c64766994b5d5645c2b4d2

PEER REVIEW

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