Differences in early and late pattern-onset visual-evoked potentials between self-reported migraineurs and controls

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ARTICLE INFO

Keywords: VEP Migraine Pattern glare Aura Visual disturbance N2

ABSTRACT

Striped patterns have been shown to induce strong visual illusions and discomforts to migraineurs in previous literature. Previous research has suggested that these unusual visual symptoms to be linked with the hyperactivity on the visual cortex of migraine sufferers. The present study searched for evidence supporting this hypothesis by comparing the visual evoked potentials (VEPs) elicited by striped patterns of specific spatial frequencies (0.5, 3, and 13 cycles-per-degree) between a group of 29 migraineurs (17 with aura/12 without) and 31 non-migraineurs. In addition, VEPs to the same striped patterns were compared between non-migraineurs who were classified as hyperexcitable versus non-hyperexcitable using a previously established behavioural pattern glare task. We found that the migraineurs had a significantly increased N2 amplitude for stimuli with 13 cpd gratings but an attenuated late negativity (LN: 400 – 500 ms after the stimuli onset) for all the spatial frequencies. Interestingly, non-migraineurs who scored as hyperexcitable appeared to have similar response patterns to the migraineurs, albeit in an attenuated form. We propose that the enhanced N2 could reflect disruption of the balance between parvocellular and magnocellular pathway, which is in support of the cortical hyperexcitation hypothesis in migraineurs. In addition, the attenuation of the late negativity could reflect a top-down feedback mechanism to suppress visual processing of an aversive stimulus.

1. Introduction

Research on visual stress has proposed that the aversive visual responses to gratings of specific spatial frequencies could be due to the cortical hyperexcitation of the visual cortex (Evans et al., 1994; Harle et al., 2006; Wilkins, 1995). This hypothesis was mainly based on the research of migraine patients, who have shown evidence of hypersensitivity to gratings in various behavioural and neurophysiological studies (Aurora and Wilkinson, 2007). The hypersensitivity here was defined as the experience of visual discomfort (e.g. headache, pain) and distortions (e.g. illusory stripes, phantom colors, shimmering, flickering, etc.) when an individual was viewing certain gratings.

Visual evoked potentials (VEPs) are EEG responses that are both time and phase-locked to the onset of a visual stimulus. Studies using magnetoencephalography (MEG) and functional magnetic resonance imaging (fMRI) revealed that the initial observable VEP components, C1 and N75 are originated from the V1 (Di Russo et al., 2005; Hatanaka et al., 1997). On the other hand, the generators of the later components, P100 and N145 have been localised to the extrastriate visual cortex (V2 – V4; Di Russo et al., 2005; Lehmann et al., 1982; Schroeder et al., 1995; Vanni et al., 2004). Importantly, the peak amplitude and latency of these early components are consistently found to be influenced by the psychophysical features of the visual stimuli such as spatial frequency, contrast and colour (Ellemberg et al., 2001; Oelkers et al., 1999; Souza et al., 2008).

The difference in VEP peak amplitude or latency obtained from group comparisons (clinical vs control) may indicate impairment of early visual processing in certain patient groups (e.g. migraine; Afra et al., 1998; Shibata et al., 1997, 1998). For example, prolonged or increased P100 was found to be associated with the visual hallucinations and other forms of visual disturbances amongst the Parkinson (Kupersmith et al., 1982) and schizophrenic populations (Foxe et al., 2001). amongst all the clinical populations who are highly susceptible to visual disturbances, the VEPs of migraine sufferers (with/without aura) have been most widely studied (e.g. Di Russo et al., 2005; Shibata et al., 2005). Previous studies on early VEP components (e.g. N75, P100, and N145) have found that migraine sufferers have increased peak-to-peak amplitudes for both N75-P100 and P100-N145

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https://doi.org/10.1016/j.nicl.2019.102122
Received 13 August 2019; Received in revised form 17 November 2019; Accepted 10 December 2019
Available online 16 December 2019
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participants had normal/corrected visual acuity (20/25 or better). Such increase in amplitudes could result from the lack of inhibitory control over the cortical pyramidal cells during visual stimulation which in turn leads to a spread of neural activity in the visual cortex (Sand et al., 2008). Heterogenous measurements on peak latencies have also been reported, with studies revealing a rather mixed set of findings including prolonged, shortened or unchanged peak latencies in migraineurs (Afra et al., 1998; Oelkers et al., 1999; Shibata et al., 1997; Tagliati et al., 1995). One particular study, Oelkers et al. (1999), found a prolonged N2 latency in migraine patients compared to control (Oelkers et al., 1999; Yilmaz et al., 2001). They attempted to account for this finding by proposing that the N2 component consists of a parvocellular “N130” (contour processing) and magnocellular “N180” complex (luminance processing). The prolonged N2 latency in the migraineurs could emerge due to an enhancement in the N180 as a result of the imbalance of the two visual pathways.

In addition to the early VEP components, previous research has also found that migraineurs also exhibit abnormality for late components (e.g. Drake et al., 1989; Mazzotta et al., 1995; Puca and Tommaso, 1999). The P3 is a positive ERP complex, which peaks maximally over central-parietal electrodes at around 300 ms after the onset of infrequent (“oddball”) stimuli occurring within a train of frequent standard stimuli. The latency of the P3 has been suggested to reflect the time it took participants to discriminate/categorise the oddball stimulus as deviant, while the amplitude decreases with their confidence in that discrimination (see Picton, 1992 for review). Previous research has found that migraineurs often have a longer P3 latency in oddball paradigm (Bockowski et al., 2004; Chen et al., 2007; Drake et al., 1989; Mazzotta et al., 1995) indicating a more prolonged time needed to discriminate the target stimuli. Studies with the primary focus on VEP between 400 – 700 ms have been somewhat limited and often reported with contradictory findings (Mickleborough et al., 2013; de Tommaso et al., 2009; Steppacher et al., 2016). This does suggest though that the differences in the VEPs of migraineurs and non-migraineurs are not restricted to early exogenous ERPs (i.e. occurring within 200 ms post-stimulus onset).

1.1. Current study

Migraineurs are known to be more susceptible to visual discomfort and distortions in viewing gratings of 2 – 4 cycles per degree (cpd) of visual angle, a phenomenon known as pattern glare (Evans and Stevenson, 2008). Here we set out to compare the VEPs elicited by gratings having 3 different spatial frequencies (0.5, 3, and 13 cycles per degree: cpd) between migraineurs and non-migraineurs, with N2 as our primary focus. Evans and Stevenson (2008) proposed that pattern glare is a consequence of over-stimulation within the same neural network in a hyperexcitable visual cortical area. Therefore, in parallel with migraineurs, non-clinical populations who have hyperexcitable visual cortex might also show symptoms of pattern glare. In order to investigate this possibility, we compared the VEPs elicited by gratings between a larger group of non-migraineurs separated into a hyperexcitable and non-hyperexcitable group according to the behavioural responses to a pattern glare task.

2. Methods

2.1. Participants

Twenty-nine migraine female patients (mean age = 20.9) and 31 healthy female controls (mean age = 19.4) participated in the first study. Seven additional healthy female subjects were later added to the second part of the study comparing hyperexcitable and non-hyperexcitable non-migraineurs (total: 38, mean age = 19.3). All the participants had normal/corrected visual acuity (20/25 or better). The participants in the control group reported no history of migraine nor any other neurological and psychiatric conditions. In the migraine group, 17 were classified as having migraine with aura and 12 with migraine without aura based on the criteria proposed by the International Headache Society (Bell et al., 2005; Olesen, 2018). They were not regularly taking prophylactic medications (and had not taken one within 2 weeks of the EEG session), nor had chronic migraine, motor migraine aura symptoms or any other forms of neurological or psychiatric conditions. Finally, these participants were studied interictally, such that they did not have a migraine attack in the week leading up to the EEG recordings, and followed up for at least 2 weeks after the recordings. This study has been approved by the Ethics Committees of the University of Birmingham (reference number: ER-NE_14-0875AP1A).

2.2. Stimuli, apparatus and questionnaires

The stimuli used in this experiment included 3 square-wave achromatic gratings: a low-frequency grating (LF) of 0.5cpd, a medium-frequency grating of 3cpd, and a high-frequency grating of 13cpd (see Fig. 1 for an example of the grating). All stimuli were presented at the centre of a 20-inch Dell P2210 LCD computer screen (60 Hz refresh rate and 1680 × 1050 pixels screen resolution) using E-prime v2.0 software, with a background luminance of 20 cd/m². The Michelson contrast of all the 3 gratings was 0.70 (cd/m²). Each of them had an identical shape with the maximum height x width of 140 mm x 180 mm with the shape of a mild ellipse different in spatial frequency (cycles-per-degree: cpd). The viewing distance was fixed at 80 cm, which gave a visual angle of 9.93 × 12.68°.

Participants also completed 2 questionnaires which measure the trait-based predisposition to anomalous perceptions: the Cortical Hyperexcitability index – II (CHI-II) (Fong et al., 2019) and the Cardiff Anomalous Perceptual Scale (CAPS) (Bell et al., 2005). The CHI-II has three factors representing different types of anomalous visual experiences, namely, (i) heighted Visual Sensitivity and Discomfort (HVSD); (ii) Aura-like Hallucinatory Experiences (AHE); (iii) Distorted Visual Perception (DVP). Similar to CHI-II, CAPS could be broken down into 3 components: Temporal Lobe Experience (TLE), Chemosensation (CS) and Clinical Psychosis (CP).

2.3. Procedures

2.3.1. The pattern-glare (PG) task

The participants completed a computerised version of the pattern-glare task, where observers reported phantom visual distortions from viewing highly irritable visual patterns (Braithwaite et al., 2015; Fong et al., 2019; Evans and Stevenson, 2008). Each trial began with a 12-second-presentation of one of the three gratings (presented in a
pseudo-random order; see Fig. 1 for the grating). Participants were instructed to gaze on a fixation point located at the centre of the grating.

After the stimuli presentation, participants gave their responses on the intensity/strength of the associated visual distortions (AVD; visual pain, physical eye strain, unease, headache, dizziness, light-headedness, faint, shadowy shape, illusory stripes, shimmering, flickering, jitter, zooming, blur, bending of lines, and colour distortions: red, green, blue, yellow) they had experienced using a 7-point Likert scale (0 = not at all, 6 = extremely; see Fig. 2 for the trial sequence). The responses for each AVD were added together to give a total AVD score for that grating (range = 0 – 120). AVD scores for each grating were obtained from the average AVD of the 3 repetitions for that spatial frequency.

The pattern glare effect could be indicated by the AVD scores of the 3 cpd condition or the AVD scores of 3 cpd subtracted from the 13 cpd condition (Evans and Stevenson, 2008; Fonget al., 2019). In the current study, the latter criterion was adopted.

2.3.2. EEG task
After the completion of the pattern glare task, we examined the EEG responses of participants elicited by the presentation of each grating. Each trial began with a 2s-fixation period where the participants were asked to fixate on a cross at the centre of the screen after which one of the gratings (HF, MF or LF) was then presented. Participants were instructed to keep their focus at the centre of the stripe patterned-disc. Then, they were asked to either hit the left-click by their index finger when their visual discomforts/distortions had reached the maximum (typically around 2 to 10 s) or the right-click by their middle finger when they did not experience any forms of visual discomforts/distortions at all after 8 s counting in their minds. Each trial was separated by an 8 s inter-stimulus interval (see Fig. 3 for the EEG task trial sequence).

Each grating was presented 50 times in pseudo-random order. The total 150 trials were divided into 10 blocks which were separating by breaks (the durations were entirely controlled by the subjects).

2.3.2.1. EEG data acquisition. The EEG signal was recorded using an EEGO Sports amplifier (ANT Neuro) and Waveguard caps containing 64 Ag/AgCl electrodes (10-20 layout including left and right mastoids). During online recordings, the electrode CPz was used as a reference while AFz was used as ground. The data was subsequently re-referenced to an average reference offline. The EEG was recorded at a sampling rate of 500 Hz, with a high pass of 0.8 Hz and low-pass of 30 Hz (implemented in the EEGOSPORTS acquisition software). Electrode impedances were kept below 20 kΩ. Two pairs of bipolar EOG electrodes were used to measure both horizontal and vertical eye movements. One was placed at the outer canthi of left and right eyes while another pair was placed at the left lid-cheek junction and above left eyebrow. Heartbeat data, which was not used in the present study, was measured by placing a pair of ECG electrodes on the left and right chest (grounded at left collar bone).

2.3.2.2. Pre-processing. The EEG data were pre-processed in Matlab using EEGLAB functions (version 14.1.2b; Delorme and Makeig, 2004). First, the data was epoched from − 500 to 1500 ms around the stimulus onset. We chose not to baseline correct the data to a pre-stimulus time period as to not confound possible baseline differences between the participant groups. Nevertheless, subsequent analyses did not reveal any baseline differences between any of the groups. Muscle and ocular artefacts (e.g. eye blinks) were removed using independent component analysis (infomax algorithm) incorporated as the default “runica” function in EEGLAB. A Principal Component Analysis (PCA) was used to reduce dimensionality of the data to 30 components before performing the independent component analysis (ICA). Trials were then inspected visually, and those with muscle artefacts and noise not corrected by the ICA were removed. Spherical interpolation function in EEGLAB was used to fix the bad electrodes in the data (see Ferree, 2000). Finally, a 20 Hz low-pass filter was applied to the data using the default settings in ‘pop_eegfiltnew’ (e.g. transition band width was 25% of the lower passband edge).

2.4. Design and analysis
The cleaned epoched data was further analysed by FieldTrip software package (Oostenveld et al., 2011) using both confirmatory and exploratory approaches. The trials epoched around the onset of each of the visual gratings were averaged to obtain VEPs. The Oz electrode was chosen to measure the early VEP components according to the latencies after the stimulus onset (Di Russo et al., 2005; Khalil et al., 2000). The
peak latency range (N2 and other components) for each of the gratings was defined by visual inspection, on the grand-averaged ERPs, collapsed across all participants. A two-tailed independent samples t-test was performed to assess the statistical significance of differences in the mean peak amplitude and peak latency within these time-intervals of the interest between groups. In addition, Bayesian analyses were conducted by JASP version 0.8.0.1, using the default Cauchy prior width (0.707) (Love et al., 2015; Rouder et al., 2012). The analysis provides relative evidence and probability on whether the data are more in favour of the alternative hypothesis (H_a) (BF_10 > 1.0) or the null-hypothesis (H_0) (BF_10 < 1.0). For example, a BF_10 of 0.1 suggests that the H_0 is 10 times more likely than the H_a. In general, a BF_10 close to 1 are not informative, while a BF_10 > 3 or < 0.33 can be interpreted as moderate evidence in favour of the H_a or H_0 respectively (Jarosz and Wiley, 2014).

As an exploratory approach, any amplitude differences within the time window 0–700 ms between-group were assessed by non-parametric cluster-based permutation analysis (Maris and Oostenveld, 2007). The adjacent spatiotemporal sample data was first clustered if they exceeded a threshold of p < .05 (cluster-alpha). The cluster with a Monte Carlo p-value smaller than 0.025 was identified as significant (simulated by 1000 partitions), thus, showing a significant group difference in amplitude.

3. Results

3.1. Migraine vs healthy control

3.1.1. VEP component analysis

As mentioned earlier, the peak latency range for each of the gratings was defined by visual inspection, on the grand-averaged ERPs, collapsed across all participants, at the occipital Oz electrode. The key component − N2 was defined as the mean amplitude between 170–240 ms for HF, 140–180 ms for MF, and 150–185 ms for LF. The independent samples t-test showed that the migraineurs had a more negative N2 amplitude in HF conditions than control group (mean: −2.67 μV vs −1.21 μV), t (58) = 2.744, uncorrected p = .008, False Discovery Rate (FDR) corrected p = .024, BF_{10} = 5.59 (see Fig. 4 & Table 1).

For exploratory purposes, we also analysed the group-differences of other early visible local peaks. The N1 was defined as the mean amplitude within the latency range of 75–115 ms and 75–100 ms for MF and LF, respectively. The P2 was defined as the mean amplitude within the range 115–140 ms, 100–130 ms, 95–125 ms for HF, MF, and LF (see Fig. 4). In addition, the peak latency for each condition was measured by the local peak latency within the range defined above. However, we did not observe any other significant differences in the mean peak amplitude of the other ERP components between the two groups across all visual contrasts, all p > .30. Since there was no systematic latency shift between the two groups of subjects across three conditions, statistics on peak latency were not reported.

3.1.2. Cluster-based permutation analyses

The non-parametric cluster-based permutation analysis was carried out on the 0–700 ms time window after the stimulus onset for three different spatial frequency conditions. The clusters were formed by significant t-stats of potential differences between migraine and control group. Given the scalp topography of the early VEP components are typically bipolar with a frontal and occipital scalp distribution, we have chosen to display only the wave-forms in significant cluster of electrodes over occipital regions.

We found that for the HF gratings, non-migraineurs relative to the migraineurs group had a significantly more negative VEP at 382–538 ms post-stimulus (p = .002, Monte Carlo p-value, corrected for multiple comparisons) maximally distributed over the parietal and occipital regions (see Fig. 5). A similar pattern was observed over the posterior electrodes for MF (384–486 ms, p = .023, Monte Carlo p-value, corrected for multiple comparisons) and LF (368–486 ms, p = .012, Monte Carlo p-value, corrected for multiple comparisons) conditions (see Fig. 6 and 7).

3.1.3. Behavioural tests

3.1.3.1. Pattern glare results. Migraineurs showed significantly more AVD response at all spatial frequency conditions than control group after FDR correction (HF: p = .004; MF: p = .021; LF: p = .004; see Table 2). However, the subtraction parameter −ΔAVD (MF - HF) comparison between migraineurs and control was not significant.

3.1.4. Post-hoc comparison for migraineurs with and without aura

We did a within group analysis comparing the VEP of patients whose migraine were associated with aura and those without aura. We found that the mean amplitude of N1 induced by MF gratings for the migraineurs with an aura was significantly reduced compared to the migraineurs without an aura (mean: −1.88 μV vs −4.20 μV), t (27) = 2.32, p = .034, BF_{10} = 2.09. Such a difference between conditions was not observed in other spatial frequencies (see Fig. 8). Apart from this, there were no other significant differences between the migraineurs with and without an aura in all other ERP and behavioural measures.

3.2. Pattern glare (PG) vs non-pattern glare (non-PG)

Finally, the non-migraine participants were split into two groups according to their ΔAVD score (AVD of MF subtracted by HF). The participants who have a ΔAVD > 3.92 were categorised as PG group (n = 15, mean age = 18.8) while those scoring less than 3.92 were categorised as a non-PG group (n = 23, mean age = 19.7). This reference score was obtained by a previous study (Pong et al., 2019).

As we did in the last section, the N2 component was first visually identified and defined by a latency range (HF: 150 – 180 ms; MF: 130 – 165 ms; LF: 140 – 180 ms). The amplitude for the component was calculated by the average potential within the above time window. We found that the PG group exhibited a more negative N2 amplitude in HF condition than non-PG group significantly (mean: −2.22 μV vs −0.38 μV), t (36) = 2.176, p = .036, BF_{10} = 1.93 (see Fig. 9).

Next, any amplitude or latency differences for other VEP components (on Oz) was further explored. The latency range averaged for a peak component was shown in Table 4. In addition, latency for the components was measured as the local peak/trough within the defined latency range.

Our exploratory analyses discovered an increased P3 amplitude for the PG-group compared to non-PG group (mean: 2.96 μV vs 0.99 μV), t (36) = 2.213, p = .033, BF_{10} = 2.04 although it did not reach significance after FDR correction. These results were summarized in Table 5. Since there was no systematic latency shift between the two groups of subjects across three conditions, statistics on peak latency were not reported.

3.2.2. Late components

The cluster-based permutation analyses at 300 - 700 ms revealed two marginally significant clusters in the MF conditions. The positive cluster (p = .061) involved 14 centro-parietal channels (CP2, CP6, P3, Pz, P4, CP4, P5, P1, P2, P6, PO5, PO3, PO4, PO6) between 410 – 478 ms (see Fig. 10). Once again, due to the dipolar nature of the VEP topography we have chosen to show the waveforms over significant electrodes over the occipital cortex. Such clusters were not observed in the other two spatial frequencies (all p > .3).
3.2.3. Behavioural measures – PG task and questionnaires

Behavioural measure differences between PG group and non-PG group were also explored. Table 6 showed that ΔAVD difference mainly resulted from a high mean AVD in MF for the PG group. For the questionnaire measures, there were positive correlations between the N1 amplitude (for both HF and MF gratings) and the HVSD score (Spearman’s rho: N1(HF) vs HVSD = 0.330, p = .040; N1(MF) vs HVSD = 0.346, p = .033), meaning a higher HVSD score was associated with a less negative/reduced N2 amplitude.

4. Discussion

In the current study, we used both a confirmatory and exploratory approach to compare the in VEPs elicited by gratings of different spatial frequencies between a group of migraineurs and non-migraineurs. We found that after the presentation of the high-frequency gratings (13 cpd), the migraineurs exhibited an enhanced negative N2. A within-group analysis found that this was observed in both of the migraine groups. However, a post-hoc analysis did reveal a N1 difference with the migraineurs with aura having a significantly reduced N1 amplitude than those without aura. Our exploratory analysis showed, for all gratings, an attenuation of the post-stimulus (400–500 ms) late negativity (LN) over occipital channels in the migraine group. In the second part of the analysis, the PG group appeared to have similar VEP responses as migraineurs, with an increased N2 for HF and decreased LN for MF.

4.1. Findings on migraine

4.1.1. Increment of N2 complex revealed cortical hyperexcitability

The enhanced N2 we observed in the migraneurs and non-migraneurs with a high-pattern glare score is in line with previous studies using pattern reversal VEP paradigm (Lahat et al., 1997, 1999; Shibata et al., 1997. We propose that our findings are specifically inline with Oelkers et al. (1999) who observed that migraineurs (with and without an aura) had anomalous N2 responses when checkerboard stimuli with a high spatial frequency were presented (2 and 4 cpd). Importantly, they observed no significant differences between the N2 of migraineurs and controls for stimuli with low spatial frequencies (0.5 and 1 cpd). To account for their findings, they proposed that the N2 complex, could be a superposition of the N130 (driven primarily by high-frequency features of the stimuli) and N180 (driven by luminance). They speculated that the N130 was primarily mediated by the parvocellular pathway and was present for both migraineurs and non-migraineurs with a high-pattern glare score.
healthy subjects whereas the N180 was mediated by the magnocellular pathway predominated in the N2 complex for migraineurs. They concluded that the N2 anomaly in the migraineurs could be accounted for by an attenuation of the N130 or a more predominant N180, in either case representing an imbalance or impairment in connectivity between the magnocellular and parvocellular systems. While our stimuli were different from Oelkers et al. (they used checkerboards, while we used gratings), we also found the anomalous N2 in migraine patients to emerge for the high-spatial frequency condition (13 cpd) mediated by the parvocellular pathway. In terms of the difference between our stimuli, animal studies also observed that the response pattern of the V1 induced by checkerboard and grating stimuli is quite similar, although the visual cortex appeared to be more sensitive to grating (De Valois et al., 1979).

This impairment in the connectivity between the two systems could be caused by cortical hyperexcitability or abnormalities in GABAergic inhibitory interneurons (Chronicle and Mulleners, 1994). In addition, the increased N180 was only visible for migraineurs when high-frequency gratings were repeatedly presented while there was a decrease in amplitude for healthy controls under the same stimulation conditions (Oelkers-Ax et al., 2005). Importantly, the N180 potentiation (lack of habituation) for migraineurs could underlie cortical hyperexcitation since it is direct evidence for the dysfunction of the inhibitory systems in the visual cortex.

Consistent with the above hypothesis, the N2 in the present study for migraineurs peaks at 200 ms instead of the commonly reported 130–145 ms, suggesting that it was predominated by the N180. Although the stimulation condition of our study was different to Oelkers et al. (1999) in which phase-shifting checkerboard pattern was used, both of our findings demonstrated that the N2 effect for migraineurs was exclusive for the high spatial frequency condition.

The neuronal responses of the primary visual cortex for gratings and checkerboards both peak at similar spatial frequency, yet they have a higher contrast sensitivity for the former pattern (De Valois et al., 1979). Therefore, square-wave grating can be considered as a stronger visual input than checkerboard with a similar psychophysiological property. Theoretically, with achromatic, high luminance contrast, high spatial frequency and stationary stimuli, the neural responses would be dominated by the parvocellular system (Merigan et al., 1991; Tobimatsu et al., 1995). In a contrast sensitivity test, it was found that...
an impaired magnocellular system did not influence visual sensitivity with low temporal frequency stimuli (Merigan and Maunsell, 1990). Therefore, the current N2 deflection could be mainly parvocellular driven. The parvocellular impairment for migraineurs has been previously reported in the literature (McKendrick and Badcock, 2003; Sand et al., 2009), though there was also evidence implying a magnocellular deficit for migraineurs (Benedek et al., 2002; McKendrick et al., 2001). However, these results should not be considered as contradictory since different stimulation conditions (e.g. contrast, luminance, spatial and temporal frequency) would trigger a heterogeneous involvement of the parvocellular and magnocellular systems, which could lead to the discrepancies in VEP findings. As a result, the abnormal N2 should be considered as a characteristic component using a parvocellular-dependent stimulation method.

It might be argued that if the increased N2 is driven by cortical hyperexcitation, a similar N2 deflection should be observed on MF condition as well. One explanation for this divergence could be that the N2 components increased with the spatial frequency of the visual input and as such only becomes visible for high-frequency condition. This is consistent with previous literature showing an enhancement of the early negative potentials as a function of grating frequency (Oeklers et al., 1999; Hudnell et al., 1990). An alternative but not mutually exclusive explanation is that there is a “phantom” positive component, namely the P200 cancelled out the negativity of N180. Some literatures showed that visual P200 is associated with motion onset (Schulte-Korne et al., 2004). Although the presentation of the stimuli was steady in the experiment, the 3 cpd grating could cause a spread of discharge beyond V1 to motion perception related regions such as V3 and V5, leading to illusions of movement (Evans and Stevenson, 2008; Ffytche et al., 1995). This mechanism could also explain why jittering and shimmering are so common as a form of motion illusions induced by gratings in 3 cpd (see Braithwaite et al., 2015; Evans and Stevenson, 2008; Fong et al., 2019). The hypothesised VEP model and the role of N130, N180 and the “phantom” P200 are summarised in Fig. 11.

4.1.2. Pathological difference between migraine subtypes

Another finding related to sensory processing is that our migraine with aura group had a significantly attenuated N1 amplitude than migraine without aura group for the MF condition, in line with previous studies (see Coppola et al., 2015; Khalil et al., 2000). The amplitude difference in early VEP components between the migraine subtypes is...
Fig. 8. Grand mean of the VEP (medium frequency) at Oz between migraine with aura (MWA) and migraine without aura (MWOA). There was a significant amplitude difference for N1.

Fig. 9. Grand mean of the VEP measured at Oz in HF (top), MF (middle) and LF (bottom) conditions for PG group vs non-PG group (shaded area indicating +/- 1 S.E.). The arrows indicated significant amplitude differences of N2 between the two groups. The differences in VEP for these two groups with migraines were also shown, with the arrow indicating the N2 for migraines. The time-intervals of interest used for the average peak amplitude is shaded in grey.
Results of independent t-tests and Bayes factor on N1, P2, and P3 amplitudes between PG group and non-PG group (with Table 5: Leynes and Addante, 2016; Friedman, 2013). In addition, affective and P1 remained unchanged after receiving the same stimulation enhanced by altering cortical hyperexcitability through rTMS while N1 (Fong et al., 2019).

A study had demonstrated that later VEP components could be enhanced by altering cortical hyperexcitability through rTMS while N1 and P1 remained unchanged after receiving the same stimulation (Thut et al., 2003). Later, Di Russo et al. (2005)’s VEP-fMRI study confirmed that the visual N1 and the later component N2 might be originated from a different neural generator. These literatures appeared to support the multi-dimension model of cortical hyperexcitability and provide an explanation to the pathological difference between migraine subgroups.

4.1.3. Late stage visual processing on gratings

Unlike the trend in early VEP components, there were no significant differences between the two migraine subgroups in late ERPs according to the cluster-based permutation analysis. However, significant group differences in late ERP amplitudes between migraine patients and healthy controls were obtained across all spatial frequencies. These differences were denoted by the LN (centred at parietal and occipital-temporal areas) peaked around 400 – 500 ms. Such activities were originated from a different neural generator. These literatures appeared to support the multi-dimension model of cortical hyperexcitability and provide an explanation to the pathological difference between migraine subgroups.

4.2. Findings on healthy PG group

4.2.1. Evidence of cortical hyperexcitability supported by early VEP components

The PG group showed increased N2 amplitude compared to the non-PG group for the HF grating. Interestingly, this finding was similar to the above observation in which migraineurs showed abnormal N2 response compared to healthy controls. However, the current N2 component peaked at around 150 ms instead of 200 ms, suggesting a potential difference in the underlying neurocognition between the two negative components. Based on the VEP waveform, the current group difference was more likely to be caused by the increment of N130 in the absence of a migraine-specific N180 (see Fig. 12). The amplitude of N130 appeared to be increased with the spatial frequency of the grating. The absence of it in the low frequency condition provides support for the notion that the PG group might have abnormal responses along the parvocellular pathway.

We hypothesised that a “phantom” P200 component could have been cancelled out by a migraine-specific predominating N180. This P200 is also thought to be associated with aberrant experience induced by the grating. In the sample of healthy population, with the absence of N180, an increased P200 (shown as P3 in Fig. 9) was observed on the PG group (who experienced excessive pattern glare in MF grating) compared to the non-PG group. The model of VEP for MF is summarised in Fig. 12. Collectively, our findings provide initial support that cortical hyperexcitability could be the basis of the experienced pattern-glare effect but now further extended to non-clinical groups and to specific EEG components. Since the abnormal N130 on non-migraine healthy images were known to elicit an enlarged LP compared to neutral images (Schupp et al., 2004). Migraineurs were found to have a reduced LP amplitude when affective images were presented regardless of the valence of pictures (de Tommaso et al., 2009). Abnormal LP was also reported in other literature with varied findings in uncertain directions - an increment or reduction (Mickleborough et al., 2013; Mickleborough et al., 2014; Steppacher et al., 2016). Although late potentials have rarely been studied in a pVEP paradigm, it is possible that the aversive gratings induce a similar top-down bias on visual processing, leading to such an LP group difference. This explanation is also supported by our behavioural data, which has shown that migraineurs have an increased visual sensitivity at all spatial frequencies in the PG task, in line with previous research with other behavioural or physiological measures (Oelkers et al., 1999; Huang et al., 2003). Therefore, this top-down bias could cause visual attention inhibition and counterbalance the discomfort caused by the hypersensitivity of migraineurs on the gratings. However, we cannot rule out the possibility that our migraine sample had a general visual attention deficit regardless of the context of the stimuli which were also found in the literature (Ince et al., 2017; Mourtan et al., 2011; Villa et al., 2009). In future studies, an appropriate baseline image, such as a non-striped pattern picture, would benefit the research by revealing whether the group effects were indeed associated with the spatial frequency of the striped patterns.

Table 4: The latency range (ms) of the early VEP component in different spatial frequency (S.F.).

| S.F. | N1 (MF) 70 – 105 | P2 (MF) 105 – 150 | P3 (MF) 150 – 200 |
|------|----------------|-----------------|------------------|
| HF   | 70 – 95        | 100 – 130       | 170 – 210        |
| MF   | 70 – 120       | 180 – 225       |                  |

Note: There was no visible N1 for LF and P3 for HF.

4.1. Late stage visual processing on gratings

Collectively, our findings provide initial support that cortical hyperexcitability could be the basis of the experienced pattern-glare effect but now further extended to non-clinical groups and to specific EEG components. Since the abnormal N130 on non-migraine healthy

Table 5: Results of independent t-tests and Bayes factor on N1, P2, and P3 amplitudes between PG group and non-PG group (with S.E. in parenthesis).

| Mean amplitude of components (μV) | PG (n = 15) | Non-PG (n = 23) | t-stat | Uncorrected p-value | FDR corrected p-value | BF10 |
|----------------------------------|-------------|-----------------|--------|---------------------|-----------------------|------|
| N1 (HF) | −0.84 (0.78) | −1.28 (0.51) | −0.75 | .46 | .54 | 0.40 |
| N1 (MF) | −2.94 (1.20) | −2.26 (0.73) | 0.52 | .61 | .61 | 0.36 |
| P2 (HF) | 0.88 (0.74) | 2.42 (0.66) | 1.52 | .14 | .28 | 0.78 |
| P2 (MF) | 1.08 (0.92) | 3.63 (0.82) | 2.02 | .05 | .18 | 1.54 |
| P2 (LF) | 4.88 (0.96) | 6.96 (0.98) | 1.44 | .16 | .28 | 0.72 |
| P3 (MF) | 2.96 (0.75) | 0.99 (0.53) | −2.21 | .03 | .18 | 2.04 |
| P3 (LF) | 0.83 (0.67) | −0.34 (0.58) | −1.31 | .20 | .28 | 0.62 |
population has never been reported, whether the deflection was resulted from a potentiation effect is unknown at present. Further investigations on the potentiation and habituation effects of PG and non-PG participants could prove revealing in this regard.

The N1 for MF and HF were found to be positively correlated (Spearman’s rho = 0.346 & 0.330) with one of the CHi-II factors – namely HVSD. If the neural source of this initial negative component was the same as the one highlighting the migraine subgroup difference (e.g. V1), then this dimension of cortical hyperexcitability could underlie everyday life pattern or light-induced visual stress symptoms as well as the pathological difference of migraine subtype.

4.2.2. Evidence of selective visual processing by late VEP

Apart from sensory processing, VEP components peaked at around 200 – 300 ms can also reflect higher-order cognitive modulation such as selective attention on spatial frequency (Proverbio et al., 2002; Zani and Proverbio, 1995, 2009). For instance, P200 was believed to be responsible for selective attention (Hackley et al., 1990; Noldy et al., 1990) and features detection (Luck and Hillyard, 1994). In our current setting, we are unable to conclude the source of the P3 deflection on the hyperexcitable participants. However, such deflection was not observed in other spatial frequencies which is consistent with the selective attention theory (Zani and Proverbio, 2009). Whether this finding implies an attentional enhancement of the PG group on MF due to their illusive perception would require more in-depth investigation.

Though the cluster-based analysis was just marginally significant, the attenuated LN on PG group in MF could be another supportive evidence on selective attention on spatial frequency. Based on the migraine sample, we proposed that the LN reduction could be either caused by a top-down visual attention inhibition or a general visual attention deficit. Results in this part seemed to support the former theory as the LN reduction only appeared in MF. Since participants in PG group are more averse to MF grating, this top-down processing could counterbalance their hypersensitivity as well as the earlier attentional enhancement by disengaging from the stimuli.

However, the limitation of our interpretation is that attention was not manipulated in our experiment apart from the verbal instructions telling the subjects to concentrate on the fixation spot. Therefore, whether the effect on LN was caused by attention awaits clarification.

Fig. 10. The average ERP (MF) over the marginally significant channels of the positive cluster (posterior region). The marginally significant channels were highlighted in bold on the topographies (both the positive and negative clusters). PG group had an attenuated VEP compared to non-PG group between 430 and 470 ms (shaded in grey).

Table 6

| Mean AVD for PG and non-PG across HF, MF and LF conditions (with S.E. in parenthesis). |
| Mean AVD | PG | Non-PG |
|----------|----|--------|
| HF       | 12.4 (1.94) | 12.2 (1.56) |
| MF       | 16.4 (2.02) | 11.5 (1.37) |
| LF       | 4.87 (1.29) | 3.52 (0.70) |

Fig. 11. Model of the migraine VEPs for high frequency (HF) and medium frequency (MF). The N2 complex can be hypothesized as a superposition of N130, N180 and P200. For the HF condition, migraineurs had an increased luminance-dependent N180. The predominating N180 outweighed the P200. For the MF condition, the N180 increase was cancelled out by a sharp P200.
5. Conclusion

In conclusion, migraine patients have an increased N2 amplitude in HF gratings compared to controls, suggesting the presence of a sensory impairment and consistent with the notion of cortical hyperexcitability. In addition, pathological differences between migraine subgroups are supported by a significantly higher N1 amplitude in the MWOA than MWA group. Apart from the early VEP, the late negativity across all spatial frequencies differ in migraineurs and healthy controls may imply migraineurs’ attentional inhibition to the striped patterns. Some current findings on healthy PG group are consistent with results on migraineurs. This similarity highlighted the contribution of cortical hyperexcitability underlying pattern induced visual disturbances and top-down suppressive control on visual gratings.

CRediT authorship contribution statement

Chun Yuen Fong: Writing - original draft, Formal analysis, Conceptualization, Methodology. Wai Him Crystal Law: Writing - review & editing, Investigation, Visualization, Software. Jason J. Braithwaite: Conceptualization, Writing - review & editing, Supervision. Ali Mazaheri: Formal analysis, Writing - review & editing, Supervision.

Acknowledgements

We thank all the participants for taking part in this study. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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