Original article

Title: Abnormal inhibition-excitation imbalance in migraine.

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Abstract:

Background: People with migraine show increased surround suppression of perceived contrast, a perceptual analogue of centre-surround antagonistic interactions in visual cortex. A proposed mechanism is that cortical 'hyperexcitability' or 'hyperresponsivity', a prominent theory in the migraine literature, drives abnormal excitatory-inhibitory balance to give increased local inhibition. The purpose of this cross-sectional study was to determine whether cortical hyperresponsivity and excitatory-inhibitory imbalance manifests in the visual cortical response of migraine sufferers.

Methods: Interictal steady-state visual evoked potentials (VEPs) in response to 0 to 97% contrast were recorded in 30 migraine participants (15 without aura, 15 with aura) and 21

non-headache controls. Monotonicity indices were calculated to determine response saturation or supersaturation. Contrast gain was modelled with a modified saturating hyperbolic function to allow for variation in excitation and inhibition.

Results: A greater proportion of migraine participants (43%) than controls (14%) exhibited significant VEP supersaturation at high contrast, based on monotonicity index (chi-square, p=0.028). Supersaturation was also evident by the trend for greater suppressive exponent values in migraine compared to control individuals (Mann-Whitney rank sum, p=0.075)

Conclusions: Supersaturation in migraine is consistent with excess excitation (hyperresponsivity) driving increased network inhibition and provides support for excitatory-inhibitory imbalance as a pathophysiological disturbance in migraine.

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INTRODUCTION

Neurones in visual cortex do not respond linearly to stimuli of increasing contrast (contrast gain). Most cells in macaque areas V1 and V2 saturate at high contrast (1). As contrast rises, the cell's excitatory response is increasingly inhibited by a 'normalisation pool' of neighbouring neurones (2, 3). This produces saturation or a plateau in response amplitude with increasing contrast. However, ~25% of V1 and V2 cells show supersaturation at high contrast, with responses decreasing rather than plateauing (4, 5). This is considered to arise from stronger network normalisation (4). Thus, net neural network output varies depending on the cortical excitatory-inhibitory balance.

Visual evoked potentials (VEP) can be recorded non-invasively to measure the massed electrical signal from human visual cortex. Cortical VEP sources in response to contrast are mostly localised to visual areas V1, V2, and V5 (6). However, the exact neural currents underlying VEP signals are incompletely understood. Based on current models of primate V1 neurophysiology, the visual cortical response is presumed to reflect net neural network output, involving excitatory feed-forward and feedback connections and inhibitory intra-V1 connections (7, 8). When excitation and inhibition is balanced, human VEP contrast gain, like most primate visual cortical cells, typically shows response saturation (see for example

(9, 10)). Supersaturation of VEP contrast gain is rarely noted in human observers, however (see (11).

Here, we consider the possibility that VEP supersaturation reflects an atypical balance between excitation and inhibition in visual cortex. Specifically, we use migraine as a model for brain excitatory-inhibitory imbalance (12), given recent behavioural evidence for altered antagonistic excitatory-inhibitory centre-surround interactions. People with migraine show increased perceptual suppression of both visual motion and contrast stimuli relative to non-headache controls (13, 14). The perceptual measures – motion duration thresholds (15) and perceived contrast suppression (16) – are common tasks that are considered analogues of neuronal centre-surround suppression.

Increased perceptual suppression, however, is counterintuitive to that predicted by abnormal cortical responsiveness in between migraine attacks, typically referred to as cortical ‘hyperresponsivity’ or ‘hyperresponsivity’(17, 18).We will refer to this presumed cortical abnormality in migraine as ‘hyperresponsivity’ throughout this paper, as this more neutral term does not imply an underlying mechanism for the neural abnormality that specifically involves altered excitation. Evidence for interictal cortical hyperresponsivity in

migraine includes reduced thresholds for inducing phosphenes with transcranial magnetic stimulation of V1 (19) and V5 (20) and increased fMRI signal intensity in V1 (21) and V5 (22). However, whether hyperresponsivity arises from altered excitation or inhibition, or both, is still unclear. The aim of this study was to measure VEP contrast gain to investigate the excitatory-inhibitory balance in migraine. If migraine hyperresponsivity arises from overall decreased inhibition, VEP responses might fail to saturate and continue to rise with contrast. Alternatively, and consistent with increased perceptual suppression in migraine, hyperresponsivity could drive excessive local network inhibition, leading to supersaturation at high contrast.

METHODS

Participants

The study was approved by the Human Research Ethics Committee of the University of Melbourne. Participants provided written informed consent according to the tenets of the Declaration of Helsinki.

A power analysis was performed using data from previous work measuring VEP amplitude at maximum (97%) contrast (23, 24), which revealed a significant decrease in VEP amplitude in migraine participants in between attacks. The analysis indicated that 18 participants in each group provided a power of > 0.80 (α=0.05) for detecting a 40% decrease (effect size d=0.86) in VEP amplitude at 97% contrast in people with migraine. Thus, twenty-one control (29 ± 7 years) and 30 migraine participants (32 ± 7 years) were recruited via advertisements and from previous studies (23, 24). Age was similar between groups (t_{49}=1.35, p=0.18).

Participants were screened to ensure normal vision and ocular health (corrected visual acuity of 6/7.5 or better on the standard logMAR chart, intraocular pressure < 21mmHg, clear ocular media and healthy retinae) and excluded for systemic disease or medications

known to affect vision or neurological state. Control participants had never experienced migraine and were free from regular headaches (less than four in the past year). Migraine participants met the International Headache Society criteria for migraine without aura (MO, n=15) or migraine with aura (MA, n=15) (25). None of the migraine participants was on medications for migraine prophylaxis. A single test session was scheduled in the interictal period at least three days removed from an attack, as VEP amplitude is known to vary with time pre- and post-migraine (26). Self-reported migraine characteristics of MO and MA participants were similar (Table 1).

Electrophysiological recordings

The methods for VEP recording according to the International Society for the Clinical Electrophysiology of Vision guidelines (28) have been described in detail elsewhere (23). In brief, VEPs were recorded monocularly using the Espion E^2 system (Diagnosys LLC, Cambridge, UK). An opaque patch was used to occlude the non-recorded eye. A checkerboard stimulus (31° field, 0.8° checks, 53 cd/m^2 mean luminance, 0.5° central fixation target) was presented at 50cm on a gamma-corrected CRT monitor (Sony G520, 100 Hz frame rate, 1024×768 pixel resolution). The stimulus temporal frequency was chosen to elicit a steady-state response (8.3 Hz), predominantly originating from areas V1

and V5 (29), as previous work consistently demonstrates perceptual anomalies in visual motion processing in migraine (14, 30-32).

Gold cup electrodes were placed according to the typical VEP montage (28), with the active electrode at O_Z overlying the visual cortex at 10% nasion-inion distance (~3 cm) above the inion. As visual cortex location can vary around this position (33, 34), two additional active electrodes were placed at 5% nasion-inion distance (~1.5 cm) above and below O_Z, with a common reference at F_Z. No difference was found between these placements ($F(1.63,55.3)=2.02$, $p=0.15$); hence, signals were averaged across three active electrodes. Electrode impedance was balanced and did not exceed 10 kOhms.

To measure contrast gain, we presented stimuli of 4, 9, 18, 37, 73, and 97% Michelson contrast. We adopted a fixed order of stimulus presentation from low to high contrast to prevent uncontrolled carry-over of contrast-dependent adaptation. In addition, each contrast condition was interleaved for one minute with a spatially homogenous grey stimulus (0% contrast) of same mean luminance (53 cd/m^2).

A total of 200 signals were recorded and averaged per contrast level, with blink artefacts ≥100 μV rejected. To achieve 200 recordings, each test period was limited to collect 25 signals (~20 seconds duration) at a time and repeated. This short duration of continuous recording was chosen as people with migraine frequently find high-contrast patterns aversive (35), and given past reportsfor 'habituation' deficits in migraine sufferers (36) when recordings are made continuously over minutes. A typical recording session lasted 30 minutes allowing for brief breaks.

Amplitudes (μV) at the second harmonic (2F, 16.7 Hz) were extracted post-hoc by Discrete Fourier Transform (see Figure 2) in Microsoft Excel (Microsoft, Redmond, WA, USA). Responses where 2F amplitude fell below noise levels at the neighbouring frequencies, 14.6 and 18.8 Hz, were discarded (37).

Modelling of contrast gain

To differentiate between monotonic and non-monotonic contrast gain, a monotonicity index (m_i) was calculated for each individual (5), based on raw VEP amplitudes:

$$m_i = 1 - \frac{R_{max} - R_{100}}{R_{max} - R_0} \qquad \text{(Equation 1)}$$

where R_{max} was the maximum amplitude across all contrasts, R_{100} was the amplitude at maximum contrast, and R_0 was the amplitude at 0% contrast.

A saturation index of 1 indicates saturation at high contrast, whereas supersaturation (reduced response at high contrast) gives an index < 1. To determine what constitutes a significant reduction in VEP amplitude at high contrast, we used non-headache control data from our previous work (24) measuring VEP amplitudes at 97% contrast at two visits. The upper 95% confidence limit of variation in VEP amplitude between the first and second test visits was 19% (data not shown). Accordingly, 19% was considered in the present study as a significant reduction in response beyond that expected from measurement variability, which is equivalent to a monotonicity index (m_i) of 0.81. Thus, individuals with m_i of less than or equal to 0.81 were considered to show significant supersaturation.

Amplitudes were normalised to the maximum contrast condition (97%) for each individual to account for inter-individual variability in VEP amplitude. Individual contrast gain was modelled using one of two forms of Equation 2 (4), a modification of the standard hyperbolic (Naka-Rushton) function (1):

$$R(c) = R_{\max} \cdot \frac{c^{n}}{c^{sn} + c_{50}^{sn}} + R_{0} \qquad \text{(Equation 2)}$$

where R_0 is the response at 0% contrast, n is the excitatory exponent, and s is the suppressive exponent. The interpretation of R_{max} and c_{50} depends on the value of s. The first form of Equation 2 is the original Naka Rushton model, where s is equal to 1. Here,the response saturates and therefore R_{max} is the response at maximum contrast, whereas c_{50} is the semi-saturation constant (contrast at which the response reaches half the maximum response). For the second form of Equation 2, when s exceeds 1, supersaturation occurs (4). In this case, R_{max} is the projected maximal response, whereas c_{50} no longer corresponds to the contrast at which the response is half-maximum (4).

Model parameter optimisation was achieved by reducing the sum-of-square error term with the Solver module of Microsoft Excel. The monotonic contrast gain of individuals showing response saturation (monotonicity index $m_i > 0.81$) was modelled with the saturating form of Equation 2 (suppressive exponent s=1). For individuals with significant supersaturation (m_i<0.81), the modelling allowed the suppressive exponent s to vary in order to account for the decline in amplitude at high contrast. All parameters in the individual models were

floated, with the additional constraints that (1) all values were positive, and (2) c_{50} (semi-saturation constant) could not exceed the maximum Michelson contrast (100%).

Statistical analysis

A $p < 0.05$ was considered significant for all statistical evaluations. Repeated-measures analysis of variance was performed in SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). Where the assumption of sphericity was violated (Mauchly's test of sphericity), the degrees of freedom were amended using a Huynh-Feldt correction (ε). The proportions of individuals in each group showing significant supersaturation (Equation 1, $m_i < 0.81$) were compared using a chi-square test. Mann-Whitney rank sum tests were used to compare individual monotonicity indices and parameter outcomes of the individual modelling of contrast gain. Spearman rank correlations were calculated to test for a relationship between VEP contrast gain and migraine characteristics.

RESULTS

Figure 1A depicts the raw VEP amplitudes in response to increasing contrast. The control and migraine groups overlap, with substantial inter-individual variability in the migraine group. The overlap of group error bars in Figure 1 (95% confidence intervals) explains the lack of significant difference between groups in raw VEP amplitude across contrast (Figure 1A; RM-ANOVA main effect of group: $F(1,40)=0.59$, $p=0.45$; group × contrast interaction: $\varepsilon=0.22$, $F(1.84,73.5)=0.37$, $p=0.67$). Nevertheless, there is a trend for the responses at low contrast (<20%) to be higher in the migraine group relative to controls, and it is clear that the degree of variability is not equal across contrasts.

To investigate the possibility that supersaturation might contribute to the significant variability in the migraine data at low contrast, we normalised the VEP amplitudes to the response at maximum (97%) contrast for each individual (Figure 1B). It is clear from these normalised data that the migraine group shows much greater variability than controls in the region of low to intermediate contrast (9-37%), with the migraine group variance at 18% contrast being ~2.5 times larger than controls ($F(29,20)=26.1$, $p<0.001$).

Migraine sufferers, on average, showed lower monotonicity indices (m_i) values than controls (Figure 2A; Mann-Whitney rank sum test: p=0.043), with a minimum m_i of 0.58 compared to 0.07 in the control and migraine groups, respectively. Significantly more people with migraine showed supersaturation than controls, based on our monotonicity index criterion (m_i <0.81) – three of 21 controls compared to 13 of 30 migraine individuals (14% versus 43%, chi-square test of proportions: p=0.028). A sub-analysis of the migraine group showed that monotonicity indices were significantly different between the MO and MA groups, with more individuals with aura showing supersaturation than without aura (Mann Whitney rank sum test: U=52.0, p=0.008). However, it is clear from the overlap in Figure 2A that supersaturation is not a finding unique to the MA group – there are individuals who have never experienced migraine aura and show supersaturation, based on monotonicity index.

Because of the significant inter-individual variability in the migraine group, we modelled individual contrast response functions using Equation 2, rather than averaging the individuals and determining a single group model. The contrast gain of the subset of individuals with a monotonicity index (m_i) equal to 1 (18 of 21 controls, 17 of 30 migraine participants) were modelled with the suppressive exponent s fixed at 1. The goodness of fit

(R^2) achieved by the saturating function was, on average, 0.90 (range: 0.64-1.00) and 0.84 (range: 0.58-0.99) in the control and migraine individuals, respectively. For the individuals with $m_i < 0.81$, the supersaturating form of Equation 2 (where s was allowed to vary) achieved mean goodness of fit (R^2) of 0.96 (control range: 0.93-1.00, migraine range: 0.89-1.00).

The individual modelling outcomes of interest – suppressive exponent s and excitatory exponent n – are depicted in Figures 2B and 2C, respectively. Complementary to the finding that monotonicity indices were significantly reduced in the migraine group relative to controls (Figure 2A), we also found an internally consistent trend for increased suppressive exponent s in the individual migraine contrast response functions (Figure 2B; Mann-Whitney rank sum test: p=0.075). Both findings point to a greater tendency for supersaturation in migraine sufferers than non-headache controls. Interestingly, the excitatory exponent n was significantly higher in the migraine group (Figure 2C; Mann-Whitney rank sum test: p=0.047).

Individual examples that are representative of saturation and supersaturation are depicted in Figures 3A and 3B, respectively. VEP contrast gain of the control individual saturates

(monotonicity index m_i=1) – the amplitude at 18% contrast is similar to that observed at maximum contrast (Figure 3A). However, the migraine individual shows significant supersaturation (m_i=0.75), with a decrease in response at higher contrast (Figure 3B).

What sets the 13 individuals with VEP supersaturation apart from the rest of the migraine group and the majority of controls? Albeit a small subset of migraine individuals, we considered whether any of the migraine characteristics was related to the monotonicity index, m_i. None of these relationships reached statistical significance (Table 1, Spearman rank correlations: p>0.05), although the highest correlation coefficient was for the number of days since last migraine (Table 1; n=13, r=-0.52, p=0.069), suggesting that VEP contrast gain might change in temporal relation to an attack.

DISCUSSION

This study finds altered contrast gain in people with migraine. Specifically, supersaturation – relative reduction in VEP response with increasing contrast - was more common in migraine sufferers than those without migraine, based on our findings of significantly reduced monotonicity indices (Figure 2A) and a trend for increased suppressive exponents (Figure 2B) in migraine individuals. Our present findings are consistent with increased perceptual surround suppression in migraine (13, 14). The cortical circuitry underlying response normalisation at the neuronal level is still not fully understood (see Priebe and Ferster for a review (38)). Nevertheless, Battista and colleagues (13, 14) recently put forth one possible explanation to reconcile their perceptual findings in migraine with current models of visual cortical neural network connectivity (7, 8) – that cortical hyperresponsivity, the presumed abnormal interictal state that predisposes people to migraine, increases contrast-dependent feedback excitation. The increase in feedback excitation subsequently drives increased network inhibition, leading to increased perceptual suppression. Similarly, excess excitation in migraine could drive a stronger contribution of the normalisation pool of visual cortical neurones, leading to supersaturation of VEP contrast gain found here. Excess excitation (‘hyperexcitability’ or ‘hyperresponsivity’) is supported by our observation from modelling individual contrast response functions that

the excitatory exponent is increased in migraine (Figure 2C). Note that the supersaturation of visual cortical responses in migraine is different to the cortical 'hyperexcitability' attributed to inhibitory dysfunction that is seen in epilepsy, where VEP contrast gain fails to saturate (39, 40). The notion of stronger network inhibition in migraine is further supported by recent electrophysiological work demonstrating reduced VEP amplitude in response to a 'windmill-dartboard' stimulus (41), which is considered to reflect increased short-range lateral inhibition (42).

While it is parsimonious to consider an imbalance in cortical excitation and inhibition as a possible underlying mechanism for VEP supersaturation in our migraine cohort, as this has been a prevailing model within the migraine literature in recent years (reviewed by Vecchia and Pietrobon (12)), there are other potential mechanisms for altered contrast gain control. The non-linear response properties of both cortical and pre-cortical cells likely contribute to non-linear contrast gain at the level of the visual cortex (reviewed by Priebe and Ferster (38)). Lateral geniculate nucleus (LGN) relay cells show contrast saturation for contrasts above 32%, thus providing a potential feedforward contribution to cortical contrast gain. Furthermore, other non-linear cellular processes such as spike threshold, synaptic

depression, and trial-to-trial response variability of cells (38) could plausibly be altered in migraine and thereby lead to abnormal cortical contrast gain control.

That we find both supersaturation and saturation of VEP contrast gain in individual observers has implications for VEP interpretation in clinical studies. In our cohort, supersaturation was not a unique characteristic of migraine – some control participants (14%) also showed supersaturation. The substantial inter-individual variability in contrast gain (Figure 1) potentially explains the variability in VEP outcomes in the migraine literature (reviewed by Ambrosini et al (43). Most previous migraine studies only record VEP at a single, high contrast (≥ 80%), and typically report increased amplitude (43). However, the opposite finding of reduced VEP amplitude has also been observed (23, 24) and is possibly explained by supersaturation in some, but not all, migraine sufferers. Contrast is one stimulus variable that could contribute to the heterogeneity of findings in migraine literature (43). Our current paradigm highlights the importance of considering responses across a range of contrasts. This can be seen in Figure 3, where VEP amplitude at 97% contrast was similar (~2.4 μV) between the two individuals prior to normalisation. The difference between migraine and control groups was only apparent once relative changes in VEP amplitude were considered on an individual basis.

One methodological point of interest is that 4 of 21 controls and 10 of 30 migraine participants (6 MO, 4 MA) were also part of the cross-sectional, interictal VEP study reported in Nguyen et al (23). Unlike the present study where the VEP was recorded in response to increasing contrast, our previous study (23) measured responses at a single high contrast (97%) only. Although the sample size of control participants who repeated VEP recordings in our two studies is small (n=4), the responses to high contrast stimuli were no different at either visit (paired t-test: t_3=0.02, p=0.99). However, the 10 repeat migraine participants showed a consistent increase in VEP amplitude (paired t-test: t_9=4.03, p=0.003). It is possible that the different methodology adopted here (sequential presentation of increasing contrast and longer exposure) may have produced differential contrast adaptation or habituation in the migraine group, despite the fixed order of presentation from low to high contrast and interleaving of a grey (0% contrast) screen in between each contrast level (see Methods). This sub-group analysis lends support to previous psychophysical literature that responses to increasing contrast and suprathreshold contrast adaptation is altered in migraine sufferers (44-46).

As migraine is an episodic condition, it is worth noting that the significant inter-individual variability in our data may be related to the timing of testing relative to an attack and reflect different stages of the migraine 'cycle'. Participants in this study were regular and current migraine sufferers, with at least 3 attacks in the past year and, on average, one attack per 1-2 months (Table 1). Our study was conducted during the interictal period, when patients were medication and migraine-free. Albeit non-significant, there was a possible relationship between days post-migraine and monotonicity index, m_i (Table 1; n=13, r=-0.52, p=0.069). Other studies have also found changes in VEP amplitude immediately before, during, and after migraine (26, 47). Taken together, these findings warrant further work to ascertain whether VEP contrast gain alters in temporal relation to an attack for a given individual, and whether these visual changes are associated with dynamic changes in neurotransmitters implicated in migraine, such as glutamate (48), GABA (49), or serotonin (50).

Given previous literature consistently reports abnormal VEP in migraine (43), VEP contrast gain was measured in this study to infer the massed visual cortical response. The exact site of neural abnormality in migraine, however, cannot be determined by our approach, as the VEP reflects the patency of input from the preceding visual pathway, as well as the complex network of intra-V1 interactions and feedback connections to V1. The steady-state

VEP paradigm used here does not distinguish between its dominant cortical sources, V1 and V5 (29). In addition to V1 anomalies (19, 21), there is evidence in migraine sufferers for structural and functional abnormalities at extrastriate levels V5 (20, 22, 51) and V3A (51, 52), convergent with abnormal visual motion perception (14, 30-32). On the other hand, subclinical structural abnormalities in LGN have also been reported in migraine (51). Thus, we cannot rule out a pre-cortical abnormality of contrast gain in migraine, given some cat retinal ganglion (53) and macaque LGN cells (54) also show supersaturation. Moreover, altered input from LGN by GABA injection reduces gain in bushbaby visual cortex (55). Our finding of VEP supersaturation provides the grounds for further work to differentiate between potential sites of altered contrast gain in migraine, for example, by comparing monocular and dichoptic responses (56). Such an approach has been adopted more recently by Thabet et al (2013) in a psychophysical study to ascertain that altered flicker contrast processing in migraine likely occurs pre-cortically

Contrast-dependence of visual electrophysiological abnormalities in migraine is potentially relevant to real-world function and the frequent observation that people with migraine find high-contrast patterns aversive (35). The relative increase in inhibition seen in the supersaturating contrast gain response may be a compensatory mechanism to reduce the

excessive neural activity elicited in response to high contrast stimuli. Supersaturation suggests that a 'ceiling' is reached earlier in migraine, which potentially underlies the previous finding that migraine sufferers set lower contrast levels on a suprathreshold contrast scaling task than controls (44). Supersaturation could also plausibly explain differences in adaptation effects of high-contrast, flickering patterns in people with migraine reported by previous authors (45, 46). A possible explanation put forth by Karanovic et al (45) for the greater influence of adaptation on flicker discrimination thresholds in the migraine group is that the adapted neural response function is steeper at the high contrast end, producing a much smaller increment threshold than the normal saturating response. Future work could include a carefully chosen and quantifiable measure of aversion, as used in previous reports (45, 46), and psychophysical tasks involving suprathreshold contrast processing to investigate the possible link with our electrophysiological measures of visual function.

In summary, people with migraine show altered contrast gain. The higher incidence of supersaturation of the contrast response function in our sample of migraine patients compared with non-headache controls, combined with the well-documented interictal perturbations in sensory processing and visual experience reported by these patients in

other reports, support the case for investigating the process of migraine by quantifying and modelling contrast processing through the use of VEPs. Supersaturation is consistent with migraine being a disorder of neural excitatory/inhibitory balance (12). We specifically considered the potential for supersaturation in migraine, but our approach of comparing visual responses to contrast may prove useful for investigating other conditions involving altered brain excitability and excitatory-inhibitory imbalance, such as schizophrenia (57), depression (58), as well as the effects of ageing (59).

Clinical relevance:

- The electrophysiological response of the visual cortex to stimuli of increasing contrast shows an altered profile in migraine sufferers relative to non-headache controls, which might underpin symptoms of visual aversion to high contrast stimuli in these individuals.
- Recording responses to a single, high-contrast stimulus may not uncover visual abnormalities in people with migraine.

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Table 1. Self-reported migraine characteristics (median [range]) of MO and MA participants, compared by Mann-Whitney rank sum tests. The MIDAS questionnaire score (27) represents the total number of days of lost productivity due to migraine over the past three months. Scores are interpreted as minimal (score 0–5), mild (score 6–10), moderate (score 11–20), or severe disability (score 21+). In the subset of migraine individuals who showed significant supersaturation (monotonicity index m_i<0.81, n=13), Spearman rank correlation coefficients were calculated between m_i and each migraine characteristic.

Migraine characteristic	MO (n = 15)	MA (n = 15)	Group difference	Correlation with m_i
Age at first migraine (years)	12 [9–25]	13 [10–32]	U=96.5, p=0.52	*r*=0.06, p=0.84
Migraine history (years)	15 [8–30]	15 [1–34]	U=108.0, p=0.87	*r*=-0.36, p=0.23
Migraines in past year	12 [3–40]	6 [3–50]	U=99.5, p=0.60	*r*=0.26, p=0.39
Weeks between migraines	4 [1–24]	8 [1–16]	U=105.5, p=0.78	*r*=-0.24, p=0.44
Estimated number of lifetime attacks	125 [60–360]	72 [14–1350]	U=84.0, p=0.25	*r*=-0.06, p=0.84
MIDAS questionnaire score (days)	6 [0–32]	5 [0–41]	U=10.0, p=0.62	*r*=0.39, p=0.18
Days after last migraine	18 [5–180]	16 [4–104]	U=93.0, p=0.43	*r*=0.52, p=0.07
Days before next migraine	9 [3–150]	20 [3–88]	U=63.5, p=0.20	*r*=-0.48, p=0.14

Figure 1. (A) Control (n=21) and migraine (n=30) raw VEP amplitudes in response to increasing contrast. (B) VEP amplitudes normalised to individual responses at maximum contrast (97%). Error bars represent 95% confidence intervals of the mean.

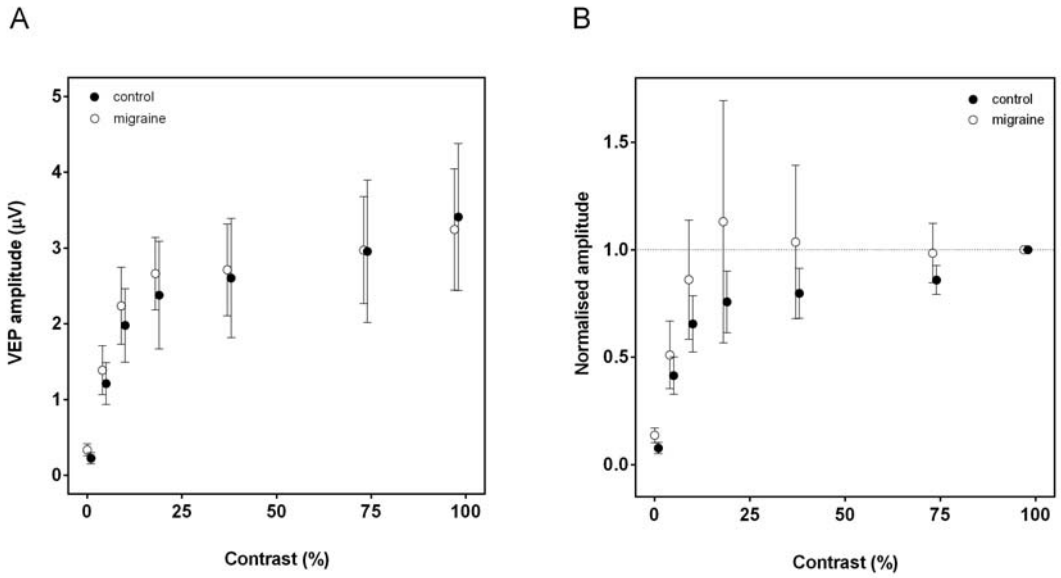


Figure 2. Individual data of the control (n=21) and migraine (n=30) groups for (A) monotonicity index m_i (B) suppressive exponent s (C) excitatory exponent n. Migraine without aura (MO, n=15) individuals are depicted by open circles, whereas migraine with aura (MA, n=15) individuals are shown as cross symbols. Supersaturation is considered significant when (A) monotonicity index $m_i < 0.81$ and (B) suppressive exponent $s > 1$, as shown by the horizontal dotted lines. The solid horizontal lines indicate the medians. The statistical outcomes of Mann Whitney rank sum tests between control and migraine groups are shown ($p<0.05$).

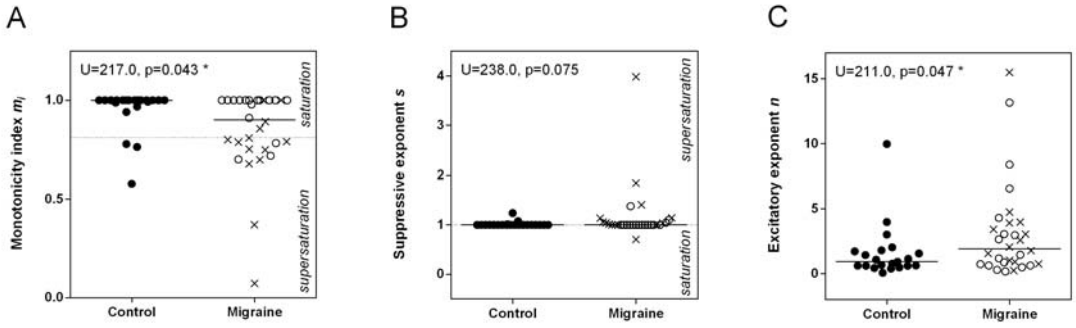
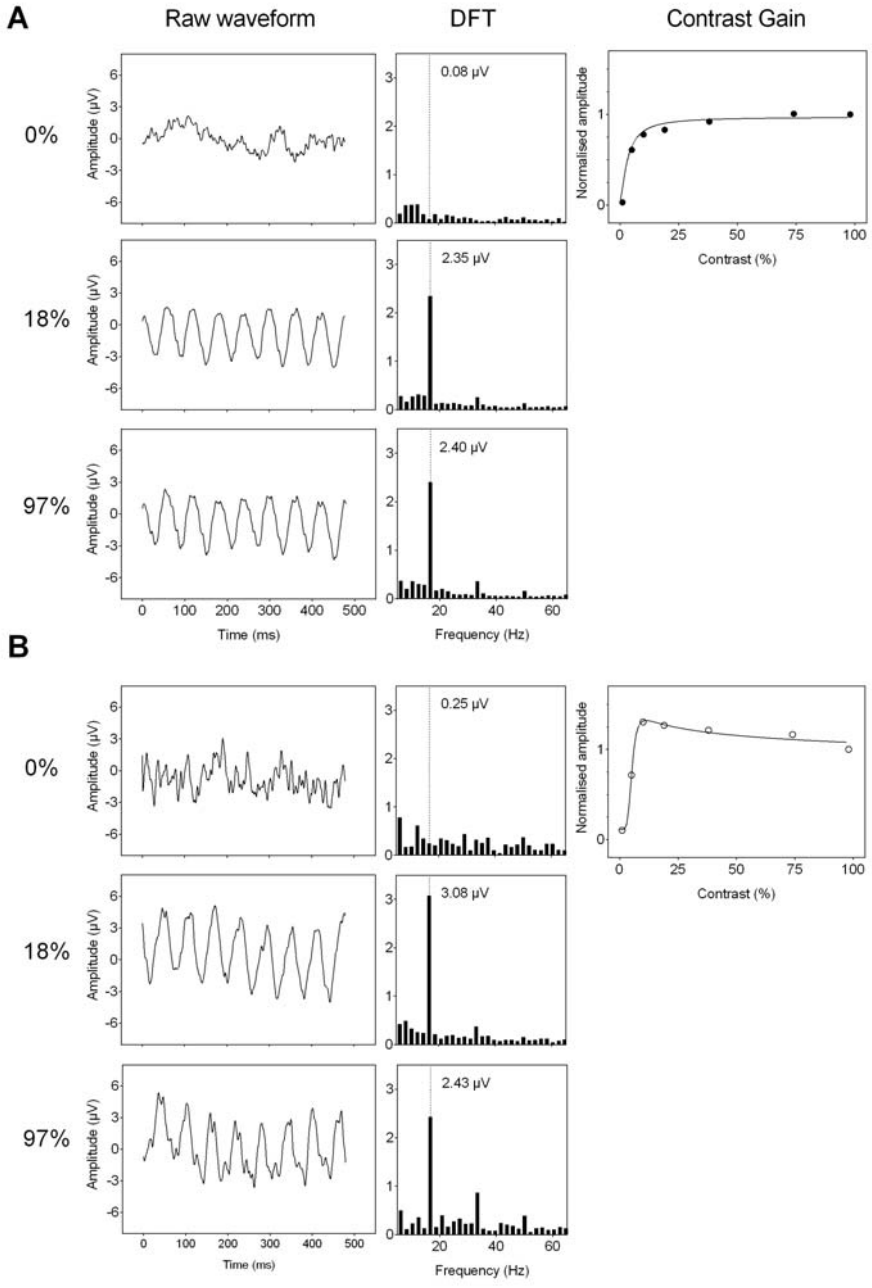


Figure 3. Representative data from a (A) control individual showing saturation (monotonicity index m_i=1) and (B) migraine individual showing supersaturation (m_i=0.75). The left column shows raw VEP waveforms at 0, 18 and 97% contrast, with corresponding Fourier spectra in the middle column following DFT (Discrete Fourier Transform). Vertical dashed lines and μV values indicate VEP amplitude at the second harmonic (16.7 Hz). Data were normalised to the response at maximum contrast (97%) to depict individual contrast gain (right column), which were modelled using Equation 2 (solid lines). Goodness of fit (R^2) values were (A) 1.00 and (B) 0.99, respectively.


A
Raw waveform
DFT
Contrast Gain
0%
18%
97%
Amplitude (μV)
0.08 μV
2.35 μV
2.40 μV
Normalised amplitude
Contrast (%)
Time (ms)
Frequency (Hz)
B
0%
18%
97%
0.25 μV
3.08 μV
2.43 μV
Normalised amplitude
Contrast (%)
Time (ms)
Frequency (Hz)