Association Between Cortical Hyperexcitability and Visual Disturbances – Evidence from Behaviour and Electroencephalogram

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Chapter I. General Introduction, background and motivation

From a neurophysiological perspective, visual disturbances such as distortions, hallucinations and visual discomforts are consequences of aberrant excitation in the visual cortex (Dahlem & Muller, 2003; Manford & Andermann, 1998). Therefore, the degree of neural excitability, namely cortical hyperexcitability, might underlie some forms of abnormal visual experiences. Such associations were well supported by clinical and non-clinical studies (see Abraham & Duffy, 2001; Salanova, Andermann, Oliver, Rasmussen, & Quesney, 1992; Weiss & Heckers, 1999).

A type of visual disturbance, namely pattern glare, is induced by viewing striped patterns in specific spatial frequencies. With support from behavioural evidence, the elicited visual discomforts and distortions were hypothesised as originated from visual cortex via cortical hyperexcitability mechanism (Conlon, Lovegrove, Barker, & Chekaluk, 2001; Evans & Stevenson, 2008; Wilkins, 1995). While pattern glare has been proposed as an indicator of cortical hyperexcitability, it remained controversial due to inconsistent findings in the literatures (Shepherd & Hine, 2013) and a lack of physiological support to their theory.

The overall objective of this thesis is to examine the role of cortical hyperexcitability in anomalous visual experiences, particularly pattern glare. In this PhD thesis, such linkage in four studies was evaluated by behavioural and electrophysiological approaches, hoping to contribute to the development of screening tools for cortical hyperexcitability and better understand the cortical hyperexcitability theoretical mechanism of producing aberrant visual perceptions.

In this Chapter I, as a general introduction to the four-studies (2 pure behavioural and 2 behavioural with EEG), a general review would be provided to introduce some relevant

literatures, starting from pattern glare, cortical hyperexcitability, to EEG studies on migraine population.

1. The Pattern Glare Effect

Pattern glare refers to the phenomenon of experiencing visual discomfort and a wide range of phantom visual experiences (illusions, distortions, hallucinations) due to the spatial features of repetitive striped-patterns. Striped patterns in certain spatial frequencies have been found to be visually irritating and are known to be epileptogenic (induce seizures) in photo-epileptic patients (Bickford, Daly, & Keith, 1953; Harding, Harding, & Wilkins, 2008; Wilkins, Binnie, & Darby, 1980; Wilkins et al., 1984; Wilkins, 1986).

The idea of convulsive neuronal responses being induced by viewing striped pattern was supported by numerous empirical findings (e.g. Harding & Fylan, 1999; Soso, Lettich, & Belgum, 1980; Wilkins et al., 1980). Wilkins and colleagues (1984) suggested that abnormal visual cortex excitation increases with the spatial frequency of gratings starting at 0.5 cycles per visual angle degree (cpd) and peaking at around 3 cpd.

Such highly aversive patterns could bring hyper-sensitive responses, for instance, illusions, distortions, hallucinations (e.g. flicker, shimmer, motions, colour) and visual discomfort (e.g. headache, nausea, dizziness) to non-epileptic population, especially those with migraine (Aurora & Wilkinson, 2007; Haigh et al., 2012; Huang et al., 2003; Oelkers et al., 1999; Wilkins, 1995), Meares-Irlen syndrome (Evans et al., 1996; Evans & Stevenson, 2008), and some specific anomalous experience among the non-clinical population (Braithwaite et al., 2013; Conlon et al., 2001). The above abnormal symptoms were thought to be originated from the cortical level rather than the earlier visual pathway. For instance, the anomalous visual perception is stronger under binocular than monocular conditions (Wilkins et al., 1984). Brain imaging techniques provide additional evidence in support of the

idea that pattern glare reflects visual cortex hyperexcitability. Supportive data includes the observation of increased BOLD signals in response to irritating patterns for migraineurs when compared to the healthy group (Huang et al., 2003; Huang et al., 2011).

2. The Pattern Glare Test

In order to quantify individual susceptibility to the pattern glare, Wilkins and Evans (2001) developed a screening test named the Pattern glare test (see Evans & Stevenson 2008 for a review). The test requires participants to view 3 square-wave striped gratings. These gratings vary in terms of their spatial frequency (see Figure 1 for the calculation of spatial frequency) with: (i) a low spatial frequency (0.5cpd); (ii) a high spatial frequency (12 cpd), and a medium frequency (3 cpd) gratings. In the original test, participants rate the number of visual distortions / anomalous experiences (from a list of predefined ones such as coloured halos, shimmering, flickering, motion, etc.). Here the dependent measure was indicated by the number of distortions on viewing the 3 cpd gratings or the number of distortions on 3 cpd subtracted by 12 cpd.

In the systematic review of Evans and Stevenson (2008), they concluded that pattern glare does not show gender differences but appears to be decreased with age. They also found that if shown after the presentation of 3 cpd gratings, the numbers of distortions induced by 12 cpd gratings would increase.

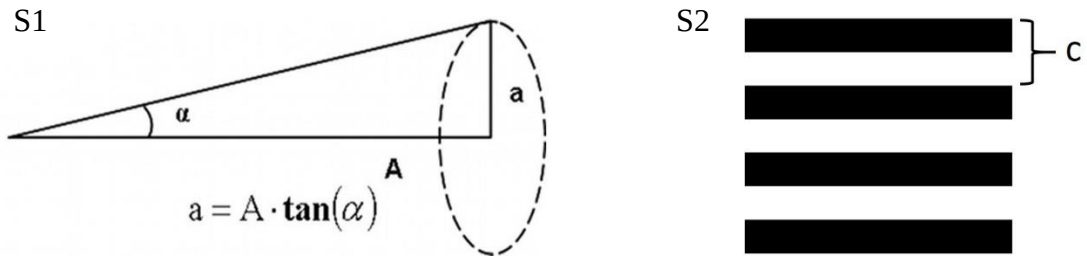

Figure 1. A demonstration on calculating the visual angle and spatial frequency. In *S1*, the visual angle (2* α) was obtained by a simple tangent function between viewing distance (A), and stimulus height (2*a); In *S2*, c indicated 1 cycle of a square wave (formed by 1 black and 1 white stripe). The spatial frequency was defined by the no. of total cycle within the stimulus per visual angle degree. *S1* was adopted from Gneo, Schmid, Conforto, and D'Alessio (2012). 3. The relationship between pattern-glare and Cortical Hyperexcitability

Several previous studies suggested that subjects who experienced extreme pattern glare effect have more visual stress symptoms such as light or pattern induced visual discomfort in everyday life (Evans & Stevenson, 2008; Harle & Evans, 2004). Example patient groups include migraine (Evans & Stevenson, 2008) and stroke sufferers (Beasley & Davies, 2012).

Perceptual processing within the sensory cortex can be modulated by the dynamic balance between the excitatory and inhibitory neural systems (e.g. via GABAergic interneurons) (Berman, Douglas, & Martin, 1992; Dehghani et al., 2016; Katzner, Busse, & Carandini, 2011). When the sensory cortex is stimulated, the firing rate of a cluster of excitatory neurons will be increased and the inhibitory neurons will mirror such firing pattern in order to maintain that dynamic balance by preventing the overshooting of excitatory activities. An intrinsic impairment (i.e. a breakdown of equilibrium) of this neural mechanism could lead to cortical hyperexcitation from over-excitation in excitatory systems or under-inhibition in inhibitory systems (Palmer, Chronicle, Rolan, & Mulleners, 2000). Such

fundamental instability has been argued as the cause of seizure (Symonds, 1959) and migraine (D'Andrea, Granella, Cataldini, Verdelli, & Balbi, 2001).

Theoretically, the imbalance of excitatory and inhibitory neural network can also contribute to pattern glare effect. GABA inhibition within the primary visual cortex (V1) controlled the visual perceptions of object orientation and direction of motion by suppressing the interneuron activity (Katzner et al., 2011). Therefore, over-stimulation in the sensory neural network is usually prevented. However, according to Wilkins (1995)'s theory, a spread of over-excitation within the sensory cortex could cause neurons to fire inappropriately by stimulating a localised cortical area. With an impaired GABAergic inhibitory system, square wave striped patterns in 3 cpd might over-stimulate the V1 by overloading the synthesis or reuptake of inhibitory neurotransmitter (e.g. GABA), resulting in the experience of perceptual illusions and distortions. As a result, pattern glare could be seen as a manifestation to cortical hyperexcitability in specific brain areas where over-stimulation occurs during the PG test. Since the gratings used in the test are oriented and highly retinotopic, these areas are likely to be the striate (visual) cortex and some extrastriate (occipital) areas which are known to be highly orientation-selective and retinotopic (Hadjikhani et al., 2001).

3. The link between Cortical Hyperexcitability, Migraine and Visual Aura

Wilkins (1995)'s theory is supported by the fact that migraine patients, who are known to have high cortical hyperexcitability, are more prone to PG effect. It has been well documented that migraine patients have a hyperexcitable visual cortex though the mechanism of how occipital hyperexcitability leading to migraine episode is unknown yet. One clinical report showed that medical treatment of sodium valproate, which suppresses the cortical hyperexcitability of the occipital cortex, could effectively reduce the frequency of migraine attacks (Bowyer, Mason, Moran, Tepley, & Mitsias, 2005).

Cortical hyperexcitability has also been proposed as the basis of migraine visual auras (a type of visual disturbance that happens before or during an migraine attack) such as scotomas, vision loss and various kinds of distorted visual perceptions, illusions and hallucinations (Aurora, Ahmed, Welch, Bhardwaj, & Ramadan, 1998; Aurora, Welch, & Al-Sayed, 2003; Aurora & Wilkinson, 2007; Chronicle, Pearson, & Mulleners, 2006; Gunaydin, Soysal, Atay, & Arpaci, 2006).

Cortical spreading depression (CSD), a slow cortical neuronal and glial depolarization wave starting from the occipital cortex, is often observed at the onset of visual aura prior to a migraine attack and is known to be related to the formation of migraines and migraine auras (Lauritzen, 1994, 2001; Leão, 1951). During the propagation of CSD, the neural membrane resistance is reduced with a substantial increase in extracellular K^+ and neurotransmitters (e.g. glutamine), and intracellular Na^+ and Ca^{2+} which results in a slow DC potential shift (Ayata, Jin, Kudo, Dalkara, & Moskowitz, 2006; Bathel et al., 2018). Although how CSD is triggered during a migraine episode is unknown, genetic and environmental factors may modulate migraine attack by lowering the cortical CSD threshold. Therefore, a more hyperexcitable visual cortex has a greater susceptibility to the progression of CSD, it might reasonably contribute to migraine visual auras (Bathel et al., 2018; Hadjikhani et al., 2001; van den Maagdenberg et al., 2004).

During headache-free periods, migraineurs have also been reported to experience elementary hallucinations, visual discomforts and extra light sensitivity in their everyday life (Chen et al., 2011; Marcus & Soso, 1989; Shams & Plant, 2011; Vanagaite et al., 1997; Welch, D'Andrea, Tepley, Barkley, & Ramadan, 1990; Wilkins, 1995). Laboratory studies, both neurophysiological and behavioural, have been conducted to investigate the underlying contributing factors to these symptoms by comparing the brain activities of migraineurs and non-migraineurs (see Aurora & Wilkinson, 2007). The reported data consistently showed that

migraineurs' brains are more hyperexcitable even during the interictal period, suggesting that such a difference in their brain reactivities might contribute to migraineurs' everyday anomalous visual experiences. A common non-evasive technique to evaluate hyperexcitability is by applying transcranial magnetic stimulation (TMS) to the occipital cortex and determine the threshold of phosphene generation. Numerous researches also report a significantly low threshold for migraine patients (Aurora, Cao, Bowyer, & Welch, 1999; Aurora & Wilkinson, 2007; Aurora, Welch, & Al-Sayed, 2003; van der Kamp, VanDenBrink, Ferrari, & van Dijk, 1996; Fumal, Bohotin, Vandenheede, & Schoenen, 2003).

Collectively, empirical findings, with neurophysiological evidence, have been consistently supportive for the hypothesis that enhanced cortical excitability contributes to the anomalous experiences of migraineurs ictally and interictally, and is involved in aberrant perceptions and migraine auras. However, whether the increased excitability is caused by over-excitation in excitatory systems, under-inhibition in inhibitory systems or both via impaired GABA-ergic dependent inhibitory mechanism or serotonin depletion is not the primary focus of this thesis.

4. Pattern Glare Findings on Migraine Patients

With the understanding of PG effect and the role of cortical hyperexcitability in mind, it is not a surprise to discover extensive literature showing that migraine patients are more averse to striped patterns (Marcus & Soso, 1989). In the standard PG test, it has also been consistently reported that migraineurs experienced more visual illusions in every spatial frequency (0.5, 3 & 12 cpd) (Evans & Stevenson, 2008; Harle & Evans, 2004; Harle, Shepherd, & Evans, 2006; Shepherd & Hine, 2013). In addition to behavioural measures,

migraineurs also exhibited stronger brain activities in response to all gratings using functional brain imaging technique (Huang et al., 2003).

According to Wilkins and Evans (2001)‘s instructions on PG test, subjects who have substantial visual stress in daily life should experience the highest degree of visual discomfort in 3 cpd and moderate discomfort in 12 cpd gratings while those who usually have less visual stress might only experience moderate level of discomfort in both 3 cpd and 12 cpd conditions. This idea is in line with Evans and Stevenson (2008)’s PG test review, which suggests that migraineurs show not only a higher 3 cpd but also a higher (3 - 12 cpd) score. Inconsistently, another research has found that migraineurs reported a similar number of visual illusions in 3 and 12 cpd while the control group had the highest number of illusions in 3 cpd among the 3 spatial frequencies (Shepherd & Hine, 2013). More details in this study revealed that migraineurs scored higher in 3 cpd but not (3 – 12) cpd compared to control. As a state measure of cortical hyperexcitability, we can expect such differences in literatures as the cortical hyperexcitability of migraineurs is known to fluctuate between attacks. For instance, it has been found that migraineurs have increased cortical hyperexcitability before attacks than interictal periods (Sand, White, Hagen, & Stovner, 2009). In addition, sleep deprivation (Civardi, et al., 2001; Scalise et al., 2006) and caffeine consumption (Shaprio, 2007) can both alternate the cerebral excitability. This known high sensitivity of PG effect highlighted the need to carefully design and precisely control the implementation of a PG test experiment, in order to fully utilise its proven value to indirectly measure cortical hyperexcitability.

5. The Pattern-Evoked Visual Potential for Migraine Patients

Apart from the behavioural PG test, contradictory findings are also frequently observed in the studies adopting the technique of electroencephalography (EEG) to evaluate

the neurophysiological abnormality of the migraine population. EEG is a non-invasive neuroimaging technique with multiple electrodes being placed along the scalp, measuring the spontaneous electrical activities over the cerebral cortex (resulted from post-synaptic potentials). These activities were reflected in a series of positive and negative voltage fluctuations (Zani & Proverbio, 2003). The evoked EEG response due to a stimulation onset is called event-related potential (ERPs). Different conditions such as the event modality (e.g. visual, auditory) and its physical features as well as brain disorders of the subjects could lead to changes on ERPs through the presence/absence, latency, duration and amplitude changes of certain peaks or their spatial distributions on the scalp (Zani & Proverbio, 2003). Studies on cortical hyperexcitability often compares the amplitude change on ERPs between two groups of subjects (target group vs. control) induced by visual/auditory stimulation (Afra, Cecchini, Sandor, & Schoenen, 2000) or direct brain stimulation such as transcranial magnetic stimulation (TMS; Kahkonen, Wilenius, Nikulin, Ollikainen, & Ilmoniemi, 2003) and transcranial direct current stimulation (tDCS; Lauro, Rosanova, Mattavelli, Convento, Pisoni, Opitz et al., 2014). An amplitude increase of certain peaks was seen as evidence of cortical hyperexcitation in those studies.

One of the most common EEG paradigms is to present gratings and compare the pattern-onset visual-evoked potential (VEP; phased locked and time locked) between migraineurs and controls. The pVEP as an ERP paradigm produced a waveform with a series of positive and negative voltage fluctuations, in which each peak and trough are considered as components underlying different types of information processing. These components are indicated by a block letter representing the polarity of the peak (N: negative; P: positive), and a number indicating the latency of the peak in milliseconds or the ordinal position of the components in the wave. In general, any anomality in the early VEP components (N75, P100, N145) indicates a possible dysfunction along the visual pathway. However, whether the exact

neural generators of these components are V1 or the extrastriate (V2-V4) remains controversial (Di Russo et al., 2005; Hatanaka et al., 1997; Shigeto, Tobimatsu, Yamamoto, Kobayashi, & Kato, 1997)

Since most of these VEP studies tested migraine patients by various types of patterns (gratings or checkerboard patterns), stimulation field, contrast, colour, spatial frequency, and temporal frequency, there is little consistency in the findings (Aurora & Wilkinson, 2007; Oelkers et al., 1999). For example, abnormal EEG responses of early components such as N75, P100, N135 had been observed in migraine patients, but there have been no conclusive directions compared with controls in terms of the latencies and amplitudes (Ambrosini & Schoenen, 2006).

If we selectively look into results that serve as direct evidence of elevated cortical hyperexcitability, migraineurs demonstrated an increase and a potentiation effect in the amplitude of those early VEP components when their visual cortices were repeatedly stimulated, while non-migraine healthy populations showed a decrease and a habituation effect in those VEP (Connolly, Gawel, Rose, 1982; Shibata, Osawa, & Iwata, 1997). Researchers often suggested that the lack of habituation is mainly caused by the dysfunction of inhibitory neurons. An alternative but not mutually exclusive explanation to these findings is proposed by Coppola and colleagues (2007a), who suggested that migraineurs' cortices could be hyper-responsive to visual stimulations.

Several studies using time-frequency (oscillation) analysis also showed consistent findings to time-locked VEP studies (e.g. Coppola et al., 2007b). Event-related oscillation has become a popular electrophysiological measure for sensory processing in recent years (Cohen, 2014; Van der Lubbe, Szumska, & Fajkowska, 2016). By wavelet transformation, an EEG signal can be broken down into different frequency band, namely δ (1-3Hz), θ (4 – 7 Hz), α (8 – 12 Hz), β (12 – 28 Hz), and γ (28+ Hz), with each of them indicating different

cognitive and sensory function (Herrmann, Grigutsch, & Busch, 2005; Klimesch, 1999; Rangaswamy & Porjesz, 2008). For example, gamma-band oscillations on primary visual cortex were associated with cortical hyperexcitability (Adjamin et al., 2004; Coppola et al., 2007b). Coppola and colleagues (2007b) found that visual stimuli evoked stronger gamma-band oscillations on migraineurs compared to healthy control. In addition, the power of gamma-band wave was shown to be increased by visual gratings in 2 – 4 cpd compared to other spatial frequencies using magnetoencephalography (Adjamian et al., 2004).

Collectively, the majority of research on cortical hyperexcitability, migraine and visual impairment have robust findings using pVEP as biomarkers. Although it is a popular paradigm in studying sensory impairment, it has not been used in the pattern glare test proposed by Wilkins and Evans (2001). If pattern glare indicated any sensory deficit or cortical hyperexcitation, abnormality in early VEP components in response to the 3 cpd or 12 cpd gratings should be observed in migraineurs.

6. Higher-order Cognitive Control during the Presentation of Gratings

The previous section described how a bottom-up (i.e. stimulus-driven) abnormal sensory response could be captured by a pVEP paradigm, which then provides support to the theory of cortical hyperexcitation. However, it is highly possible that top-down cognitive control is involved in the perceptual processing of gratings, which brings in a confounding effect in PG test or any pVEP tasks. For example, the posterior attentional system (including parietal and occipital-temporal cortex, the pulvinar and the superior system) was hypothesised to selectively modulate the visual information processing projected from the striate cortex (Zani & Proverbio, 2003). Object recognition regarding the spatial frequency of visual stimuli was known to occur in the early stage of visual processing. Depending on the attentional strategies used by subjects, the effect of bottom-up attention could strengthen their

visual responses by setting an early sensory filter for an object, resulting in an increased evoked potential as early as 60 – 70 ms after the visual stimuli onset. Previous research has shown that possible indicators for an effect of attentional modulation for spatial frequency include an increase in amplitudes of P1, N1, and N2 had been shown to indicate an effect of attentional modulation for spatial frequency (Proverbio, Zani, & Mangun, 1993).

7. Overview of the Present Thesis

This thesis presents four studies that sought to examine the presence and role of cortical hyperexcitability underlying aberrant / anomalous perceptions in neurotypical and self-reported migraine groups. The current thesis developed new screening tools for assessing and conceptualising cortical hyperexcitability leading to essential advancements in our understanding of its presence and its role in different forms of anomalous experience.

In chapter II, the latent structure of a proxy measure was uncovered and constructed to reflect cortical hyperexcitability, namely Cortical Hyperexcitability Index – II (*CHi-II*), by conducting an exploratory factor analysis on the behavioural data that indicates the frequency and intensity of the 300 non-clinical participants' everyday life anomalous visual experiences.

In chapter III, a revised pattern glare test was employed to investigate a direct linkage between everyday life visual stress symptoms and pattern glare. The quantitative analyses were implemented by exploring the statistical relationships between the scores of the extracted factors on *CHi-II* and pattern glare scores and on a set of migraine patients and healthy controls.

In chapter IV, where the gratings typically used in a pattern glare test were revised as visual stimuli with a VEP paradigm. The association between cortical hyperexcitability and pattern glare was examined by electrophysiological measurement. Here the early (0 – 200 ms) and late VEP (300 –700 ms) components are compared between the groups of self-reported migraineurs and neurotypical participants.

Finally, aiming to isolate the effect of cortical hyperexcitability from migraine, the above VEP study on a clinically normal sample was replicated in chapter V. In order to observe how cortical hyperexcitability may influence the VEPs, non-clinical subjects were

split into hyperexcitable and non-hyperexcitable based on their pattern glare scores. The early and late VEP components are, again, compared between these two groups.

Chapter II. Study 1: the Cortical Hyperexcitability index-II (CHi-II) – a Revised Proxy Screening Measure for Visual Cortical Hyperexcitability

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Abstract of Study 1

Visual cortical hyperexcitability is now known to be an underlying factor for aberrant visual experience, including hallucinations, and pattern or light-induced visual discomfort. Such factors have also been observed in neurological and non-clinical groups (albeit in an attenuated form) – consistent with the notion of a continuum of anomalous experiences. Utilising an exploratory factor analysis (EFA) approach (n = 300), Study 1 developed a revised proxy screening measure for visual cortical hyperexcitability - the Cortical Hyperexcitability index – II(CHi-II). The EFA revealed a stable 3-factor solution which can be characterised as; (i) Heightened Visual Sensitivity and Discomfort (HVSD); (ii) Aura-like Hallucinatory Experience (AHE); and, (iii) Distorted Visual Perception (DVP).

1. Introduction of Study 1

Aberrant excitation in the cerebral cortex has long been associated with the formation of both elementary and complex hallucinations (Elliott, Joyce, & Shorvon, 2009; Ffytche et al., 1998; Manford & Andermann, 1998; McGuire, Murray, &, Shah, 1993; Panayiotopoulos, 1994; Penfield & Perot, 1963; Sass & Parnas, 2003). For example, patients who have been diagnosed with complex partial seizures of the temporal lobe, migraine with aura, and schizophrenia will commonly report a host of auric hallucinatory experiences – and all these conditions/disorders are associated with excessive neural activities (see Abraham & Duffy, 2001; Dahlem & Muller, 2003; Dahlem, Engelmann, Lowel & Muller, 2000; Hadjikhani et al., 2001; Lauritzen, 1994, 2001; Leão, 1951; McNally, McCarley, & Brown, 2013; Merabet, Kobayashi, Barton & Pascual-Leone, 2003; Penfield & Jasper, 1954; Reggia & Montgomery, 1996; Salanova, Andermann, Oliver, Rasmussen, & Quesney, 1992; van den Maagdenberg et al., 2004; Weiss & Heckers, 1999).

Neurological studies have supported the association between the underlying degree of visual cortical hyperexcitability and resultant aberrant experience (Abraham & Duffy, 2001; Dahlem & Muller, 2003; Salanova et al., 1992; Weiss & Heckers, 1999). Previous studies utilising transcranial magnetic stimulation (TMS) protocols have shown that migraineurs with aura had a lower phosphene threshold relative to non-migraine control groups and migraineurs without aura (Aurora et al., 1999; Aurora, Welch, & Al-Sayed, 2003; Aurora & Wilkinson, 2007; Fumal, Bohotin, Vandenheede, & Schoenen, 2003). In addition, the amplitude of visually evoked potentials (VEPs) has been shown to be higher in migraine populations relative to control groups (Connolly, Gawel, & Rose, 1982; Shibata, Osawa, & Iwata, 1997) and neuroimaging studies have demonstrated that the phenomenological content of aura varies in sympathy with the rate and range of cortical spreading depression in sensory cortex – providing a direct link between the presence of hyperexcitable states and visual

hallucination / aura (Hadjikhani et al., 2001). Collectively, these findings support the view that cortical hyperexcitability is an underlying contributing factor for predisposition to anomalous experience.

1.1. Quantifying Cortical Hyperexcitability

One approach to quantifying cortical hyperexcitability has been to use trait-based questionnaires/screens. However, many of them were based primarily on intuition, had not been formally explored or validated via factor analysis, or had not been fully explored in relation to other more direct state-based measures. Examples would include the Meares–Irlen (MI) Scale (Hollis & Allen, 2006; Irlen, 1983) and the Visual Discomfort Scale (VDS: Conlon, Lovegrove, Chekaluk, & Pattison, 1999). The former measure utilised a basic yes / no response to a small number of questions, and the latter had a poor question structure making it problematic to interpret which anomalous perceptions were being endorsed (see Braithwaite, Marchant, Takahashi, Dewe, & Watson, 2015a for further discussion).

More recently Braithwaite and colleagues (2015a) were the first to use exploratory factor analysis (EFA) to produce a verified proxy measure of cortical hyperexcitability – termed the Cortical Hyperexcitability index, or '*CHi*'. The EFA produced a 3-factor solution suggesting that the different items/experiences may reflect a non-unitary notion of cortical hyperexcitability. While an important development, the resulting 3-factor solution had an unexpected and not entirely intuitive structure in that it divorced both positive and negative hallucinatory experiences onto separate, though correlated, factors. In addition, a number of items did not survive the EFA process and were dropped from the final index.

One behavioural paradigm used to quantify state-based cortical hyperexcitability is the "pattern-glare" (PG) task. Viewing striped gratings with a spatial frequency of approximately three cycles-per-degree of visual angle, can be highly irritable to observers,

can induce increased visual stress (eye strain/visual pain) and cause the perception of phantom visual distortions (Evans & Drasdo, 1991; Wilkins, 1995; Wilkins & Nimmo-Smith, 1984; see Evans & Stevenson, 2008, for a review). Pattern-glare refers to a host of phenomena (visual distortions, illusions, nausea, dizziness, etc) that are induced from viewing these aversive visual stimuli (Evans & Stevenson, 2008; Wilkins, 1995; Wilkins et al., 1984).

One account proposed for the occurrence of these phenomena is that potent gratings over-stimulate localised groups of visual neurons causing them to fire inappropriately - the increased likelihood of which is thought to reflect a high degree of cortical hyperexcitability. It follows that susceptibility to such visual distortions should vary in sympathy with, and reflect, elevated degrees of latent cortical hyperexcitability. In line with this view, elevated degrees of pattern glare are associated with migraine with aura (Aurora & Wilkinson, 2007; Friedman & De Ver Dye, 2009; Haigh, Karanovic, Wilkinson, & Wilkins, 2012; Harle & Evans, 2004; Huang, Cooper, Satana, Kaufman, & Cao, 2003; Oelkers et al., 1999; Marcus & Soso, 1989; Wilkins, 1995, 1984), with visual stress (Meares-Irlen (MI) syndrome: Evans, Busby, Jeanes, & Wilkins, 1995; Evans & Stevenson, 2008), photosensitive epilepsy and stroke (Beasley & Davies, 2012; Evans, 2005; Evans & Stevenson, 2008; Harding & Fylan, 1999; Harding, Harding, & Wilkins, 2008; Soso, Lettich, & Belgum, 1980; Wilkins, 1986; Wilkins, Binnie, & Darby, 1980; Wilkins et al., 1984; 1980) and certain hallucinations in the non-clinical population (Braithwaite, Broglia, Bagshaw, & Wilkins, 2013; Braithwaite et al., 2013).

In addition, neuroimaging studies have demonstrated significantly increased Blood Oxygenation Level Dependent activation in visual association cortex but only for migraineurs with aura and only for the presentations of the critical, irritable stimuli (and not baseline gratings: Huang et al., 2003; Huang et al., 2011). Furthermore, the degree of visual distortion

experienced by observers has been shown to correlate with the level of neural activities in the visual association cortex (Datta, Aguirre, Hu, Detre, & Cucchiara, 2013; Welch, Bowyer, Aurora, Moran, & Tepley, 2001) and there is evidence from near-infrared spectroscopy (NIRS) to suggest that migraineurs' brain generates faster neural responses to the irritable gratings (relative to controls: Coutts, Cooper, Elwell, & Wilkins, 2012). Collectively, these findings indicate a relationship between aberrant neural processes (brain-imaging) and anomalous experience (pattern-glare) and support the usage of the PG task as an index for cortical hyperexcitability.

1.2. Overview of Study 1

Irrespective of these findings, there is currently only one validated proxy trait-based measure to quantify cortical hyperexcitability and its role underlying different forms of aberrant experience. The availability of a useful screening measure for cortical hyperexcitability could have great utility for scientific, clinical and neuroscientific research. As well as revealing interesting clusters of experiences in its own right, such a measure can be inexpensive and straightforward to implement – making it a pragmatic approach for many investigations. It could also act as a covariate alongside neuroscientific methods such as neuroimaging and electroencephalography helping to bridge the theoretical gap between aberrant neural processes and resultant anomalous experiences of a specific type or theme.

With this in mind, the present study aimed to provide a revised and improved proxy screening measure of cortical hyperexcitability (the *CHi-II*) that might also reflect a more intuitive factor structure than that seen previously. Furthermore, we significantly expand on our previous work by combining our new trait-based measure (Study 1) with a computerised PG task carried out on self-reported migraineurs and a control group (Study 2). Therefore, on top of developing a revised and improved measure, it was further examined here with a

neurological group known to reflect increased degrees of cortical hyperexcitability and with an established behavioural task capable of inducing aberrant perceptions also thought to reflect increased degrees of state-based cortical hyperexcitability. As well as any resultant factor structure being informative, it was predicted that not all factors might be reliably associated with cortical hyperexcitability – as some aberrant perceptions may reflect more pre-cortical / ocular processes (Conlon et al., 1999). Knowing which experiences cluster onto related factors and which factors would then be associated with elevated pattern-glare scores, and for a migraine-group, would significantly expand our understanding and provide a truer representation of cortically mediated processes.

In this study, we constructed the Cortical Hyperexcitability index – II (*CHi-II*), which is a revised version of the original Cortical Hyperexcitability index (*CHi*) with several methodological amendments. First, some poor loadings or non-loadings from the original study were removed from the measure. Second, some items were modified with more detailed and specific descriptions added, for certain anomalous visual experiences. Third, more items relating to elementary hallucinations and distortions were added. Finally, an exploratory factor analysis (EFA) was conducted on a new large independent group of non-clinical participants in order to uncover the latent structure of the *CHi-II* (Study 1). This was followed up with an additional study that sought to determine the relationships between the separate factors of the trait-based *CHi-II* and a computerised PG task, which provided a state-based measure of cortical hyperexcitability (Study 2).

2. Methods

2.1. Participants

Three hundred participants from the University of Birmingham were recruited to participate in the study (T1). Of these, 232 (54.0%) returned 14 – 35 days later (T2) to explore the test-retest validity of the *CHi-II* measure. The mean age of the participants was 19.5 (age range 17-40 years), of which 258 (86%) were female, 268 (89.3%) were right-handers. All participants received either research credits or a small financial payment in return of their participation. All participants were given a pre-screening questionnaire prior to their participation in the experiment. The questions included whether the subjects had (i) any ocular conditions (e.g. astigmatisms/colour blindness/optic neuritis/accommodation errors), (ii) ever undergone any form of neurosurgery (including eye surgery), (iii) been diagnosed with migraine (with or without aura / hallucination), (iv) been diagnosed with epilepsy (with or without aura / hallucination) or seizures of unknown origin, (v) ever suffered from neurological conditions / disorders (and whether they were taking medication as a form of treatment), (vi) ever suffered from a psychiatric condition (and whether they were taking medication as a form of treatment). Participants who gave a positive response to any of the listed questions were excluded from the study. Informed consent was obtained for all the participants.

2.2. Cortical Hyperexcitability index - II (*CHi-II*) – a revised scale of *CHi*

The *CHi-II* was composed of 30 items, of which 16 were original *CHi* items. Eight items were either adapted from the Cardiff Anomalous Perception Scale (*CAPS*; Bell, Halligan, & Ellis, 2005), the Cambridge Depersonalization Scale (*CDS*; Sierra & Berrios, 2000), the Meares-Irlen scale (*MI*; Hollis & Allen, 2006) or the Visual Discomfort Scale

(*VDS*; Conlon et al., 1999) and 6 items were utterly new. In addition, 11 items were modified with more details to make them more specific and precise. The last modification was the removal of 5 items from the original *CHi* questionnaire because they loaded poorly onto the original factor structure of *CHi* (see Braithwaite et al., 2015a; see Table 1.).

Each item of the *CHi-II* contained a question about a specific experience followed by two 7-point unipolar Likert scales to measure participants' corresponding 'frequency' (0 = never and 6 = all the time) and 'intensity' (0 = not at all and 6 = extremely intense) of such experiences[1]. The ratings of frequency and intensity for each question were summed to provide a score for that item (max. = 12). The index for a subject's cortical hyperexcitability is the arithmetic sum of scores for all 30 items (max. score = 360).

[1] In the original CHi, the response scale ranged from 1 to 7 because it was not clear whether a zero value would be treated the same as the other non-zero values. Subsequent pilot testing has demonstrated that this is not an issue for the current measure.

Table 1. Item change of CHi-II compared to CHi and the source of the questions.

Question	Change compared to CHi	Source
1) Vision more sensitive to external sensory information?	Same	CHi original item
2) Overwhelmed by visual information?	Same	CHi original item
3) Visual perception seems heightened or enhanced?	Same	CHi original item
4) Irritation from indoor lights?	Modified	CHi original item
5) Everyday objects look different?	Modified	Adapted from CAPS/ CDS
6) Ever experienced transient flashes or spots of white light?	Modified	CHi original item
7) Find certain environments irritating?	Same	CHi original item
8) Ever seen fleeting shapes?	Split from Q8.	CAPS item
9) Ever experienced flashes of colour?	Split from Q8.	CAPS item
10) Find the appearance of things or people changes?	Modified	CAPS item
11) Felt dizzy / nauseous due to strong light or patterns?	Same	CHi original item
12) Lights or colours seem brighter or more intense?	Same	CAPS item
13) Experienced visual discomfort from certain patterns?	Modified	CHi original item
14) Had a headache / migraine induced by visual information?	Same	CHi original item
15) Experienced visual distortions when you look around?	New	New
16) Working on computer for long periods irritates eyes?	Modified	Adapted from MI
17) Noticed perceptual distortions when you are fatigued?	Modified	CHi original item
18) Fluorescent lights irritate your eyes?	Modified	Adapted from MI & VDS
19) Had an out-of-body experience?	Modified	CHi original item
20) Headlights from oncoming traffic irritate eyes?	Modified	Adapted from MI
21) Experienced visual discomfort from reading?	Same	CHi original item
22) Experienced a narrowing of your visual field?	Same	CHi original item
23) Experienced flashes of moving patterns?	Modified	CHi original item
24) Experienced loss of visual information?	Split from Q24.	CHi original item
25) Ever seen white/black dots across your visual field?	New	New
26) Ever seen coloured shapes, balls or patterns?	New	New
27) Ever had loss of vision surrounded by zigzag patterns?	Split from Q24.	CHi original item
28) Ever experienced spiral, tunnel or funnel-like shape?	New	New
29) Ever experienced 'spider-web' patterns?	New	New
30) Experienced the world draining in colour and vibrancy?	New	New

2.3. Analysis

In order to uncover the factor structure of the *CHi-II*, an Exploratory Factor Analysis (EFA) was conducted, complemented with a parallel analysis (PA: Hayton, Allen, & Scarpello, 2004; Horn, 1965). Two multivariate normality (MVN) tests were conducted separately by the "psych" and "MVN" package installed under the R statistical program (version 3.3.2, R Development Core Team, 2016; see Revelle, 2014; Korkmaz, Goksuluk, & Zararsiz, 2014). The reliability of the scale was based on internal consistency (Cronbach's alpha) and test-retest reliability (correlations between T1 and T2).

3. Results

3.1. Descriptive Statistic

The overall mean score of *CHi-II* was 64.6 (median = 58.0), with a standard deviation of 36.6 (range = 2-201). The *CHi-II* score distribution was moderately right-skewed, with skewness of .811, (*S.E* = .141) but a negligible Kurtosis of .587 (*S.E.* = .281). To further examine the normality of the total score, a Shapiro-Wilk test was conducted which suggested a non-normal distribution, $W = .956$ (df = 300), $p < .001$ (which is to be expected for a measure that may reflect multiple factors).

3.2. Factor Extraction Method

The Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy number of factors was .88, and Bartlett's Test of Sphericity was also significant ($\chi^2 = 2840$ (df =435), $p < .001$), which both justified the factorability of the current data set (Kaiser & Rice, 1974; Tabachnik & Fidell, 2007; Williams et al., 2009).

In order to construct a model and generate different dimensions to represent the current variables in *CHi-II*, conducting an Exploratory Factor Analysis (EFA) instead of Principal Component Analysis (PCA) is a more reliable option to uncover the latent structure of *CHi-II* (Conway & Huffcutt, 2003; Fabrigar, Wegenerm, MacCallum, & Strahan, 1999; Henson & Roberts, 2006; Widaman, 1993; Williams, Onsman, & Brown, 2009). The Principal Axis Factoring (PAF) method of factor extraction is a better choice if the data violate the assumption of multivariate normality (MVN; see Costello & Osborne, 2005; Fabrigar et al., 1999). The result of Mardia's MVN test and Royston's MVN test both suggested that the data did not follow a multivariate normal distribution (multivariate skewness = 352, $p < .001$; multivariate kurtosis = 1384, $p < .001$; $H = 2579$, $p < .001$), therefore the use of PAF was justified (see Korkmaz, Goksuluk, & Zararsiz, 2014 for an R package guide for MVN's test).

3.3. Rotation Methods

The goal of rotating the factors is to achieve a simple and interpretable structure that attempts to have each variable saliently loaded (≥ 0.4) onto only one of the extracted factors but poorly loaded (< 0.1) onto any other factors (Brown, 2009; Yong & Pearce, 2013). The previous study on *CHi* showed that all the extracted factors correlated with each other significantly (all $r > 0.5$; Braithwaite et al., 2015a), which supports the usage of oblique Promax rotation instead of orthogonal solutions (see Fabrigar et al., 1999; Hendrickson & White, 1964; Williams et al., 2010).

3.4. Number of Factors to extract

Initially, a visual analysis of the Scree Test implied a 4-factor model (Cattell, 1966). However, a more objective parallel analysis (PA) for PAF was also conducted (see Figure 2

for the scree plot). A set of random factors was generated using Monte-Carlo simulations with the same number of variables and sample size compared to the data set (Horn, 1965; Ledesma & Valero-Mora, 2007). The factors from the actual data set with higher eigenvalues than the simulated one were retained. In order to reduce the over-extraction problem of PA, alpha was set at 0.01 (99% percentile; Glorfeld, 1995). As a result, 5 factors were obtained. Therefore, the 5-factor model (from PA) together with the 4-factor model (form the Scree Test) were both explored. However, neither the 4th factor nor the 5th factors had more than three items loading onto them, making them unstable and unreliable, hence justifying the removal of them from the final model (see Beavers et al., 2013; Costello & Osborne, 2005).

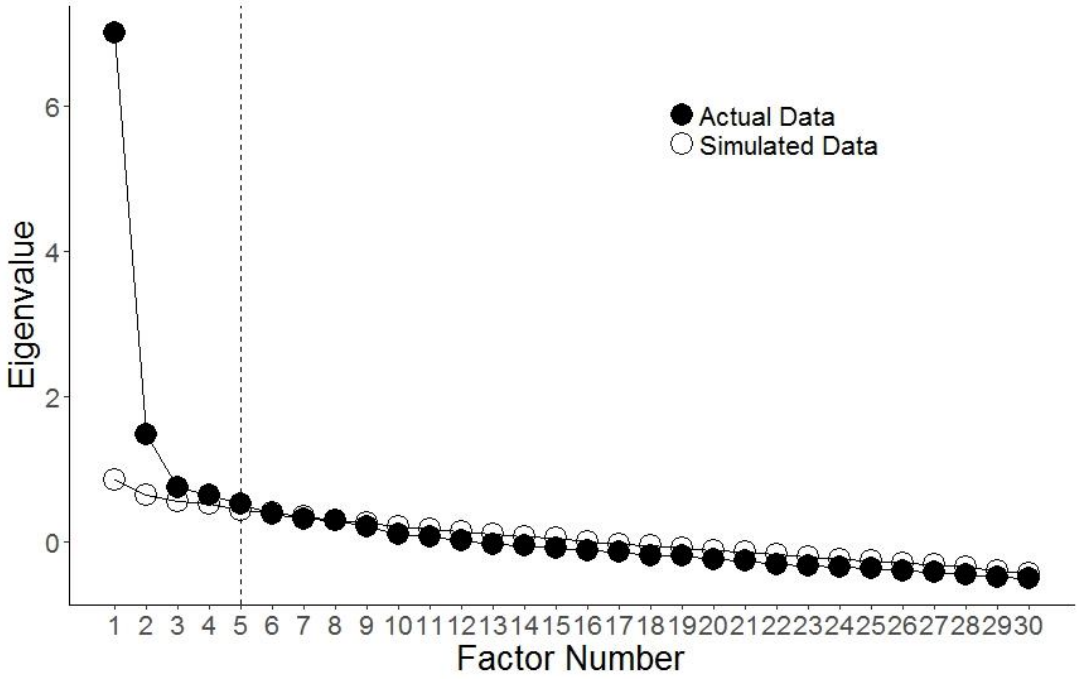

Figure 2. A parallel analysis scree plot of the PAF. It suggested that 5 factors should be retained.

3.5. Final Model

As a result, 3 factors were extracted using the Principal axis factoring with the rotation method set as Promax with a kappa of 4. The Promax rotation converged within 6 iterations. The finalized 3-factor model explained 38.6% of the variance and 31.9% after

extraction (See Table 2 for the factor structure). The items without any loadings of .40 or above were dropped (Tabachnick & Fidell, 2014). Four items failed to meet this criterion (*Question 2. Do you ever feel overwhelmed by visual information?; Question 17. Have you ever noticed the presence of perceptual distortions when you have been tired or fatigued?; Question 25. Have you ever experienced a spread of tiny white / black dots resembling the 'static' of a badly-tuned television superimposed across your visual field?; and Question 29. Have you ever experienced transient illusory 'spider-web' type patterns superimposed on the visual world?*), and therefore were removed from the final model. No items cross-loaded onto different factors. All three factors contained at least 6 loadings, which is regarded as stable.

Eleven-items loaded onto Factor 1, which primarily reflected visual irritation or discomfort across a host of circumstances. Ten out of the eleven items (90%) overlapped with the Factor - *"Heightened Visual Sensitivity and Discomfort"* in the original *CHi* (see Braithwaite et al., 2015a) and so this title was retained as the title of this factor in the present case. Factor 2 items were primarily "*Aura-Like Visual Hallucinatory Experience*" which included 9 items that were related to visual aura-like experiences such as phosphenes, flashes of colour and other elementary visual hallucinations (including partial loss of visual information). These items overlapped with both the factor *"negative aura-type visual aberrations"* and '*positive aura-type visual aberrations' from the* original *CHi.* Factor 3 contained 6 items related primarily to "*distorted visual perception*".

Table 2. The factor structure of the *CHi-II*

	Factor			Communalities	
	1	2	3	Initial	Extraction
4) Irritation from indoor lights?	**.785**	-.059	-.149	.514	.481
11) Felt dizzy / nauseous due to strong light or patterns?	**.723**	.076	-.145	.481	.488
13) Experienced visual discomfort from certain patterns?	**.687**	.020	-.074	.467	.438
18) Fluorescent lights irritate your eyes?	**.685**	-.071	-.020	.444	.408
16) Working on computer for long periods irritates eyes?	**.627**	-.106	.040	.425	.355
12) Lights or colours seem brighter or more intense?	**.619**	-.128	.136	.466	.397
14) Had a headache / migraine induced by visual information?	**.585**	.220	-.208	.431	.395
7) Find certain environments irritating?	**.534**	.033	.116	.485	.388
20) Headlights from oncoming traffic irritate eyes?	**.457**	-.025	.035	.302	.214
1) Vision more sensitive to external sensory information?	**.431**	.076	.223	.494	.396
21) Experienced visual discomfort from reading?	**.421**	-.114	.184	.356	.227
23) Experienced flashes of moving patterns?	.046	**.589**	-.053	.409	.342
24) Experienced loss of visual information?	-.001	**.563**	-.073	.356	.273
9) Ever experienced flashes of colour?	.016	**.544**	-.014	.412	.297
8) Ever seen fleeting shapes?	-.005	**.540**	.112	.415	.372
27) Ever had loss of vision surrounded by zigzag patterns?	-.128	**.501**	-.025	.373	.186
26) Ever seen coloured shapes, balls or patterns?	.001	**.466**	-.029	.300	.203
6) Ever experienced transient flashes or spots of white light?	.263	**.435**	.031	.456	.409
28) Ever experienced spiral, tunnel or funnel-like shape?	-.160	**.434**	.129	.317	.199
22) Experienced a narrowing of your visual field?	-.051	**.411**	.259	.334	.328
19) Had an out-of-body experience?	-.339	.105	**.629**	.305	.339
30) Experienced the world draining in colour and vibrancy?	.008	-.131	**.606**	.264	.295
3) Visual perception seems heightened or enhanced?	.271	-.116	**.476**	.435	.348
10) Find the appearance of things or people changes?	.062	.050	**.448**	.316	.266
5) Everyday objects look different?	.108	.022	**.415**	.325	.244
15) Experienced visual distortions when you look around?	.227	.013	**.412**	.403	.327
2) Overwhelmed by visual information?	.359	.108	.234	.489	.354
17) Noticed perceptual distortions when you are fatigued?	.341	.219	.144	.440	.355
25) Ever seen white/black dots across your visual field?	.154	.108	.199	.225	.151
29) Ever experienced ‘spider-web’ patterns?	.058	.329	-.096	.238	.099

*Note: Item loadings for each factor (> .40) are listed in decreasing magnitude order (In **BOLD**). The shaded items are not loaded into any factors.*

3.6. Reliability of the Factor Model

The correlations between the factors are summarized in Table 3. Similar to *CHi*, all the correlations between the factors were higher than 0.50, which suggests that there was more than 25% common variance between the factors. The significant correlations between the factors further justified the usage of oblique rotation methods in our EFA.

One hundred and ninety-eight subjects participated in T2 for the *CHi-II* questionnaire revisit. The average period between T1 and T2 was 16.8 days. The test-retest reliability coefficient of the total *CHi-II* scores between T1 and T2 was .81, suggesting a good stability for the *CHi-II* questionnaire as a trait scale. None of the inter-items' correlations exceeded 0.7, suggesting no items should be removed due to redundancy (Boyle, 1992). The Cronbach's alpha of *CHi-II* was high at 0.90 (see Table 4). The first two factors both had an acceptable alpha (>.70) while the internal consistency of factor 3 was slightly lower (0.65 – 0.70).

Table 3. The correlation matrix between each of the extracted factors.

Factor	1	2	3
1			
2	.55		
3	.52	.59	

Table 4. The Cronbach's alpha for the *CHi-II* scale and the 3 factors

		Factor		
	CHi-II (full scale)	1	2	3
Cronbach's alpha	.90	.86	.76	.67

4. Discussion

The revised and improved *CHi-II* produced a 3-factor model obtained from the exploratory factor analysis. The EFA revealed separate and distinct loadings for different phenomenological aspects relating to visual aberrant experiences. Each factor is now discussed.

Factor 1 - Heightened Visual Sensitivity and Discomfort (*HVSD*)

Ten out of the eleven items of this factor overlapped with the largest factor from the original *CHi* (Braithwaite et al., 2015a). This factor explained the largest amount of common variance with the highest eigenvalues among the extracted factors. The experiences that loaded onto this factor appear to be related to excessive light / pattern induced sensitivity and discomfort. Interestingly, there were no perceptual distortions at all on this factor. In addition, the Cronbach's alpha (> .80) suggested that the responses to these items were highly consistent with each other – an observation further bolstered by the near-perfect replication of the original study for this factor. Pattern and light-induced visual stress symptoms (which can include induced somatic discomforts) are consistent with the notion of elevated hyperexcitability in visual cortex and have been well documented in studies on migraine and non-clinical samples predisposed to aberrant perceptions and hallucinations (Braithwaite et al., 2013; Braithwaite, Mevorach, & Takahashi., 2015; Harle, Shepherd, & Evans, 2006; Huang et al., 2003; Marcus & Soso, 1989; Wilkins, 1995).

Factor 2 – Aura-Like Hallucinatory Experiences (*AHE*)

This factor consisted of 9 items that related primarily to hallucinatory visual experiences, either describing low-level elementary hallucinations (phosphenes, flashes, colours, patterns and spots) or loss of visual information (scotoma, tunnel vision, blurred vision, visual field defects or complete blindness), and therefore, was named here as *"aura-like hallucinatory experience"*. Three items could be regarded as scotoma, describing 3 different ways of diminished visions, and therefore were considered as a negative aura. Six items could be considered as positive aura experiences since they were low-level visual hallucinations superimposed onto the viewable environment. Unlike the original study, both positive and negative aura-like experiences converged to form one single and stable factor, which is arguably a more parsimonious solution relative to the original *CHi* measure. The superior sample size and good reliability / consistency in the present study would suggest that the present factor structure is much improved relative to the original study.

Factor 3 – Distorted Visual Perception (*DVP*)

This "Distorted Visual Perception" factor contained 6 items, associated primarily with visual distortions. Five items can be classified as visual distortions since they described changes of visual perceptions (e.g. distortions in colour, shapes, etc) to people, objects, or the physical environment. The only exception to this was the item on out-of-body experiences (OBEs), which also loaded onto this factor and is conceptualised as a complex hallucination resulting from a breakdown in multisensory integration (Blanke & Arzy, 2005; Blanke et al., 2005; Blanke, Landis, Spinelli, & Seeck, 2004; Braithwaite &

Dent, 2011; Braithwaite et al., 2011). It was also the most robust loading item on this factor. The explanation for this is not entirely obvious or clear. It is noteworthy that although the OBE item may sound qualitatively different to the other items on this factor, body image distortions and indeed OBEs have been previously reported by migraine patients (a condition associated with cortically mediated hyperexcitability: Ilik & Ilik, 2014; Lippman, 1953; Morrison, 1990).

One possibility might be that the notion of 'distortions' can also be extended to body-experiences (introception) as well as perceptions of the outside world (extroception). For example, the OBE is reliant on both a failure of multisensory integration and a hallucinatory mental model of the self in space and time (Blanke & Mohr, 2005; Braithwaite & Dent, 2011; Brugger, 2002). One admittedly speculatory possibility is that the former process can be viewed more like a distortion in body perception and the latter as an additional hallucinatory component. Therefore it might be the case that the association between this question and the notion of distorted perception pertains to the first part of this complex process and not the latter (though both are correlated). Unfortunately, the current *CHi-II* measure did not utilise any additional questions on body-distortion experiences to explore the utility of such speculations.

There were 4 items (Q2, Q17, Q25, Q29) failing to load onto any of the above factors. As a result, 26 items survived in the final EFA model. Interestingly, these 3 common factors all contained an intuitive descriptor that summarized the characteristics of the loaded items consistently and coherently (see Figure 3).

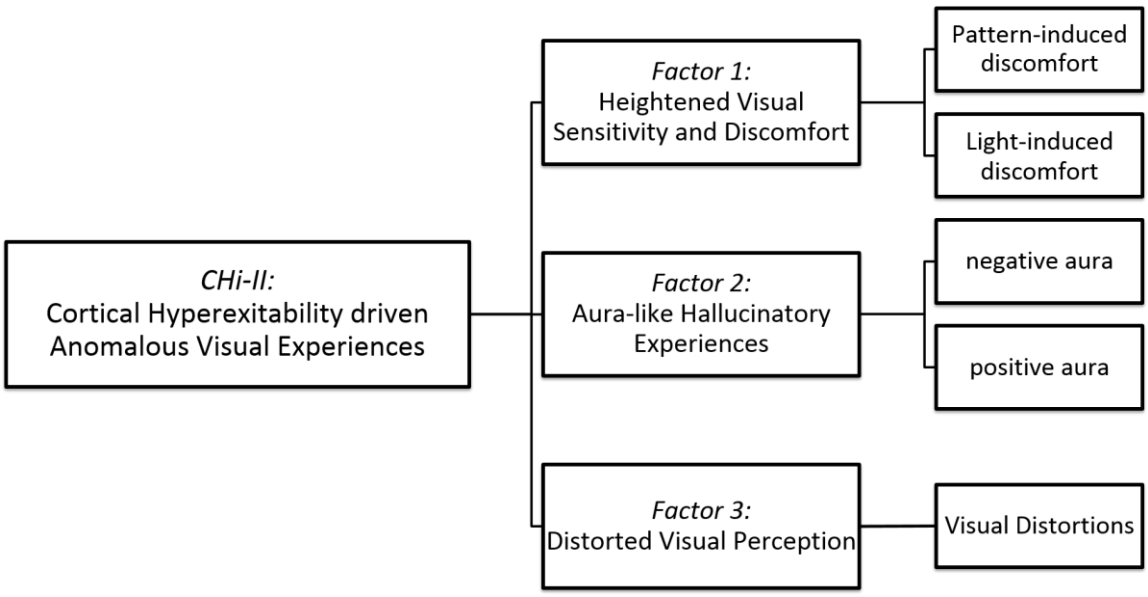

Figure 3. A summary of the 3-factor structure of the *CHi-II.*

To summarise, the EFA revealed that the *CHi-II* could be broken down into 3 stable and precise factors representing separate but inter-correlated dimensions. In our second study, we continued to evaluate the utility of *CHi-II* as a proxy measure of cortical hyperexcitability by exploring its relationship with a computer-based PG task and with a migraine group. If each factor represents diverse neurocognitive contributions to the concept of visual cortical hyperexcitability, then selective correlations may exist between the *CHi-II* factors and more objective and established computer-based assessments of symptoms reflecting cortical hyperexcitability.

Chapter III. Study 2: The Correlations between Pattern Glare and Cortical Hyperexcitability index - II

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Abstract of Study 2

Study 2 tested both a self-reported migraine group and a control group on the *CHi-II* in conjunction with a computerised pattern-glare task that is known to reflect visual cortical hyperexcitability. The migraine group produced significantly elevated scores on both the *AHE* and *HVSD* factors of the *CHi-II*, relative to controls. Among the non-migraine group, subjects who scored higher in the pattern-glare task also produced significantly elevated scores on the *AHE* factor compared to those with low pattern-glare task scores. Collectively, these findings support the utility of the *CHi-II* as an indirect proxy measure for signs of cortical hyperexcitability and reveal new categorical distinctions for the nature of the anomalous perceptions. These perceptions may well reflect diverse neurocognitive underpinnings leading to advancements in our understanding of aberrations in conscious experience.

1. Introduction of Study 2

Study 2 aimed to explore further the utility of the new *CHi-II* measure, and its factor structure, in relation to the concept of cortical hyperexcitability and its relationship to aberrant visual experiences. The development of *CHi-II* was based on the notion that cortical hyperexcitability could be considered as a continuum, where a stronger background (trait-based) level of cortical hyperexcitability would lead to a higher frequency and intensity to some forms of anomalous visual perceptions. As a result, if both *CHi-II* and the pattern-glare effect reflect cortical hyperexcitability, there should be a positive relationship between the trait-based measure (*CHi-II*) and the state-based behavioural measure (i.e. the PG task) not just among migraineurs but also in the non-clinical populations.

Aberrant perceptions, hallucinations and delusions can often co-occur and can be seen collectively in psychosis, schizophrenia and broader neurological conditions and disorders (Yung et al., 2009; Verdoux & van Os, 2002). Such co-occurrence has also been documented for non-clinical groups in the absence of any salient pathology or disorder (Allen et al., 2010; Freeman & Garety, 2003; Lataster et al., 2006). For the present purposes, it becomes useful and prudent to ensure, as much as possible, that the *CHi-II* and our PG task tap into the mechanisms underlying aberrant perceptions and not aberrant beliefs or delusions. Aberrant beliefs could be present and mediating responses, to some degree, on PG tasks where participants are merely biased to responding positively and hence elevating responses to all gratings.

Therefore, to examine that our factors of interest are indeed more related to valid measures of anomalous perceptions and do not reflect strong contaminations from

anomalous beliefs, in Study 2 we also administered a questionnaire measure to quantify predisposition to anomalous beliefs. To do this, the Community Assessment of Psychic Experiences (*CAPE:* Stefanis et al., 2002), which was designed to measure the psychosis proneness of the general population by their symptomatic thoughts, feelings, impressions and beliefs, was administered.

The effects from the newly devised *CHi-II* and the pattern-glare task should be specific to proxy measures of cortical hyperexcitability that underlie *anomalous perceptions* (and perhaps only some of the factors relative to others) but should not be related to other trait measures of *aberrant beliefs* (thus also controlling for aspects of suggestion and response bias which are common in hallucinators with psychosis / schizophrenia: Yung et al., 2009; Verdoux & van Os, 2002)[2]. Therefore, Study 2 explored how the factors of the *CHi-II* measure were selectively associated with pattern-glare assessments of cortical hyperexcitability and how pattern-glare was associated with measures of additional aberrant beliefs and not just aberrant perceptions.

Study 2 was conducted with both self-reported migraineurs and non-clinical participants. First, the PG effect and the scores of *CHi-II* between migraineurs and the controls were compared. Second, participants with high PG effect were compared with those with lower PG effect based on their *CHi-II* scores. However, correlations on behavioural responses could also be driven by response style to questionnaires (Lee, Jones, Mineyama, & Zhang, 2002). For example, if a group of participants tended to give

[2] Unless of course those aberrant beliefs are tied to and driven by the occurrence of aberrant perceptions, although certainly possible with patient groups, we felt this less likely in non-clinical participants.

more extreme responses, we would expect them to do so throughout all the measures consistently. As a result, a high score in *CHi-II* would often come with more associated visual distortions (AVD) regardless of any visual cortical activities. To reduce such an effect coming from response bias, we used heightened responses to the low-frequency grating as exclusion criteria. In addition, a subtraction parameter of AVD (between high frequency and medium frequency), instead of AVD of medium frequency alone, was used as a measure of PG effect. Furthermore, an additional trait measurement of aberrant beliefs (which are not thought to be driven directly by cortical hyperexcitability occurring in early sensory areas: *Community Assessment of Psychic Experiences*) was administered.

It was hypothesized that; (i) migraineurs would score higher on the *CHi-II* measure and show evidence of higher cortical hyperexcitability via the PG task compared to the control group; and that, (ii) control participants who produce elevated scores on the PG task would also be associated with higher *CHi-II* scores (and perhaps only for some of the factors). Such observations should neither be found in the migraineurs nor the high-scoring PG non-clinical group for the Community assessment of psychic experiences (*CAPE*) measure.

2. Methods

2.1. Participants

A total of 354 participants took part in this study. Of these, 300 had also taken part in Study 1. In addition, for the present study, 54 new participants were recruited and 27 of them were self-declared migraineurs. All the migraineurs were free from attack for

at least 7 days before taking part in the experiment. All participants gave full informed consent to the experiment. Eleven subjects were rejected at the end (reasons were explained in the result section), which gave a final sample size of 343. Control participants reported no general conditions of headache as such factors may still reflect different forms of migraine or other forms of headache.

The mean age of this sample was 19.6 (range = 17 – 40). Among the subjects, 296 (86.3%) were female, and 306 (89.2%) were right-handed. All subjects were given a pre-screening questionnaire prior to their participation. Subjects who reported that they (i) had undergone any neurosurgery (included eye surgery), (ii) had any form of history of epilepsy (or seizures of unknown origin), (iii) had ever suffered from any neurological conditions (other than migraine), and taken medication as treatment, or (iv) had ever suffered from psychiatric conditions (and taken medication as treatment) were excluded from the study. Normal or corrected to normal vision without visual impairment had been self-reported by all participants.

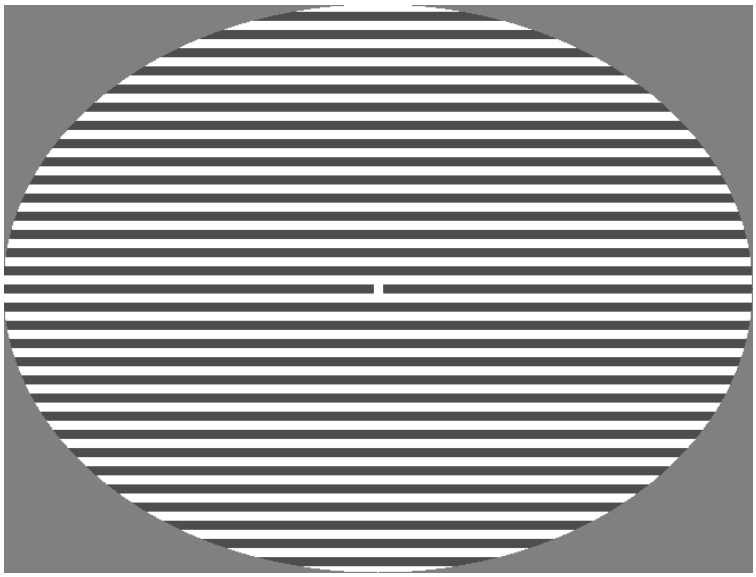
2.2. Materials and Procedures

2.2.1. The Pattern-glare task. The computerized pattern-glare (PG) task was a modified version of that reported previously (Braithwaite et al., 2015b; Braithwaite et al., 2013a, 2013b; Evans & Stevenson, 2008). The main modifications came in the form of a more sensitive Likert-type response for each distortion reported, which now depicted the actual 'intensity' of the perceived distortion rather than just its mere presence. The PG task consisted of presenting three square-wave achromatic elliptical gratings that differed only in terms of their respective spatial frequency (cycles-per-degree: cpd). The three

frequencies were: a baseline low frequency grating (LF) of 0.5cpd, the crucial medium frequency grating (MF) of 3cpd, and a baseline high frequency grating (HF) of 15cpd (see Figure 4 for an example of the grating). Each grating was presented three times in a pseudo-random order. A restriction was programmed into the task so as not to present the same grating twice in a row.

All gratings had a Michelson contrast of 0.70 (cd/m^2). The screen background luminance was 20 cd/m^2. Gratings were presented in the centre of a 16-inch Samsung SyncMaster 793DF computer screen (60Hz refresh rate and 1280x960 pixels screen resolution) using E-prime v2.0 software. The stimuli had a maximum height x width of 120 mm x 155 mm with the shape of a mild ellipse. The viewing distance was fixed and set at 80 cm from the screen, which provided a visual angle of 8.53 x 11.0 degrees.

Figure 4. An example of the medium frequency square-wave pattern-glare stimuli.



Every trial started by presenting one of the three gratings. Participants were told to focus on a centrally located fixation point on the grating. Participants also were informed that if

the grating / stimuli were too uncomfortable to look at, that they could press the 'spacebar' button, which removed the stimulus from the screen (repressing made it return). Spacebar presses were also counted and recorded by the computer programme as an additional measure. The individual stimuli remained on the screen for a viewing period of 12-seconds and then removed from view. After an inter-stimulus interval of 1 second, participants were then presented with a screen that posed a series of questions pertaining to different distortions (which we termed associated visual distortions: AVDs) and a 7-point Likert scale response pertaining to the intensity/ strength of the individual AVD that was experienced (0 = not at all, 6 = extremely; see Figure 5 for the trial sequence).

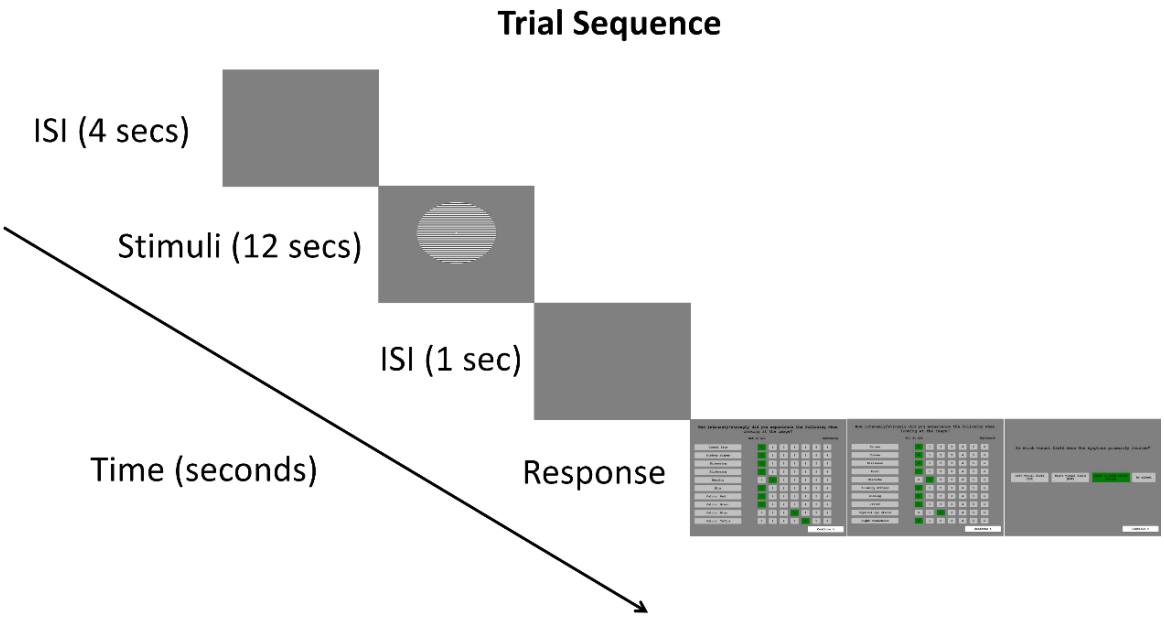


Figure 5. A trial sequence for the PG task.

A response of zero was taken to indicate that the participant did not experience that distortion while viewing the grating. Any non-zero response was taken to indicate the

presence of that distortion, at the intensity indicated. Twenty AVDs were provided across two separate screen presentations which participants completed at their own pace. These Likert responses, for each AVD, were then summed for that particular grating (range = 0 – 120). Participants were then also asked to rate whether the AVDs were experienced more in the left visual field (LVF), the right visual field (RVF), both visual fields or not at all. Individual trials (for each grating) were separated by an inter-stimulus interval of 4 seconds before the next trial and questions were presented (see Table 5).

Table 5. The set of questions that being asked after each presentation of a PG stimulus.

Questions	Responses
How strong/intense are the following when looking at the pattern? 1. Visual pain, 2. physical eye strain, 3. Unease 4. Nausea 5. headache, 6. dizziness, 7. light-headedness, 8. faint 9. Shadowy shape, 10. Illusory stripes, 11. Shimmering, 12. flickering, 13. jitter, 14. Zooming 15. blur, 16. bending of lines, 17. Red, 18. green, 19. blue, 20. yellow	0, 1, 2, 3, 4, 5, 6 (0 denoted as not at all and 6 denoted as extremely)
Are the effects mainly in the	Left visual field (LVF) Right visual field (RVF) About the same in both visual fields No effect

A practice trial was given to the participants prior to the actual experiment to make sure that they understood the task, the nature of the AVD questions, and how to provide responses. This practice trial used a low-frequency checkerboard (0.5cpd) stimulus, which was not irritating to view. The experiment was carried out in a dimly lit laboratory.

The task itself took approximately 15 minutes to complete, and the whole experiment (including the completion of questionnaires and screening criteria) took 40 minutes.

2.2.2. Questionnaire measures. Participants completed 2 questionnaires that sought to measure trait-based predisposition to anomalous perceptions or anomalous beliefs. These measures were: (1) our new Cortical Hyperexcitability Index-II (*CHi-II*), and (2) the Community Assessment of Psychic Experience (*CAPE*; Stefanis et al., 2002). All the questionnaires were digitized, programmed (in *Microsoft Access 2013)* and presented on a computer.

2.2.2.1. Cortical Hyperexcitability index – II (CHi-II). From the results of Study 1, the three factors of the *CHi-II* were explored separately in relation to the pattern-glare task. The version of *CHi-II* being used in this study consisted of the 26 items that survived in the EFA from Study 1. Both frequency and intensity were summed for each question (providing a score of 0 – 12 for that item), which gives a maximum overall score of 312.

2.2.2.2. Community Assessment of Psychic Experiences (CAPE). To measure a component of belief rather than perception, and also control for suggestibility in our subjects, the *CAPE* questionnaire measure was administered. The *CAPE* is a 42-item self-reporting assessment for schizotypal symptoms built on a 3-dimensional model proposed by Stefanis and colleagues (2002). The three dimensions are positive symptoms (*POS*), depression symptoms (*DEP*) and negative symptoms (*NEG*). Each item consists of two 4-point scales (0-3) to represent the symptom frequency (‘never’, ‘sometimes’, ‘often’, ‘nearly always’) and level of distress (‘not distressed’, ‘a bit distressed’, ‘quite distressed’ and ‘very distressed’) caused by that experience. Adding up the scores of every item gives an overall index in a maximum score of 252. Although the *CAPE* does have some

questions that might pertain to anomalous perceptions, the vast majority of questions pertain more to beliefs, thoughts, impressions and feelings. If elevated pattern-glare scores reflect response biases, then these biases should be present in the *CAPE* measure, predicting a positive correlation between *CAPE* and PG scores.

3. Results

To complement the frequentist approach, we have conducted Bayesian analyses using analytical software - *JASP* version 0.7.5.6, with the Cauchy prior width set as the default value 0.707 (Love et al., 2015; Rouder, Morey, Speckman, & Province, 2012). The analysis estimates a Bayes Factor (BF_{10}) to make a comparison on the likelihood of whether the data are more in favour of the alternative hypothesis ($BF_{10} > 1.0$) or the null-hypothesis ($BF_{10} < 1.0$). For example, a BF_{10} of 10 suggests that the data fit 10 times better with the alternative hypothesis than the null hypothesis. In contrast, a BF_{10} of 0.10 suggests that the data fit 10 times better with the null rather than the alternative hypothesis (Jarosz & Wiley, 2014). According to Jarosz and Wiley (2014), a BF_{10} of 3 – 10 can be interpreted as moderate evidence in favour of the alternative hypothesis, 10 – 100 can be considered strong, and > 100 considered very strong and decisive.

In line with previous recommendations, the LF grating was used as baseline stimuli in the sense that the responses to this grating are used to screen for response bias and therefore, were not formally analysed. The 95th percentile of the AVD score for LF grating was 18.3, with a 95% confidence interval (CI) of 15.7 – 21.7. Participants who scored higher than the upper limit of the CI were discarded from the sample. Based on these criteria, 11 subjects were removed from the sample, which gave a final sample size

of 343. There were no clicks on 'spacebar' and no lateralized responses of AVDs – so these factors were not analysed further. To establish a baseline-corrected measure of pattern-glare, the AVD scores for the HF baseline grating were subtracted from the AVD scores for the MF grating – ΔAVD (MF - HF; see Wilkins & Evans, 2001; Evans & Stevenson, 2008).

3.1. The PG effect for the Control group

Among the sample, 316 participants were defined as non-migraineurs. We inspected the distribution of the AVDs for each spatial frequency, and these are summarised in Table 6. Based on the current version of PG task, the upper limit of the normal range for ΔAVD was determined by the 95th percentile, and it was 10.5 (95% CI: 8.7 – 14.8; see Table 6).

Table 6. Descriptive statistics of the AVD score for the control group.

	LF (0.5 cpd)	MF (3 cpd)	HF (15 cpd)	MF – HF (3 – 15 cpd)
Mean	4.53	12.6	11.6	1.00
Range	0 – 21.33	0 – 74.7	0 – 64.3	-19 - 26
Percentiles				
5	0	1.95	1.33	-8.00
25	1.00	5.33	4.67	-2.00
50	2.67	9.67	8.67	0.67
75	6.58	16.6	15.3	3.92
95	14.8	32.2	31.8	10.5

The sample was split into two groups at the 75th percentile of the ΔAVD. Subjects with a ΔAVD higher than 3.92 were classified into the high PG group while subjects with a ΔAVD lower than 3.92 became the low PG group. A one-way multivariate analysis of

variance (MANOVA) was conducted to examine the mean score differences of *CHi-II* and *CAPE* between the high PG group and low PG group. The result suggested a significant multivariate effect, F (2, 313) = 3.21, p = .042; Wilk's λ = .98, partial η^2 = .02. Six post-hoc one-way ANOVAs were then conducted to compare the mean differences of each subscale of the questionnaire individually between the two groups with the False Discovery Rate correction being applied to correct for multiple comparisons (Benjamini & Hochberg, 1995). This revealed a significant effect of group on Factor 2 of the *CHi-II*, supporting the idea that participants with a higher ΔAVD scored significantly higher on *the aura-like hallucinatory experiences* (*AHE*) of *CHi-II* than participants with a lower ΔAVD score. There were no significant effects on the other *CHi-II* factors. Interestingly, there were also no reliable effects in relation to any components of the *CAPE* measure (see Table 7).

Table 7. The mean questionnaire scores and the results of ANOVAs for PG group vs non-PG group comparisons (with the *S.E.* in parentheses).

Questionnaire	PG group (n = 79)	Non-PG group (n = 237)	*p*-value	*FDR* adjusted p-value	BF_{10}
HVSD	41.4(2.56)	36.1(1.21)	.038	.114	1.09
AHE	13.5(1.22)	9.77(0.67)	.007	.042	4.66
DVP	7.85(0.92)	6.56(0.46)	.181	.236	0.33
POS	13.6(0.90)	12.2(0.58)	.232	.236	0.28
DEP	15.8(0.87)	14.6(0.50)	.236	.236	0.28
NEG	21.2(1.22)	19.4(0.71)	.203	.236	0.31

Note: HVSD: Heighted Visual Sensitivity and Discomfort; AHE: Aura-Like Hallucinatory Experiences; DVP: Distorted Visual Perception; POS: positive symptoms; DEP: depressive symptoms; NEG: negative symptoms

3.2 The PG effect of Migraineurs vs. Non-Migraineurs

To compare the pattern glare effect between migraineurs and non-migraineurs, a one-way between-subject ANOVA was conducted on ΔAVD. The results showed that the migraineurs group had a significantly higher ΔAVD, F = (1, 341) = 5.75, p = .017, BF_{10} = 2.23 (see Figure 6). In addition, such group differences were not observed on the AVD score of both the low frequency and high frequency baseline gratings (both F < 0.1).

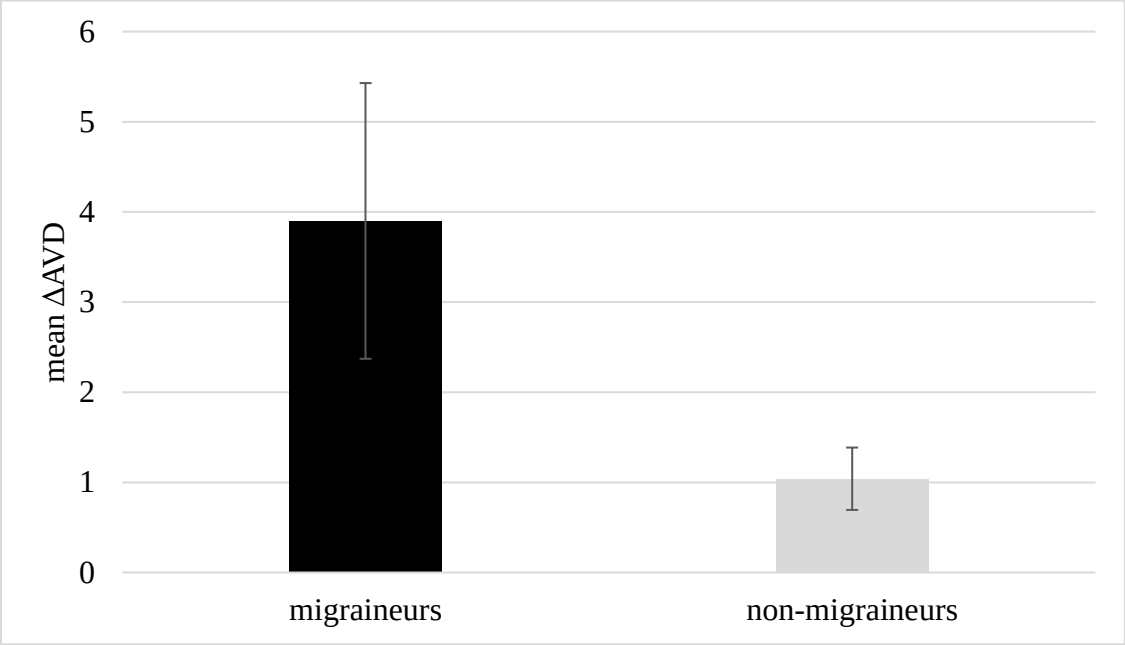


Figure 6. The difference in mean ΔAVD between migraineurs and non-migraineurs. Error bars = +/- 1 *S.E.*

A MANOVA was used to compare the *CHi-II* and *CAPE* scores between migraineurs and non-migraineurs. The result suggested that there was a statistically significant difference in the questionnaire scores, F (2, 340) = 6.13, p = .002; Wilk's λ = .97, partial η2 = .035. Post-hoc tests showed that migraineurs scored significantly higher for *AHE*, F (1, 341) = 9.194, p = .003, BF_{10} = 12.6 and *HVSD*, F (1, 341) = 8.259, p =

.004, BF_{10} = 8.31 respectively (see Table 8). In contrast, there were no significant group differences in *DVP* or any components of the *CAPE* measure.

Table 8. The mean questionnaire scores and the results of ANOVAs for migraineurs vs non-migraineurs comparisons (with the *S.E.* in parentheses)

Questionnaire score	Migraineurs (n = 27)	Non-migraineurs (n = 316)	*p*-value	*FDR* adjusted p-value	BF_{10}
HVSD	49.9(5.23)	37.4(1.12)	.003	.012	12.6
AHE	16.9(2.57)	10.6(0.59)	.004	.012	8.31
DVP	5.89(1.00)	6.88(0.42)	.494	.741	0.26
POS	9.78(1.40)	12.6(0.49)	.107	.214	0.67
DEP	14.6(1.52)	14.9(0.43)	.823	.823	0.22
NEG	20.6(2.38)	19.8(0.61)	.741	.823	0.22

Note: HVSD: Heighted Visual Sensitivity and Discomfort; AHE: Aura-Like Hallucinatory Experiences; DVP: Distorted Visual Perception; POS: positive symptoms; DEP: depressive symptoms; NEG: negative symptoms

4. General Discussion

The present study examined distinct forms of anomalous experience and the underlying role of both trait-based and state-based signs cortical hyperexcitability in both a self-declared migraine and non-neurological group. Several new findings were revealed.

Study 1 examined a revised, and an improved indirect proxy measure of cortical hyperexcitability by exploring experiences thought to reflect underlying hyperexcitability across a variety of conditions and disorders. Alongside Study 2, the present investigation was methodologically improved in a number of important ways, which included the recruitment of a larger sample, an examination of test-retest reliability, and a more intuitive loading of items onto factors.

The significantly separable factors, revealed by the EFA and the PA, suggest several dimensions underlying different thematic types of anomalous experience. This is consistent with the notion that not all forms of experience may necessarily reflect the same processes or networks. This observation significantly extends previous research, which has generally clumped all forms of aberrant experience into one unitary notion of cortical hyperexcitability, visual stress, or photophobia (Aurora et al., 1999; Aurora & Wilkinson, 2007; Conlon et al., 1999; Wilkins, 1995). Also, the item-loadings of the *CHi-II* appear to be more intuitive than that reported previously – suggesting an improved utility as an indirect proxy measure.

The utility of this model was examined further in Study 2 via comparison to a computer-based pattern-glare assessment of cortical hyperexcitability and extended further still with a self-reported migraine group. Within the control group, people who reported a stronger PG effect also scored higher on the *aura-like hallucinatory experiences* (*AHE*; $p = 0.007$, $BF_{10} = 4.66$) factor, relative to those reporting weaker PG effects. This supports the hypothesis that there is a relationship between state-based PG effects and the presence of trait-based aura-like experiences represented on this factor (i.e., phosphenes, flashes, colours, scotomas, tunnel vision, etc.). However, the association with the PG effect was not reliable, after correction for multiple comparisons, for the *heightened visual sensitivity and discomfort* (*HVSD; p* = .114, $BF_{10} = 1.09$) factor and was completely unobservable for the *distorted visual perception* (*DVP*; $p = .236$, $BF_{10} = 0.33$).

In addition, the present findings support the notion that migraineurs generally have a more hyperexcitable visual cortex compared to the control group with a higher PG

effect (p = .017, BF_{10} = 2.23). As expected and is consistent with previous migraine research, the migraine group was significantly more susceptible to aura-like hallucinations and visual stress symptoms relative to the non-migraine control group by scoring higher in the *AHE factor* (*p* = 0.004, BF_{10} = 8.31) and the *HVSD* factor (*p* = 0.003, BF_{10} = 12.6). As with the control group, those reporting migraine did not appear to score significantly higher on the *DVP* factor than controls.

One common issue in research on hallucinations / aberrant perceptions is the extent to which the findings can be accounted for in terms of generic underlying response bias. Hallucinating participants can be predisposed to such biases (Deviant Response pattern; Berg, 1955, 1959; Berg & Collier, 1953); however, there are a host of reasons why this view is unlikely to be a tenable counter-explanation for the present findings. For example, although generic response biases have indeed been documented in hallucinating groups, this association is related more to those with such experiences occurring with psychosis and schizophrenia – and thus not necessarily a group predisposed to anomalous perceptions per-se (Adams & Berg, 1961; Berg, 1955; Cowen, Staiman, & Wolitzky, 1961; Peters et al., 2013; Sechrest & Jackson, 1963;). In addition, the observation of clear, separable and intuitive factors for the *CHi-II* measure is not tractable to the notion of a generic underlying response bias, which should influence the endorsement of all items roughly equally. Clearly, this did not happen. Furthermore, participants scoring high on responses to the low-frequency grating of the pattern-glare task (taken as an index of a generic response bias) were removed from the sample (Study 2). Finally, it is noteworthy that none of the factors from the *CAPE* measure were significantly related to PG scores – providing direct evidence here that any predisposition to aberrant beliefs

(intuitions, thoughts, feelings, reasoning etc.) is not associated to the predisposition to aberrant perceptions elicited by the presentation of aversive visual gratings. Put simply, PG effects do not appear to reflect a predisposition to endorse questions erroneously. Collectively, the findings reported in the present study do not appear to be mediated by aberrant belief processes or generic response biases commonly seen in broader research on hallucinations occurring in psychosis and schizophrenia.

4.1 Theoretical Implications

The existence of the three-factor model suggests multiple contributions to the general concept of cortical hyperexcitability. This fractionation provides researchers with new and refined precision in delineating these underlying features – not all of which may actually reflect hyperexcitability at the cortical level.

The results of *AHE* indicate that a more hyperexcitable visual cortex is more susceptible to elementary hallucinations (both of a positive and negative nature: see also Aurora & Wilkinson, 2007; Boulloche et al., 2010; Chen et al., 2011; Denuelle et al., 2011; Huang et al., 2003; Wilkins, 1995; Wilkins et al., 2004). According to the cortical spreading depression (CSD) model for migraine, CSD is more likely to occur in, and propagate over, a hyperexcitable cortex, including primary and extrastriate visual cortex, generating positive or negative aura symptoms such as fortification, phosphenes, colours, and scotomas (Bowyer et al., 2001; Braithwaite et al., 2015a; Hadjikhani et al., 2001; VanValkenburgh, 2005).

Although CSD is thought to originate in the visual cortex, it is not the only region responsible for mediating aura experiences. Multiple cortical regions beyond the visual

area can be activated throughout a migraine attack with distinct implications for reported phenomenology (Bowyer et al., 2001; Cao et al., 1999; Cao, Aurora, Nagesh, Patel, & Welch, 2002; Dahlem, Engelmann, Lowel, & Muller, 2000; Dahlem & Hadjikhani, 2009; Hadjikhani et al., 2001; Lauritzen, 1994, 2001; Welch, Cao, Aurora, Wiggins, & Vikingstad, 1998; Zhang et al., 2010). For example, several researchers have proposed that the trigeminovascular system could be modulated by the visual cortex amongst other associated neural structures such as somatosensory insular cortex and the subcortical region (e.g. hypothalamus and brainstem), causing migraine headaches and photophobia symptoms (see Noseda et al., 2011; Noseda & Burstein, 2013).

In addition, if CSD depolarizes the cortical regions that process vestibular signals (e.g. posterior insula and temporoparietal junctions), symptoms such as vertigo, dizziness, nausea and motion sickness could be formed (Cutrer & Baloh, 1992; Lempert, Neuhauser, & Daroff, 2009). Collectively, the excitability of any structures within the cortico-subcortical-trigeminovascular networks could possibly make an impact on *HVSD* symptoms. This might help to explain why the PG effect was strongly associated with the *AHE* in both populations but only associated with responses on the *HVSD* for the migraine group – as only this group may have also experienced pain-related symptoms along with visual symptoms.

The failure of the *DVP* factor to be associated with PG scores for both migraineurs and high-PG scoring control participants might suggest that *DVP* related experiences do not reflect aberrations in cortical areas or processes responsible for mediating the responses evoked by aversive patterns. Although *DVP* factor is positively correlated with *AHE* and *HVSD* (both > .50), and occur as migraine aura symptoms like

them, they are far less common compared to these two factors (Russell & Olesen, 1996). Statistically speaking, the eigenvalue and internal consistency of the *DVP* factor was the lowest amongst the 3 factors, which means that there were larger amounts of unexplained variances and the items are less likely to covariate with each other. Taken all this into account, it is possible that the *DVP* score may be driven by an even more extensive range of abnormal neural activities than the other two factors which may indeed reflect a truer representation of what has commonly become known as cortical hyperexcitability.

It is particularly noteworthy that in the current study, we found that the high susceptibility to visual aura-like symptoms is not limited to migraine patients, but also observed amongst non-migraine populations. In line with previous studies, our findings support the idea that healthy participants might also show signs of aberrant neural responses and anomalous experiences – similar to that seen (albeit in an attenuated form) for the migraine group. This is also consistent with the theory of a continuum of predisposition to anomalous visual experiences and hallucinations (McCreery & Claridge, 2002; Langer, Cangas, & Gallego, 2010; Schwartzman, Maravic, Kranczioch, & Barnes, 2008; Serper, Dill, Chang, Kot, & Elliot, 2005).

4.2 Limitations & Future Research

The *CHi-II* is based on previous research from earlier measures and established research from the cognitive neurosciences. However, it should be acknowledged that questionnaire measures are not, in and of themselves, a direct instrument for quantifying underlying neural processes – more the sorts of experiences associated with aberrant neural processes. Perhaps the most useful and helpful way to view and utilise such tools

is as an indirect 'proxy' measure indicative of aberrant neural processes that can reflect hyperexcitability – or is known to in the broader literature.

Nonetheless, the items making up the *CHi-II* have been associated with increased levels of cortical activation revealed by more direct measures from the cognitive neurosciences which include neuroimaging, neurophysiology and behavioural studies (Adjamian et al., 2004; Aurora, Ahmad, Welch, Bhardhwaj, & Ramadan, 1998; Boulloche et al., 2010; Chouinard, Zhou, Hrybouski, Kim, & Cummine, 2012; Coutts et al., 2012; Dahlem & Chronicle, 2004; Datta et al., 2013; Huang et al., 2003; Huang et al., 2011; Martín et al., 2011; Welch et al., 2001). Furthermore, the selective role for the different factors in relation to the level of pattern-glare reported is revealing and suggests some specificity in the thematic nature of the experiences reported.

Another possible argument might be that the inter-correlations among the items were caused by their semantic overlaps rather than driven by the associated underlying neurological/ mechanisms. First, the internal consistency and inter-correlations of the items did not suggest redundancy of any items. Second, most of the items listed in *CHi-II* were semantically specific to describe some cortical hyperexcitability related symptoms. These items were documented as experienced by patient groups such as migraine with aura and Meares-Irlen syndrome who are known to have increased level of cortical excitability. Importantly, the second part of this study showed that the latent factors were associated with the visual discomforts and distortions caused by the gratings. Therefore, both intuitively and statistically speaking, the *CHi-II* is a behaviorally based rather than semantically based trait scale.

However, we do not rule out the possibility that there are any other underlying factors co-existing with cortical hyperexcitability to drive the latent structure and the association between the scales and the PG task. For example, the *HVSD* scale and the visual discomfort response in PG task could be mediated by perception and tolerance of pain. Therefore, we can expect the existence of diversified brain regions (including but not limited to insula, somatosensory cortex, thalamus, cerebellum and brainstem) that are engaged in the processing of visually induced pain and headache (Bahra, Matharu, Buchel, Frackowiak, & Goadsby, 2001; Coppola et al., 2010, 2018; Tso, Trujillo, Guo, Goadsby, & Seeley, 2015; Vincent & Hadjikhani, 2007). Further research using the *HVSD* and *AHE* factor as covariates of more objective measurements (e.g. brain-imaging or electroencephalography) to reflect the actual aberrant neurophysiological activity of the visual cortex is recommended. Not only it would help to confirm the factor structures but also the *CHi-II* itself can complement those experimental protocols by providing a formally established behavioural construct to connect aberrant visual perceptions and the underlying brain activities together.

The present study is limited in that the migraine group was not particularly large, was based on self-reports, and there was no direct medical screening or finer-grained delineation of migraine / headache sub-types. As a consequence, our findings here should be view as tentative.

However, the unequal group size of our migraine and healthy control samples (27 vs 316) may influence the robustness of our findings by violating the assumption of homogeneity of variances (Martin & Games, 1977). The Levene's test showed that there was a significant difference on variances of the *HVSD* between migraineurs and the

healthy control (F = 10.324, p = .001). To better control the Type 1 error rates, Welch's t-test was further conducted (Algina, oshima, & Lin, 1994). Although the result also reached significance, t (28.4) = 5.44, p = .027, the power of this finding could be lower than our original result which could be influential to the external validity of the scale. Therefore, the current study would be benefited by re-testing on another sample with equal group size in the future.

Building on the current findings, future research would benefit from a more comprehensive and fine-grained analysis of the migraine condition, and its sub-divisions, in relation to the separate *CHi-II* factors and the PG task. Although the current sample was not sufficient to explore these factors in full, it was sufficient to establish the scientific premise that our self-declared migraineurs did indeed display signs of significantly increased levels of PG experiences, arguably reflecting aberrant levels of cortical hyperexcitability. This observation was further extended here in that migraineurs displayed distinct ratings exclusively to the *AHE* and *HVSD* factors – a degree of specificity not previously observed.

The utility of the *CHi-II* can be further examined via coupling its use to more objective methods such as brain stimulation (magnetic and electric) and neuroimaging (Aurora et al., 1998; Antal, Kriener, Lang, Boros, & Paulus, 2011; Huang et al., 2003; Kanai, Paulus, & Walsh, 2010). Indeed a recent study demonstrated, for the first time, that pattern-glare effects could be increased via anodal stimulation montages using transcranial direct current stimulation (tDCS), but more so for those who already displayed lability for cortical hyperexcitability (Braithwaite et al., 2016).

It would also be prudent to determine how the separate factors from the *CHi-II* dovetail with different neurological, psychiatric, and clinical disorders. As with the migraine group reported in the present findings, hyperexcitable groups may only score high on some factors and not others, with such patterns providing informative covariates in a broader assessment of aberrant neural processes and resultant anomalous experience. In conclusion, we propose that the *CHi-II* is an improved and comprehensive indirect proxy measure of aberrant perceptions, which might reflect cortical hyperexcitability. Its factor structure and the novel findings reported here suggest it could have considerable scientific and clinical utility.

Chapter IV. Study 3: Examining the Early and Late Pattern-Onset Visual-Evoked Potentials in Self-Reported Migraineurs

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This chapter would be re-formatted for publication purposes. The chapter presented here was written entirely by the author. The research and analyses were ideas of the author and the co-supervisors, Ali Mazaheri and Jason Braithwaite. Programming of the experiment, data collection and analyses, proofreading and formatting of this study have partly been contributed by the research assistant, Wai Him Crystal Law.

Abstract of Study 3

Striped patterns have been shown to induce strong illusions and discomfort to migraineurs in previous studies. In the current scalp electroencephalography (EEG) study, visual evoked potentials (VEPs) induced by gratings in three different spatial frequencies (0.5, 3, and 13 cycle per degree: cpd) were compared between a group of 29 migraineurs (female, mean age = 20.9) and 31 non-migraineurs (female, mean age = 19.4). We found that the migraineurs had a significantly larger visual evoked 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. The enhanced N2 component was a sign of over-stimulation, implying a grating-induced cortical hyperexcitation on migraineurs. The attenuation of the LN could reflect a top-down feedback mechanism to suppress the hyperexcitation.

1. Introduction of Study 3

Previous research has proposed that an individual's excessive aversion to visual gratings of a specific spatial frequency could be due to a cortical hyperexcitation of the visual cortex (Braithwaite, Broglia, Bagshaw, & Wilkins, 2013; Evans, Cook, Richards, & Drasdo, 1994; Harle, Shepherd, & Evans, 2006; Wilkins, 1995). This hypothesis was mainly based on the research of migraine patients, who have elevated cortical hyperexcitability, consistently showing hypersensitivity to those gratings (Aurora & Wilkinson, 2007).

1.1. Early pattern visual evoked potential (pVEP) component

Visual evoked potential (VEP) has been used to evaluate the abnormality of visual processing of patient groups (e.g. migraine; Afra, Cecchini, DePasqua, Albert, & Schoenen, 1998; Shibata, Osawa, & Iwata, 1997,1998). The most common paradigm compares the pattern VEPs (pVEPs) at the mid-line occipital area (Oz) between clinical patients and healthy controls using stimuli of either pattern-reversal or steady (pattern onset) checkerboard-patterns varied in psychophysical features such as contrast and spatial frequency. For pattern-onset VEP, the first observable component after the pattern onset is at 70 – 90 ms named C1, with its polarity depending on the stimulus' vertical position: upper half presentation yields a negative potential while lower half leads to a positive potential (Jeffreys & Axford, 1972; Mangun, Hillyard, & Luck, 1993). For a centrally fixated stimulus, the contribution from upper field and lower field tends to cancel out; therefore C1 may not be visible (Musselwhite & Jeffreys, 1985). The next component is a positive wave peaked at 100 – 130 ms (P1), then a negative wave

complex peaked at 140 – 190 ms (N1) (Di Russo et al., 2001). For pattern-reversal VEP, the first negative component peaks at around 75 ms (N75), followed by a positive peak at 100 ms (P100) and a trough at 145 ms (N145) (Di Russo et al., 2005).

Studies using magnetoencephalography (MEG) and functional magnetic resonance imaging (fMRI) suggest that the C1 and N75 are originated from the V1 (Di Russo et al., 2005; Foxe et al., 2008; Hatanaka et al., 1997). On the other hand, the generators of the following components - P100 and N145 have been localised to the extrastriate visual cortex (V2 – V4; Di Russo et al., 2005; Lehmann, Darcey, & Skrandies, 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, Hammarrenger, Lepore, Roy, & Guillemot, 2001; Oelkers et al., 1999; Souza et al., 2008).

1.2. General pVEP findings on aberrant experience and migraine

Given that the pVEPs are originated from V1, V2 – V4, the difference in their peak amplitude or latency obtained from group comparisons (clinical vs control) may indicate impairment of early visual processing in the testing patient groups. Such dysfunction and impairment along the early visual pathway also provided a neurophysiological basis to the aberrant visual experiences of the patient group (Feinsod, Abramsky, & Auerbach, 1973). For example, prolonged or increased P100 were found to be associated with the visual hallucinations and other forms of visual disturbances amongst the Parkinson and schizophrenic populations (Matsui et al., 2005; Rady,

Elsheshai, Elkholy, Abou-El-Wafa, & Ramadan, 2011; Saitoh, Adachi-Usami, Mizota, & Fujimoto, 2001). Also, a recent study showed that P1 deflection could appear in the neurotypical subject who had out-of-body experiences (Milne, Dunn, Zhao, & Jones, 2019). Among all the clinical populations who are highly susceptible to visual disturbances, the pVEPs of migraine sufferers (with/without aura) have been most widely studied (e.g. Di Russo et al., 2005; Shibata, Yamane, Iwata, & Ohkawa, 2005), and will be the main focus of the present study.

The pVEP is highly sensitive to methodological deviations in the physical features of the stimuli. This nature contributes to the wide range of varying results in relevant studies, leading to different conclusions and hypothesis drawn by researchers. For instance, several studies have demonstrated that migraine sufferers have increased peak-to-peak amplitudes for both N75-P100 and P100-N145 interictally compared to healthy controls (Oelkers et al., 1999; Shibata, Osawa, & Iwata, 1997a, 1997b, 1998). These findings could be a consequence of cortical hyperexcitability in migraine patients (though see Ambrosini & Schoenen, 2006; Sener, Haktanir, & Demirci, 1997: for failures to replicate). Heterogenous measurements on peak latencies have also been reported, with studies revealing all possible results including prolonged, shortened or unchanged peak latencies in migraineurs (Afra et al., 1998; Oelkers et al., 1999; Shibata et al., 1997; Tagliati, Sabbadini, Bernardi, & Silvestrini, 1995).

Oelkers et al. (1999) are one of those who found a prolonged N2 latency in migraine patients compared to control (Oelkers et al., 1999; Yilmaz et al., 2001). They explain it by proposing N2 as a parvocellular “N130” and magnocellular “N180” complex component. Since migraineurs have a stronger N180 compared to N130, the

resultant N2 complex is predominated by the late N180 component causing the elongation of N2 latency.

Bockowski and colleagues (2004) have also revealed a longer latency of N2 but in a migraine without aura (MWOA) group, compared to the migraine with aura (MWA) group and people with tension-type headache (Bockowski, Sobaniec, Solowiej, & Smigielska-Kuzia, 2004). Their findings, alongside other reports, suggest that different migraine subtypes or migraine features are correlated with VEP amplitude and peak latency (Jancic et al., 2016; Khalil, Legg, & Anderson, 2000; Shibata et al., 1997).

Another variable said to be correlated to pVEPs amplitude in migraineurs is the duration of migraine (with aura) history. A few research have shown that this duration is negatively correlated with N75-P100 amplitude which implying a close relationship between migraine, visual disturbances and impaired visual processing (Jancic et al., 2016; Khalil et al., 2000). In addition, Jancic et al. (2016) have found that the presence of tunnel vision visual aura is indeed negatively correlated with N75-P100 and P100-N145 amplitude. Although these results generally have low statistical power with a small sample size ($n < 10$), they should still be considered as a possible explanation for the inconsistency of VEP findings in migraine research.

1.3. Late VEP components

It should be noted that the various evoked components do not exclusively reflect sensory processing, but also other higher-order cognitive function such as top-down attention, expectation (Picton, 1994), and memory (Puca et al., 1992; Puca & Tommaso, 1999). Researches on migraine have found that apart from the early VEP components,

migraineurs also exhibit abnormality for late components (e.g. Drake, Pakalnis, & Padamadan, 1989; Mazzotta, Alberti, Santucci, & Gallai, 1995; Puca & Tommaso, 1999).

The P3, is a positive potential, peaking maximally over central-parietal electrodes at around 300ms post-stimulus after 'oddball stimuli', infrequent deviant stimuli (e.g. an X) occurring within a train of frequent standard stimuli (e.g. an O). The latency of the P300 has been suggested to reflect the time it took participants to discriminate/categorise the oddball stimulus as deviant, while the amplitude decrease 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. In terms of P3 amplitude, while some researchers find that migraine patients have an increase in N2-P3 amplitude (Mazzotta et al., 1995), other studies report a reduction in P3 amplitude in migraineurs (Bockowski et al., 2007; Chen et al., 2007; Drake et al., 1989).

Despite the known abnormality of P3 in migraine patients, studies with the primary focus on VEP between 400 – 700 ms have been somewhat limited. Tommaso et al. (2009) discovered that migraineurs have a reduction in late positive potential (LPP) over Pz when they are presented with both pleasant or unpleasant pictures. This result contradicts Steppacher, Schindler, and Kissler (2016)'s findings which show an increment of LPP in fronto-central and parietal areas for migraineurs. Besides, Mickleborough et al., (2013) found that migraineurs have an increased mean amplitude in 400 – 600 ms when unfamiliar logos are presented. Despite the contradictory findings and difference in the visual task context, researches of late ERP seemed to cohesively

suggest that the abnormal cognitive processing of migraineurs are beyond sensory, and links with a higher cognitive level, namely selective visual attention. Such top-down processing bias might influence the late component, which is more likely generated from the extrastriate cortex, than the V1-generated early component (Clark & Hillyard, 1996).

1.4. Current study

Migraineurs are known to be more susceptible to visual discomforts and distortions in a pattern glare (PG) task, particularly for gratings of 2 – 4 cycles per degree (cpd), yet whether it is originated from cortical hyperexcitability mechanism is unknown (Evans & Stevenson, 2008). In the current EEG study, it was set out to investigate if gratings having 3 different spatial frequencies (0.5, 3, and 13 cycle per degree: cpd) elicited different visual evoked potentials (VEPs) between migraineurs and non-migraineurs. The difference in VEP responses could provide a neurological basis to the visual disturbances induced by the gratings.

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 study. All the participants had normal/corrected visual acuity (20/25 or better). The participants in the neurotypical 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 (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.

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 Figure 7 for an example of the grating). All stimuli were presented at the centre of a 20-inch Dell P2210 LCD computer screen (60Hz refresh rate and 1680x1050 pixels screen resolution) using E-prime v2.0 software, with a background luminance of 20 cd/m^2. The Michelson contrast of all the 3 gratings was 0.70 (cd/m^2). 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 x 12.68 degrees.

Participants also completed 2 questionnaires which measure the trait-based predisposition to anomalous perceptions: the *Cortical Hyperexcitability index – II (CHi-II)* (Fong, Takahashi, & Braithwaite, 2019) and the *Cardiff Anomalous Perceptual Scale*

(CAPS) (Bell, Halligan, & Ellis, 2005). The *CHi-II* has three factors representing different types of anomalous visual experiences, namely, (i) *Heightened 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 task. The first session of this study was a simple behavioural task named pattern-glare (PG; Braithwaite, Mevorach, & Takahashi, 2015; Braithwaite et al., 2013a, 2013b; Evans & Stevenson, 2008). Each trial began with a 12 second-presentation of one of the three gratings (presented in a pseudo-random order; see Figure 7 for the grating). Participants were instructed to gaze on a fixation point locating 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, nausea, 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 Figure 8 for the trial sequence). The responses for each AVD were added together to give a total AVD score for that grating (range = 0 – 120). Each grating was presented 3 times across 9 trials, and the 3 AVD scores were averaged to form a final AVD score for that particular grating.

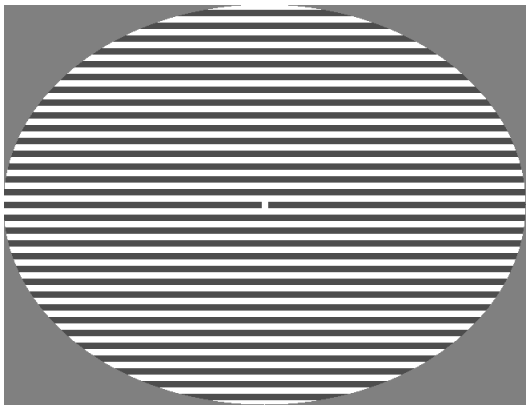

Figure 7. An example of the medium frequency square-wave grating.

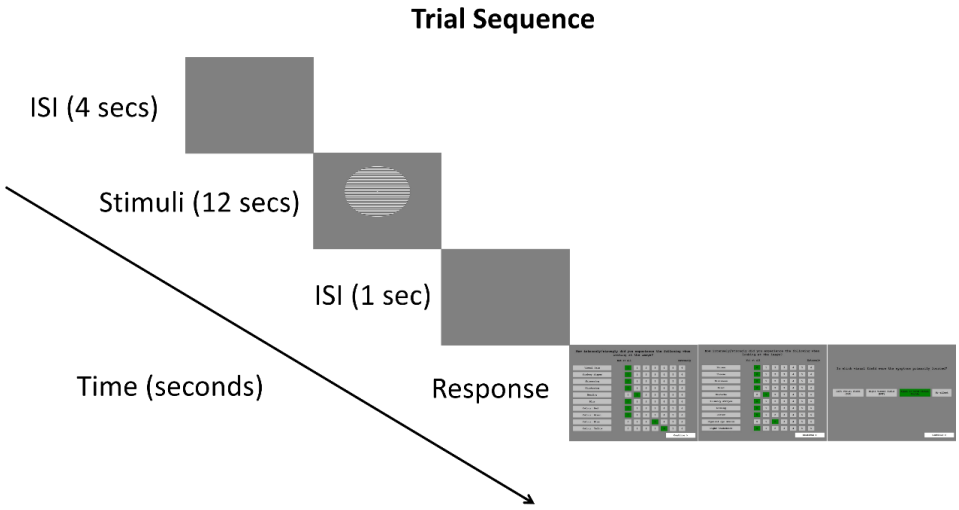

Figure 8. Trial sequence for the PG task.

2.3.2. EEG task. In the second part of the study, we recorded the EEG of the participants during the presentations of the gratings. 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. Participants were also instructed to either hit the left click by their index finger when their visual discomforts/distortions had

reached the maximum (typically around 2 to 10 seconds) or the right click by their middle finger when they did not experience any forms of visual discomforts/distortions at all after 8 seconds counting in their minds. Each trial was also separated by an 8s inter-stimulus interval (see Figure 9 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).

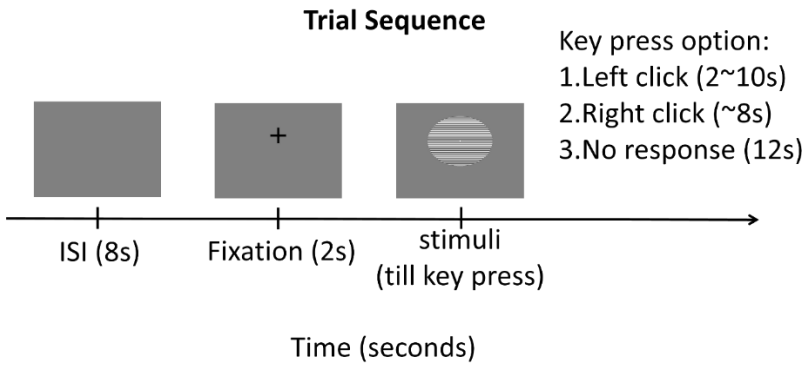

Figure 9. Trial sequence for the EEG task. The behaviour response (key press) was not analysed in the current study.

2.3.2.1. EEG Data Acquisition. The EEG signal was recorded by the EEGO Sports system (ANT Neuro) and Waveguard caps containing 64 Ag/AgCl electrodes (10/10 systems including left and right mastoids). Electrodes at CPz was used as reference while AFz was used as ground. After analogue to digital conversion, EEG data (sampling rate 500 Hz, impedances < 20 kΩ) was amplified with a high pass of 0.8 Hz and low-pass of 30 Hz. 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 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 was pre-processed in Matlab using EEGLAB functions (version 14.1.2b; Delorme & Makeig, 2004). First, the data was epoched from -500 to 1500 ms around the stimulus onset. Next, the extracted epochs were broken down into 30 components by Independent Component Analysis (ICA) using Principal Component Analysis (PCA) as the extracting method. Components that reflected muscle and ocular artefacts (e.g. eye blinks) were removed. Trials were 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, CPz reference montage was replaced by average reference prior to any further analysis.

2.4. Design and Analysis

The cleaned ERP data was further analysed by FieldTrip software package (Oostenveld, Fries, Maris, & Schoffelen, 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, Legg, & Anderson, 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, Morey, Speckman, & Province, 2012). The analysis provides relative evidence and probability on whether the data are more in favor 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 a moderate evidence in favor of the H_A or H_0 respectively (Jarosz & Wiley, 2014).

As an exploratory approach, any amplitude differences within time window 0 – 700 ms between migraine and the control group were assessed by non-parametric cluster-based permutation analysis (Maris & Oostenveld, 2007). The adjacent spatiotemporal sample data was first clustered if they exceeded a threshold of $p < 0.05$ (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. VEP Component Analysis

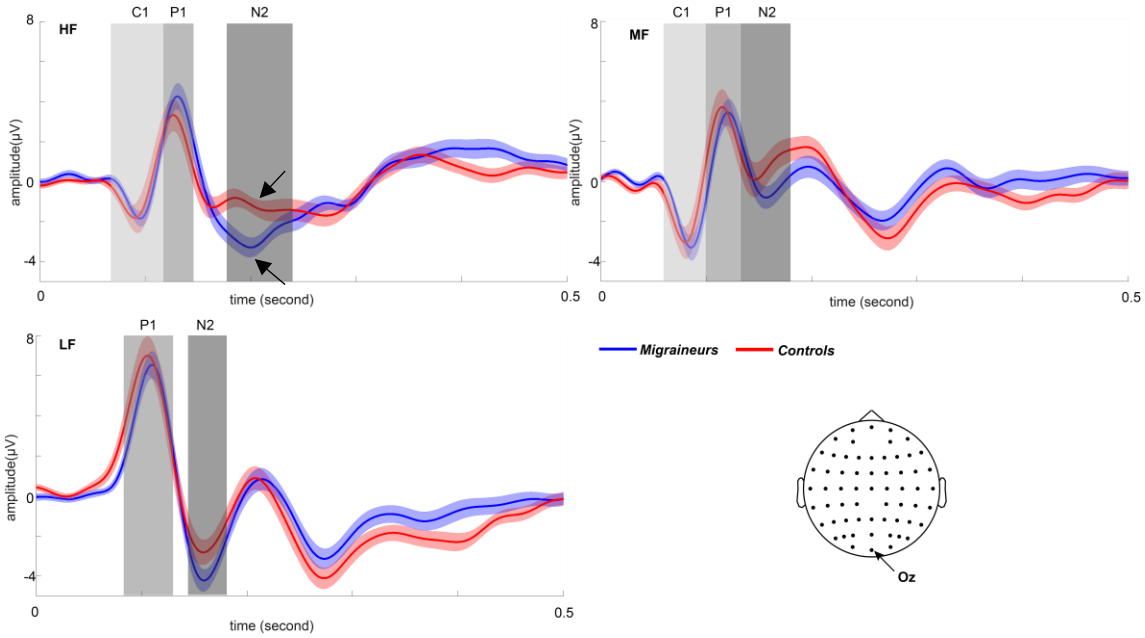

Figure 10. Grand mean of the ERP measured at Oz in HF (left), MF (middle) and LF (right) conditions for migraineurs vs healthy control (shaded area indicating +/- 1 SE). The arrows indicated significant amplitude differences between the two groups. The time-intervals of interest used for the average peak amplitude is shaded in grey.

As mentioned previously, 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 complex (named as N2 for convenience) 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 = 0.008, False Discovery Rate (FDR) corrected p = .024, BF_{10} = 5.59 (see Figure 10 & Table 9).

Table 9. Results of independent t-test and Bayes factor on N2 amplitudes between migraineurs and control with standard error in parenthesis.

Mean amplitude of components (μV)	Migraine (n = 29)	Control (n = 31)	uncorrected *p*-value	*FDR-corrected p-value*	BF_{10}
HF	**-2.67 (0.40)**	**-1.21 (0.35)**	**.008**	**.024**	**5.59**
MF	-0.28 (0.49)	0.80 (0.66)	.20	.20	0.53
LF	-3.39 (0.47)	-2.23 (0.57)	.12	.18	0.73

For exploratory purposes, we also analysed the group-differences of other early visible local peaks. The C1 was defined as the mean amplitude within the latency range of 75 – 115 ms and 75 – 100 ms for HF and MF, respectively. The P1 was defined as the mean amplitude within the range 115 – 140 ms, 100 – 130 ms, 95 – 125 ms for HF, MF and LF (see Figure 10). 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.

3.2. 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. Since there were no significant clusters for MWA vs MWOA and MWA vs MWOA vs control comparisons, the following analyses were migraine vs control, with MWA and MWOA collapsed into a migraine group. The clusters were formed by significant t-stats of potential differences between migraine and control group.

One significant positive cluster and one significant negative cluster for each spatial frequency were obtained from the cluster-based permutation analyses. Due to the dipolar topography of the VEP, only the positive clusters (posterior regions involving parietal and occipital-temporal channels) were reported. Positive clusters indicated more positive/less negative amplitudes for the migraine group than control and negative clusters were the opposite.

Migraineurs had an attenuated VEP between 382 – 538 ms (p = .002) maximally distributed over the parietal and occipital-temporal channels for HF (see Figure 11). Such attenuation in amplitude was also observed in the posterior regions for MF (384 – 486 ms, p = .023) and LF (368 – 486 ms, p = .012) conditions (see Figure 12 & 13).

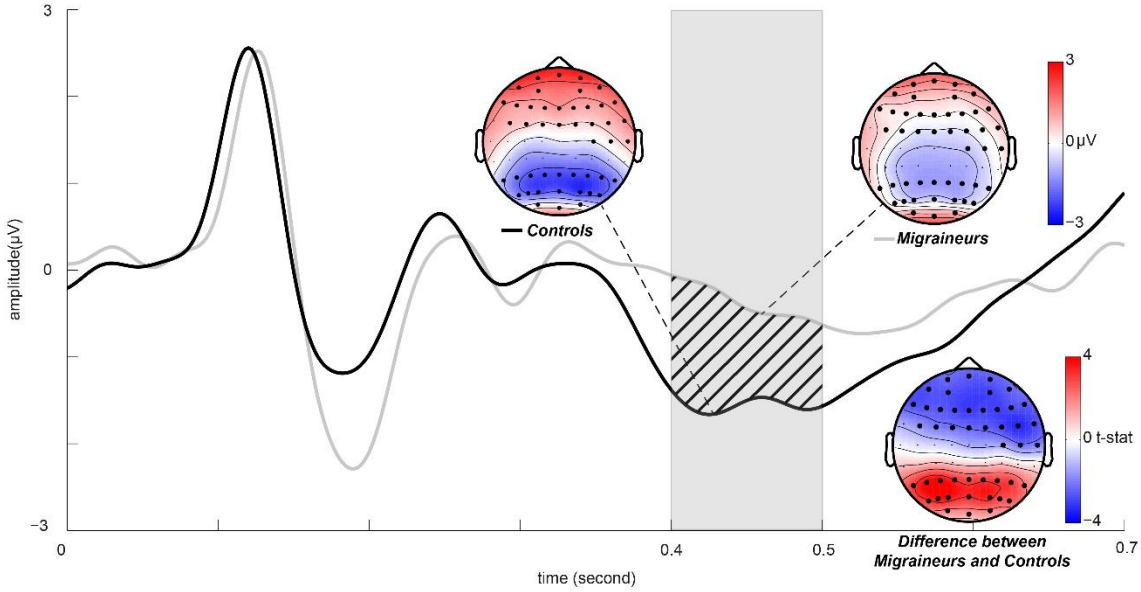

Figure 11. The average ERP (HF) over the significant channels of the positive cluster (posterior region). The significant channels were highlighted in bold on the topographies (both the positive and negative clusters). Migraineurs had an attenuated VEP compared to control between 400 and 500 ms (shaded in grey).

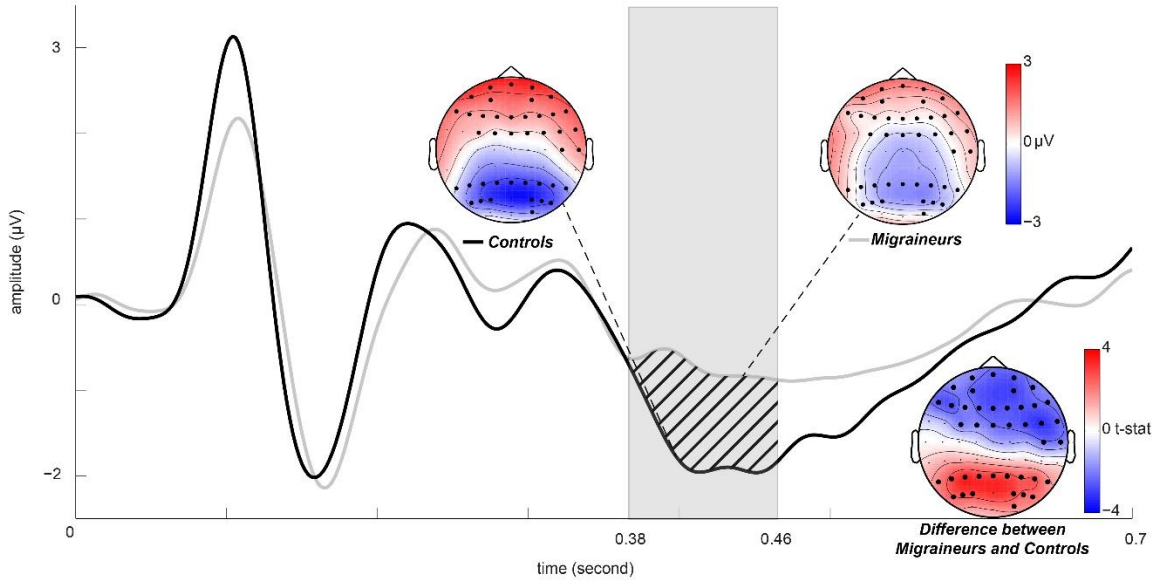

Figure 12. The average ERP (MF) over the significant channels of the positive cluster (posterior region). The significant channels were highlighted in bold on the topographies (both the positive and negative clusters). Migraineurs had an attenuated VEP compared to control between 380 and 460 ms (shaded in grey).

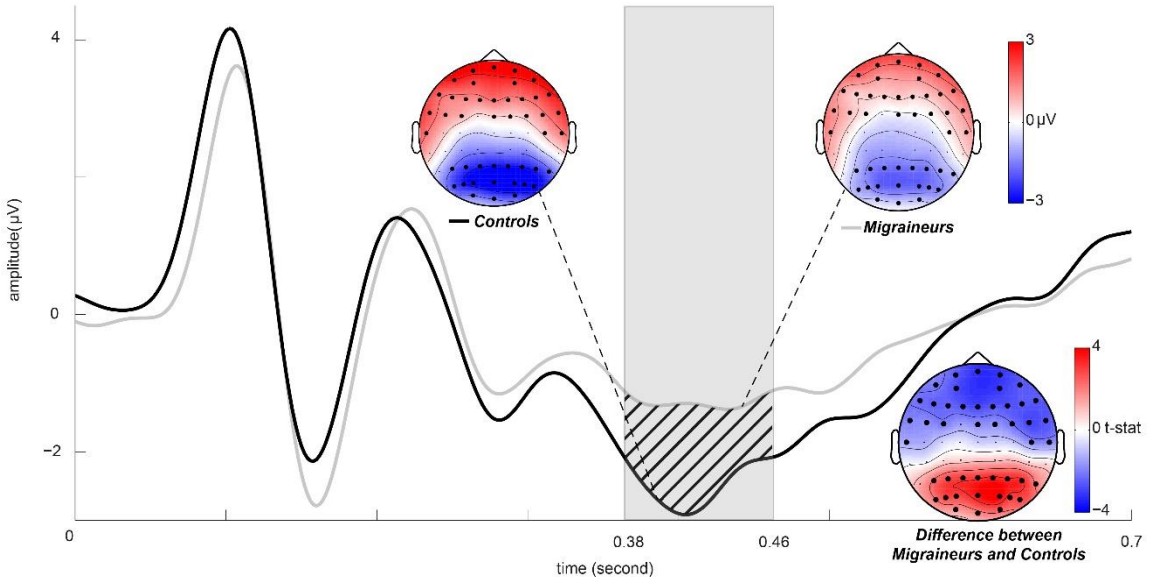

Figure 13. The average ERP (LF) over the significant channels of the positive cluster (posterior region). The significant channels were highlighted in bold on the topographies (both the positive and negative clusters). Migraineurs had an attenuated VEP compared to control between 380 and 460 ms (shaded in grey).

3.3. Behavioural Tests

3.3.1. Pattern Glare Results. Migraineurs significantly showed more AVD response at all spatial frequency conditions than control group (HF: $p = 0.002$; MF: $p = 0.016$; LF: $p = 0.001$; see Table 10). However, the subtraction parameter – ΔAVD (MF - HF) between migraineurs and control was not significant.

Table 10. Mean AVD and Bayes factor for migraine vs control across HF, MF and LF conditions (with standard error in parenthesis)

Mean AVD	Migraineurs	Control	*t*-stat	Uncorrected *p*-value	*FDR-corrected p-value*
HF	**19.2 (1.94)**	**11.3 (1.56)**	**-3.20**	**.002**	**.004**
MF	**18.4 (2.02)**	**12.4 (1.37)**	**-3.47**	**.016**	**.021**
LF	**8.23 (1.29)**	**3.24 (0.70)**	**-2.48**	**.001**	**.004**
MF – HF (ΔAVD)	-0.81 (1.28)	1.14 (0.81)	1.31	.20	.20

3.3.2. *CHi-II* and *CAPS*. Migraineurs scored significantly higher than controls in *HVSD* (FDR adjusted $p < 0.001$) and *AHE* (FDR adjusted $p = 0.003$). Although there were mean group differences in *DVP* and *TLE*, they were marginally non-significant (see table for the mean score, *p*-value for t-test, FDR adjusted *p*-value and Bayes factor).

Table 11. The mean questionnaire score for the subscales of *CHi-II* and *CAPS* (with standard error in parenthesis)

Questionnaire score	Migraineurs (n = 29)	Control (n = 31)	*t*-stat	Uncorrected *p*-value	*FDR* corrected *p*-value	BF_{10}
HVSD	**61.1(3.74)**	**31.7(3.53)**	**-5.72**	**<.001**	**<0.001**	**>30000**
AHE	**24.8(3.36)**	**11.4(2.28)**	**-3.34**	**.001**	**.003**	**22.4**
DVP	10.1(1.43)	5.97(1.45)	-2.04	.046	.069	1.47
TLE	24.0(3.21)	15.3(2.60)	-2.14	.037	.069	1.72
CS	12.8(2.81)	13.3(3.34)	0.11	.910	.910	0.26
CP	5.48(1.37)	4.32(1.72)	-0.52	.603	.724	0.30

Note: HVSD: Heightened Visual Sensitivity and Discomfort; AHE: Aura-Like Hallucinatory Experiences; DVP: Distorted Visual Perception; TLE: Temporal Lobe Experience; CS: Chemosensation; CP: Clinical Psychosis

3.4. Post-hoc Comparison for MWA vs MWOA

The mean amplitude of C1 for MWA patients (mean ± 1 *S.E.* = -1.88 ± 0.53 μV) in MF condition was significantly reduced compared to MWOA patients (mean ± 1 *S.E.* = -4.20 ± 0.99 μV), $t(27) = 2.32$, $p = .034$, $BF_{10} = 2.09$. Such a difference between conditions was not observed in other spatial frequencies (see Figure 14). Apart from this, there were no other significant differences between MWA and MWOA in all other ERP and behavioural measures.

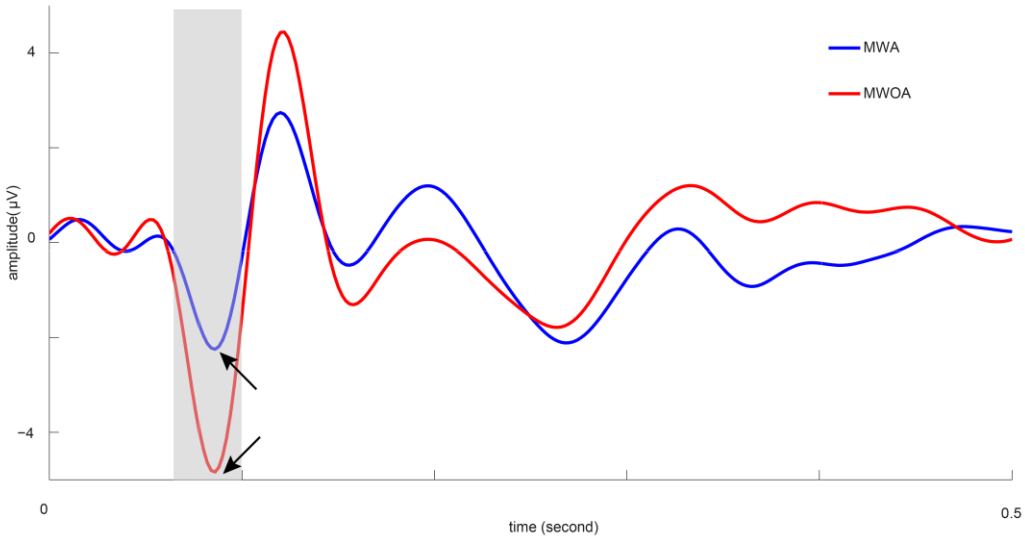

Figure 14. Grand mean of the ERP (MF) at Oz between migraine with aura (MWA) and migraine without aura (MWOA). There was a significant amplitude difference for C1. The time-intervals for C1 is shaded in grey.

4. Discussion

Over the past two decades, the vast majority of EEG studies on migraine has focused on the analysis of early VEP components, with the reason being that abnormalities in such components are consistently observed in migraineurs. The inclusion of a "pattern glare" (PG) task to our study is a new element. Also, the data analysis was extended from VEP components – C1, P1, and N2 to the late ERPs. To utilise the advantage of PG task, we have presented both migraineurs and control groups stripe patterns of 0.5, 3, and 13 cpd, which were identified as the most critical spatial frequencies to reflect one's sensitivity to visual discomforts and distortions by PG studies. The mechanisms and constitutional differences of migraine patients will be discussed, based on the comparison of the EEG and behavioural responses between the 2

groups. It should also be noted that the primary focus of our discussion will be the amplitude results since no reliable or significant difference on latencies for all spatial frequencies between our migraine samples and healthy controls was reported.

In the current study, we used both a confirmatory and exploratory approach to investigate differences in VEPs elicited by different frequency gratings. We found that after the presentation of the high frequency gratings (13 cpd), migraineurs exhibited a more salient and negative N2. Interestingly, a within-group analysis found that this was observed in both migraine sufferers with and without auras. However, a post-hoc analysis did reveal an C1 difference with migraine sufferers with an aura having a significantly reduced C1 amplitude than those without aura. Finally, our exploratory analysis showed, for all gratings, an attenuation of the late (400-500ms) post-stimulus negativity over occipital channels in the migraine group.

4.1. Increment of N2 complex revealed cortical hyperexcitability

The enhanced N2 we observed is in line with previous studies using pattern reversal VEP paradigm (Lahat, Nadit, & Barr, et al., 1997; Lahat, Barr, & Barzilai et al., 1999; Shibata et al., 1997). Oelkers et al. (1999) proposed that the N2 complex in medium (or high) frequency grating could be a superposition of N130 and N180 components. N130 is described as contour specific and visible for both migraine and healthy subjects evoked by high frequency grating while N180 is luminance dependent and relatively predominating in the N2 complex for migraineurs (Oelkers et al., 1999). Consistent with Oelkers et al. (1999)'s findings, the N2 in the present study for migraineurs peaks at 200 ms instead of the commonly reported 130 – 145 ms suggested

that it was predominated by a luminance-dependent N180. It is, however, not clear whether there is any amplitude change for N130. Nonetheless, the abnormal N2 reflected an imbalance between the magnocellular (sensitive to luminance: N180) and parvocellular (sensitive to contrast and high spatial frequency: N130) system. The impairment in the connectivity between these two systems could be potentially caused by cortical hyperexcitation or abnormality from GABAergic inhibitory interneurons (Chronicle and Mulleners, 1994).

However, one might argue that if the increased N2 is driven by cortical hyperexcitability, a similar N2 deflection should be observed on MF condition as well. One straightforward mechanism, which is partly consistent with Oelkers et al. (1999)'s findings, could be that the N2 components increased with the spatial frequency of the visual input. Therefore, the amplitude deflection only becomes visible for high frequency condition. An alternative but not mutually exclusive explanation is that there is a "phantom" positive component, namely P200 cancelled out the negativity of N180. Some literatures showed that visual P200 is associated with motion onset (Schulte-Korne, Deimel, & Remschmidt, 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 & Stevenson, 2008; Ffytche, Skidmore, & Zeki, 1995). This mechanism could also explain why jittering and shimming are so common as a form of motion illusions induced by gratings in 3 cpd (see Braithwaite et al., 2013; Evans & Stevenson, 2008; Fong at al., 2019). The hypothesised VEP model and the role of N130, N180 and the "phantom" P200 were summarised in Figure 15.

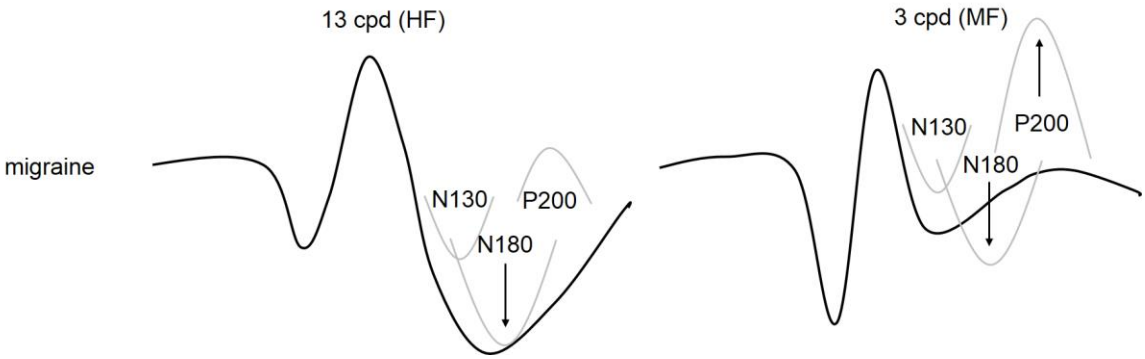

Figure 15. Model of the migraine VEPs for HF and MF. The N2 complex can be hypothesised as a superposition of N130, N180 and P200. For the HF condition, migraineurs had an increased luminance-dependent N180. The predominating N180 outweighed the P200. For the MF condition, the N180 increase was cancelled out by a sharp P200.

4.2. Pathological difference between migraine subtypes

Another finding related to sensory processing is that our MWA group had a significantly attenuated C1 amplitude than MWOA group for the MF condition, in line with previous studies (see Coppola et al., 2015; Khalil, Legg, & Anderson, 2000). The amplitude difference in early VEP components between the migraine subtypes is said to be linked with the presence and history of aura, as discovered by above literatures who report similar findings. They suggested that the presence and a prolonged suffer from aura in the long run (history) will reduce the amplitudes in early components, probably through ischaemia-induced neural damage during the experience of aura. However, it is unlikely that the C1 difference in the present study was due to neural damage from aura history with a young age sample.

On the other hand, we could argue that the present finding was due to enhanced cortical hyperexcitability for MWOA compared to MWA. Although both migraine

sufferers (with/without aura) were known to have elevated cortical hyperexcitability, a different dimension of cortical hyperexcitability could underlie their pathological differences. In other words, migraineurs with and without aura share the same elevated cortical hyperexcitability on one dimension but differ on another dimension. This multi-dimensional concept of cortical hyperexcitability was proposed by our previous study (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, Theoret, Pfenning, Ives, & Kampmann, 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.

4.3. 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 late negativity (LN; centred at parietal and occipital-temporal areas) peaked around 400 – 500 ms. Such activities were significantly attenuated in the migraine sample, i.e. a reduction in amplitude in LN was observed.

Late potentials (LP) are widely agreed to be associated with stimulus recognition and selective attentional processing (Cuthbert et al., 2000; Schupp, Junghofer, Weike, & Hamm, 2004; Ritter & Ruchkin, 1992). For example, affective 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 valance of pictures (Tommaso et al., 2009). Abnormal LP was also reported in other literatures with varied findings in uncertain directions - an increment or reduction (Mickleborough et al., 2013; 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, Cooper, Satana, Kaufman, & Cao, 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 the context of the stimuli which were also found in the literature (Ince, Erdogan-Bakar, & Unal-Cevik, 2017; Moutran 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.

Although the role of attentional processing has mainly been linked with late components (e.g. P300), there is evidence that it can also affect early components (Zani & Proverbio, 1995). For instance, selectively attended object could elicit an increased amplitude to visual evoked components as early as 70 – 80 ms (Zani & Proverbio, 1995). Therefore, alongside methodological difference such as stimuli variations in pattern contrast, spatial and temporal frequencies, selective attention could also contribute to our findings and any discrepancies with the literatures (Ambrosini & Schoenen, 2006; Zani & Proverbio, 2003).

Future directions will also include frequency analyses on the current data set. Since oscillatory activities of the gamma-band (Adjamin et al., 2004) and alpha-band (Jensen & Mazaheri, 2010) were associated with cortical hyperexcitability and functional inhibition respectively in previous literatures, the analysis on frequency domain will provide a stronger support to the functional interpretation of the current findings.

4.4. Conclusion

In conclusion, migraine patients have an increased N2 amplitude in HF gratings compared to controls, hinting a sensory impairment consistent with the cortical hyperexcitability mechanism. In addition, pathological differences between migraine subgroups are supported by a significantly higher C1 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. Therefore, alongside methodological difference, selective

attentional processing can also contribute to the high inconsistency in findings of migraine EEG studies.

Chapter V. Study 4: The Early and Late Pattern Visual Evoked Potential for Healthy Populations with Strong Pattern Glare Symptoms

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This chapter would be re-formatted for publication purposes. The chapter presented here was written entirely by the author. The research and analyses were ideas of the author and the co-supervisors, Ali Mazaheri and Jason Braithwaite. Programming of the experiment, data collection and analyses, proofreading and formatting of this study have partly been contributed by the research assistant, Crystal Wai Him Law.

Abstract of Study 4

Pattern glare (PG) is believed to be caused by cortical hyperexcitation induced by visually irritating striped patterns based on migraine study. On the other hand, PG effect as an indicator of hyperexcitation could also be seen in some non-clinical populations. This study aimed to investigate the PG effect and cortical hyperexcitability amongst non-clinical subjects via electroencephalography (EEG) technique. Thirty-eight female participants were split in accordance with their PG score (a priori was adopted from Fong, Takahashi, & Braithwaite, 2019) into PG group and non-PG group. PG group showed the sign of cortical hyperexcitation of an increase N2. Also, there was a marginally significant decline of late negativity (centred at parietal and occipital-temporal area) for the PG group. Such an effect might suggest a top-down suppressive control to attention in order to reduce the visual discomfort induced by the grating.

1. Introduction of Study 4

1.1. Hyperexcitability and Pattern Glare

Migraine patients were known to have high cortical hyperexcitability which was indicated by having a lower phosphene induction threshold from transcranial magnetic stimulation (TMS) on their occipital cortices (Aurora, Cao, Bowyer, & Welch, 1999). This enhanced cortex excitability was compatible to the cortical spreading depression (CSD) model, and therefore could be hypothesised as the basis of migraine and migraine aura experience (see Bowyer et al., 2001; Hadjikhani et al., 2001). On the other hand, behavioural studies showed that migraine patients are averse to striped patterns (Evans & Stevenson, 2008; Haigh, Karanovic, Wilkinson, & Wilkins, 2012). It is however debatable whether cortical hyperexcitability is responsible for the migraineurs' aversiveness to striped patterns.

Evans and Stevenson (2008) proposed that gratings in specific spatial frequency and orientation could induce illusory perception by over-stimulating the same nerve network on visual cortical area, leading to the breakdown of the inhibitory process of the interneurons. Therefore, in parallel with migraineurs, other populations who have hyperexcitable visual cortex might also show symptoms of pattern glare. For example, clinical patients such as schizophrenia, dementia and non-clinical population who had out-of-body experience or visual discomfort also showed increased sensitivity and responsiveness to patterns (Braithwaite, Broglia, Bagshaw, & Wilkins, 2013; Conlon & Humphreys, 2001; Conlon, Lovegrove, Barker, & Chekaluk, 2001; Foxe, Doniger, & Javitt, 2001; Wright, Harding, & Orwin, 1986). The hypersensitivity was mainly

attributed to medium and high spatial frequency also suggested that the latent sensory impairment could be contributed by the parvocellular system (Skottun, 2000).

Pattern (checkerboard or striped) visual evoked potential (VEP) is the most popular paradigm to be adopted to test the pathological difference between migraine patients and healthy population. By using pattern onset or pattern reversal stimulation, some research found that migraine patients had amplitude or latency differences in early VEP component compared to the healthy population while others did not find the same result (Aurora & Wilkinson, 2007). Apart from early VEP components, migraineurs also showed abnormal late potential suggesting that they might also have higher order cognitive processing difference such as selective attention on specific visual stimuli (Tommaso et al., 2009).

1.2. Current Study

The current study aimed to investigate how cortical hyperexcitability contributes to the phenomenon of experiencing visual disturbances to gratings, also known as pattern glare amongst the healthy population. This was achieved by separating the non-clinical samples into a hyperexcitable or non-hyperexcitable group according to the behavioural responses to pattern glare task (associated visual distortion score: AVD) and compare the pVEP between the two groups. The role of selective visual attention would also be investigated by comparing the group difference of late potential in different spatial frequencies. We hypothesised that hyperexcitable subjects would show similar VEP response pattern similar to migraine patients.

2. Methods

2.1. Participants

Thirty-eight healthy female student (mean age = 19.3, range = 18 – 24) from the University of Birmingham consented to take part in the current study. All the participants had no migraine/epileptic history nor any neurological, psychiatric, ocular conditions. Visual acuity was measured before the start of the experiment with all subjects having a visual acuity better than 20/25. This study has been approved by the Ethics committees of the University of Birmingham.

2.2. Stimuli, Apparatus, & Questionnaires

The stimuli consisted of 3 square-wave achromatic gratings in the identical shape of a mild ellipse (max. height x width = 140 mm x 180 mm): a low-frequency grating (LF) of 0.5cpd, a medium-frequency grating of 3cpd, and a high-frequency grating of 13cpd. Participants were placed 80 cm away from the centre of a 20-inch Dell P2210 LCD computer screen (60Hz refresh rate and 1680x1050 pixels screen resolution), which gave a visual angle of 9.93 x 12.68 degrees. The screen background luminance was set as 20 cd/m^2 while the Michelson contrast of all the stimuli was 0.70 (cd/m^2).

Participants also completed a behavioural questionnaire, which is a proxy measure of cortical hyperexcitability: *Cortical Hyperexcitability index – II (CHi-II).* This measure has a 3-factor structure representing different dimensions anomalous visual symptoms, namely *Heightened Visual Sensitivity and Discomfort (HVSD), Aura-Like Hallucinatory Experiences (AHE)* and *Distorted Visual Perception (DVP)*.

2.3. Procedures

2.3.1. Pattern Glare Task. The format of this pattern glare task has been used in our previous studies (see Figure 16 for the trial sequence). Participants gave their responses by rating the intensity of the associated visual distortions (AVD; visual pain, physical eye strain, unease, nausea, 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 seen or felt in a 7-point Likert scale (0 = not at all, 6 = extremely). AVD scores for each grating were obtained from the average AVD of the 3 repetitions for that spatial frequency.

The participants were split into two groups according to a ΔAVD score (AVD of MF subtracted by HF). Subjects who have a ΔAVD > 3.92 were categorised as PG group while those scoring less than 3.92 were categorised as a non-PG group. This reference score was obtained by our previous study (Fong et al., 2019).

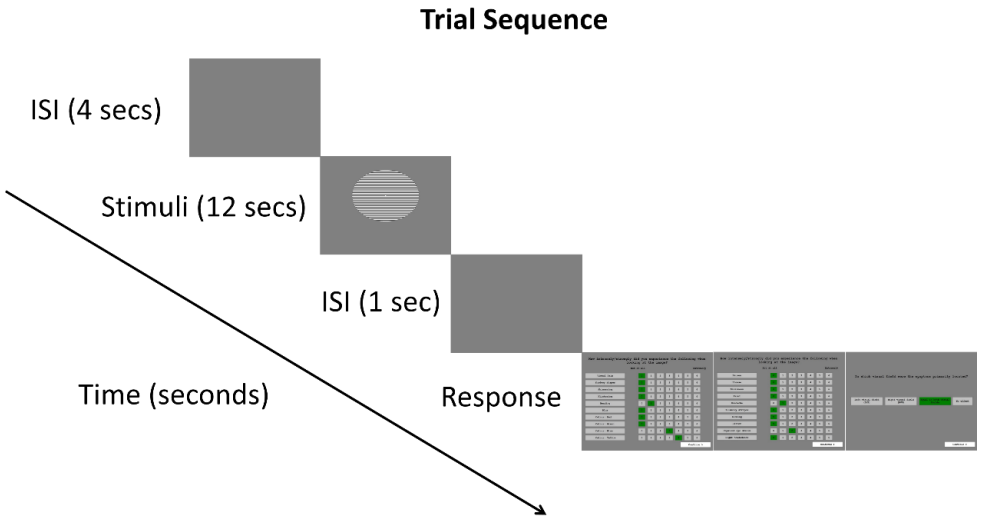

Figure 16. Trial sequence for the PG task. The trial began with a 4-sec inter-stimulus interval followed by a 12-sec presentation of one of the three gratings (in pseudo-random order). Participants were instructed to maintain their focus on a fixation dot at the centre of the stimulus.

2.3.2. EEG task. EEG was measured during the presentations of the 3 types of gratings (HF, MF or LF). Participants were instructed to focus on a fixation point at the centre of the screen in the 2-sec fixation period (see Figure 17). After that, they were told to maintain their focus at the same position where the centre of the gratings was located. Participants were required to either click the left button by their index finger when their visual discomforts/distortions had reached the maximum (roughly 2 to 10 seconds) or the right button by their middle finger when they did not feel/see any forms of visual discomforts/distortions after an 8-sec counting in their minds. The trial was then separated by an 8-sec inter-stimulus interval.

There were 50 repetitions for each grating which were presented in pseudo-random order. The 150 trials were evenly distributed into 10 blocks, with 15 trials in each of them. Each block was separated by a short break (not controlled).

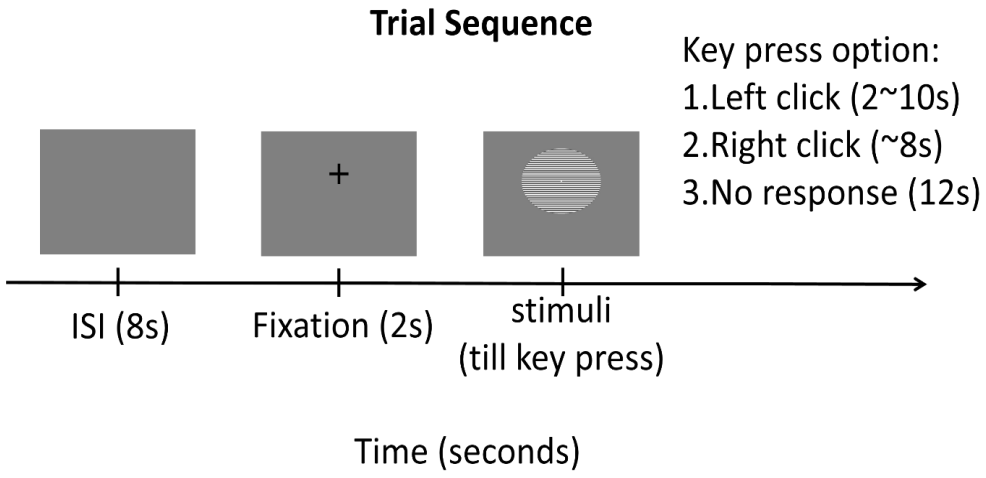

Figure 17. Trial sequence image of the EEG task. The behaviour response (key press) was not analysed in the current study.

2.3.2.1. EEG Data Acquisition. EEGs were recorded by the eego™ sports system (ANT Neuro) and Waveguard caps from 64 channels (Ag/AgCl electrodes in 10/10 systems including left and right mastoids). Electrodes at CPz and AFz were used as reference and ground respectively. The impedance of each electrode was kept under 20 kΩ before the start of the experiment. The digital EEG data was sampled at a rate of 500 Hz and with bandpass filter – 0.8 – 30 Hz applied. Horizontal and vertical eyeball movements were captured by two pairs of bipolar EOG electrodes placing at (1) outer canthi of left and right eyes, (2) 1 cm below the left eye and 1 cm above the left eyebrow. ECG electrodes were placed on the left and right chest, also left collar bone as ground to measure the heart rate activity. The heartbeat data was not used in the present study.

2.3.2.2. Pre-processing. Visual evoked potential data was pre-processed by Matlab toolbox – EEGLAB (version 14.1.2b; Delorme & Makeig, 2004). The epoched data (-500 to 1500 ms between stimuli onset) were analysed by Independent Component Analysis (ICA) using Principal Component Analysis (PCA) with 30 components being extracted. Muscle artefacts and eye blink represented components were removed. Any trials with muscle artefacts and noise not corrected by the ICA were removed after visual inspection. Besides, the bad electrodes were fixed by interpolation using the Spherical interpolation function in EEGLAB (see Ferree, 2000). Finally, the data was re-referenced to an average reference composed of all 64 electrodes (not including the ECG and EOG electrodes).

2.4. Design and Analysis

The ERP data set was analysed by FieldTrip toolbox (Oostenveld, Fries, Maris, & Schoffelen, 2011). The VEP components on Oz was first visually identified, and the

mean amplitude within the latency range (see Table 12) was calculated. The latency for the components was measured as the local peak/trough within the defined latency range. Any significant amplitude difference in late ERP component was measured by non-parametric cluster-based permutation analysis in the time window 300 – 600 ms (Maris & Oostenveld, 2007) if the clusters had a Monte Carlo *p*-value lower than 0.025. It is not possible to interpret the subtraction ERP waveform evoked by two physically different stimuli. Therefore, in contrast to the behavioural measure, ERP for each condition (LF, MF and HF) were analysed separately.

Table 12. The latency range (ms) of the early VEP component in different spatial frequency (S.F.)

S.F.	C1	P1	N2	P2
HF	70 – 110	110 – 150	150 –180	
MF	70 – 95	100 –130	130 – 165	170 – 210
LF		90 – 120	140 – 180	180 – 225

Note: There was no visible C1 for LF and P2 for HF. The N2 complex (N1+N2) was named as N2 for convenience.

3. Results

3.1. Early Components (C1, P1, N2, P2)

PG group exhibited a more negative N2 complex in HF conditions than non-PG group significantly (mean: -2.22 μV vs -0.38 μV), t (36) = 2.176, p = .036, BF_{10} = 1.93 (see Figure 18). In addition, PG group showed a significantly increased P2 amplitude compared to non-PG group (mean: 2.96 μV vs 0.99 μV), t (36) = 2.213, p = .033, BF_{10} = 2.04. PG group also had a reduced P1 for MF (mean: 3.46 μV vs 1.02 μV, p = .05) and HF (mean: 2.83 μV vs 0.94 μV, p = .07) compared to the non-PG group although they were only marginally significant. These results were summarized in Table 13. Since there was no systematic latency shift between the two groups of subjects across three conditions, statistics on peak latency were not reported.

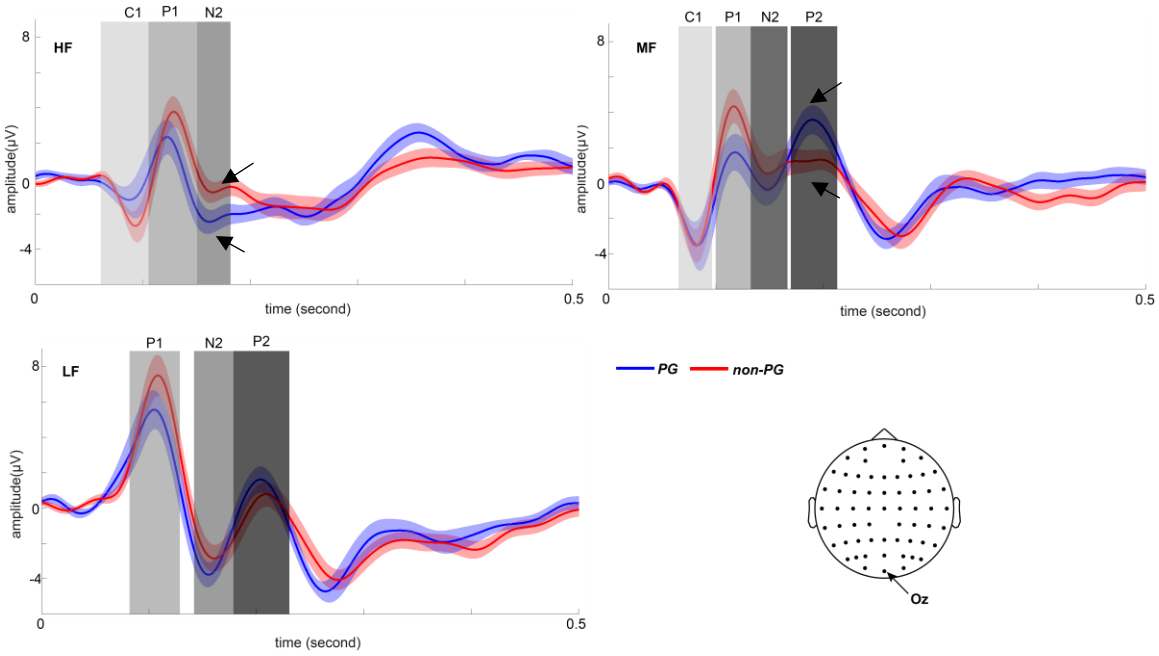

Figure 18. Grand mean of the ERP measured at Oz in HF, MF and LF conditions for PG group vs non-PG group (shaded area indicating +/- 1 *S.E.*). The arrows indicated significant amplitude differences between the two groups. The time-intervals of interest used for the average peak amplitude is shaded in grey.

Table 13. Results of independent t-tests and Bayes factor on C1, P1, N2 and P2 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)	p-value	BF_{10}
C1 (HF)	-0.61 (0.83)	-1.28 (0.58)	.50	0.39
C1 (MF)	-2.94 (1.20)	-2.26 (0.73)	.61	0.36
P1 (HF)	**0.94 (0.78)**	**2.83 (0.64)**	**.07**	**1.23**
P1 (MF)	**1.02 (0.88)**	**3.46 (0.78)**	**.05**	**1.52**
P1 (LF)	4.88 (0.96)	6.96 (0.98)	.16	0.72
N2 (HF)	**-2.22 (0.60)**	**-0.38 (0.56)**	**.04**	**1.93**
N2 (MF)	0.15 (0.88)	0.97 (0.94)	.55	0.37
N2 (LF)	-2.76 (0.61)	-2.30 (0.71)	.61	0.35
P2 (MF)	**2.96 (0.75)**	**0.99 (0.53)**	**.03**	**2.04**
P2 (LF)	0.83 (0.67)	-0.34 (0.58)	.20	0.62

3.2. Late components

The cluster-based permutation analyses at 300 - 700 ms revealed two marginally significant clusters in the MF conditions. The positive cluster (p = 0.061) involved 14 centro-parietal channels (CP2, CP6, P3, Pz, P4, CP4, P5, P1, P2, P6, PO5, PO3, PO4, PO6) between 410 – 478 ms (see Figure 19). Due to the dipolar nature of the VEP topography, only the positive clusters were reported. Such clusters were not observed in the other two spatial frequencies (all p > 0.3).

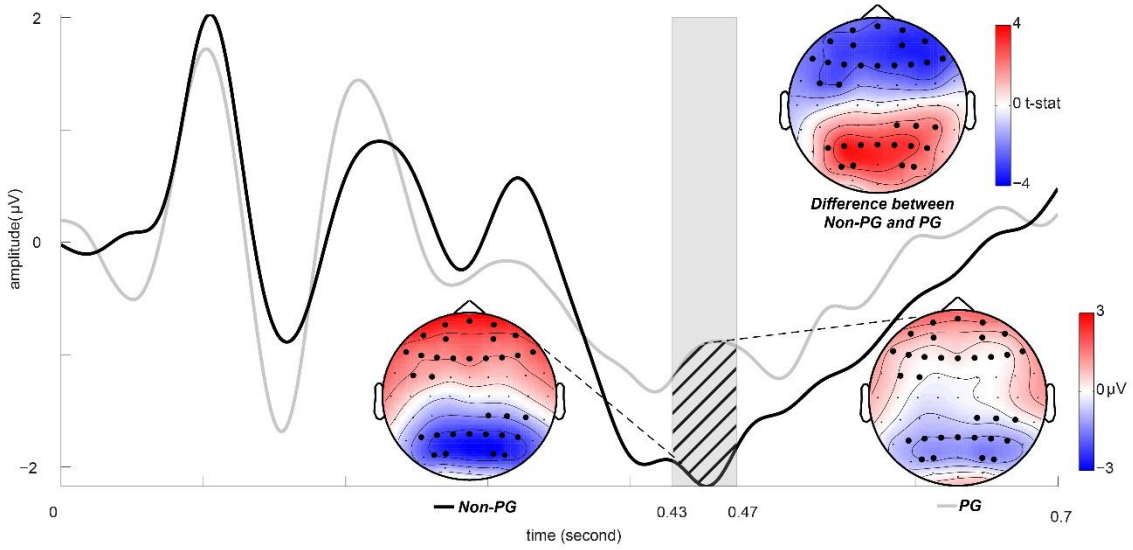

Figure 19. The average ERP (MF) over the marginally significant channels of the positive cluster (posterior region). The marginally significant channels were highlighted in bold on the topographies (both the positive and negative clusters). PG group had an attenuated VEP compared to non-PG group between 430 and 470 ms (shaded in grey). 3.3.

Behavioural measures – PG task and questionnaires

Results of the PG task were used as a grouping variable in this study. The mean AVD responses for each condition were summarized in Table 14. Table 14 showed that the group ΔAVD difference mainly resulted from a high mean AVD in MF for the PG group.

Table 14. 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)

For the questionnaire measures, there was a positive correlation between the C1 amplitude for the MF grating and the *HVSD* score (Spearman's rho = .346, p = .033), meaning a higher *HVSD* score was associated with a less negative/reduced N2 amplitude.

4. Discussions

The present experiment was the first study to investigate the pattern glare effect amongst the non-clinical population by electroencephalography. The current samples were split into PG group and non-PG group according to the subtraction parameter – ΔAVD (> 3.92 = PG, < 3.92 = non-PG) of the PG task. Behaviourally, the PG group had a more aversive response (i.e., excessive visual distortions and discomfort) to the grating with a medium frequency (3 cpd) than the non-PG group. The subsequent analyses examined the electrophysiological underpinnings of the PG effect by exploring the early and late ERP difference between these two neurotypical / non-clinical groups.

4.1. 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 previous 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 Figure 20). The amplitude of N130 appeared to be increased with the spatial frequency of the grating. As mentioned in the previous chapter, N130 is contour-specific and therefore, provides the support that the PG group might have abnormal responses along the parvocellular pathway similar to migraine patients (Oelkers et al., 1999). Such abnormality was believed to be caused by impaired GABAergic inhibitory system, which can manifest itself as cortical hyperexcitation (Chronicle and Mulleners, 1994).

In the previous experimental chapter, it was hypothesised that a "phantom" P200 component was cancelled out by a migraine-specific predominating N180. This P200 is also thought to be associated with the aberrant experience induced by the grating. In this study, in the absence of N180, an increased P200 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 was summarised in Figure 20.

Collectively, our findings provide further 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.

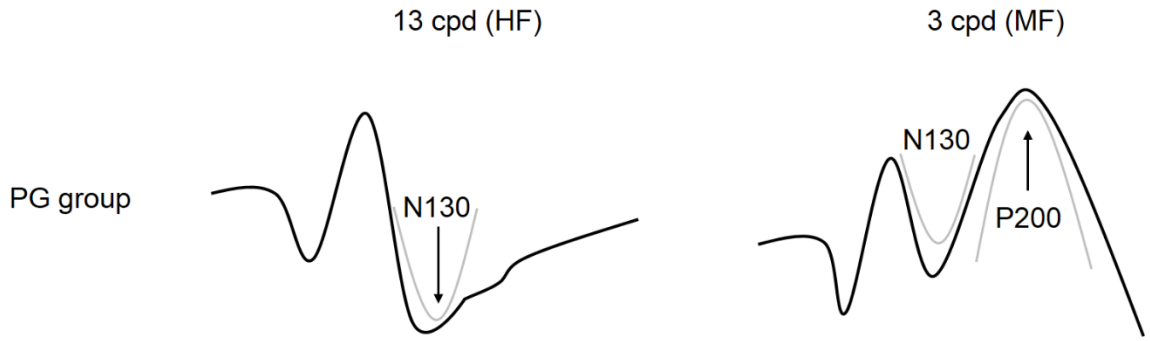

Figure 20. Model of the PG group VEPs for HF and MF. The N2 complex was hypothesised as a superposition of N130, N180 and P200 in the previous chapter while N180 is absent or attenuated for the present non-migraine sample. For the HF condition, PG group had an increased N130. For the MF condition, in the absence of the migraine-specific N180, the aberrant experience-associated P200 become visible.

The C1 for MF was found to be positively correlated (Spearman's rho = .346) with one of the *CHi-II* factors – namely *HVSD.* If the neural source of this C1 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.

However, the PG group showed a deficit in P1 for the MF grating, which appeared as contradictory to the notion of cortical hyperexcitability. P1 is an exogenous component primarily influenced by the contour, contrast and spatial frequency of the stimuli. A reduced P1 has been previously reported in patients who suffered from migraine aura for 30 years (Khalil, Legg, & Anderson, 2000). They suggested that reduced amplitudes could be due to neural damage caused by ischaemia during the repeated experience of migraine aura. As our sample are all young, healthy female adults, their suggestion did not seem to be compatible with our data. A more likely explanation

is that there is a latency shift of the N130 for PG group due to individual difference cancelled out the positivity of P1.

4.2. Evidence of Selective Visual Processing by Late VEP

Apart from the sensory level, the amplitude of some early VEP components can also reflect higher-order cognitive modulation such as selective attention on spatial frequency (Proverbio et al., 2002; Zani & Proverbio, 1995, 2009). For instance, P2 was believed to be responsible for selective attention (Hackley, Woldorff, & Hillyard, 1990; Noldy, Stelmack, & Campbell, 1990) and features detection (Luck & Hillyard, 1994). The increased P2 for PG group was not observed in other spatial frequencies which could be due to the attentional enhancement of PG group on MF due to their high susceptibility to visual discomfort and distortions on that grating. The neural generator for this P2 is different from the sensory driven P2. Unfortunately, the present study could not make a definite conclusion on whether the sensory or attentional pathway drove the P2 deflection.

Though the cluster-based analysis was just marginally significant, the attenuated late negativity (LN) on PG group in MF could be another supportive evidence on selective attention on spatial frequency. Similar LN has previously been reported in our study on migraine subjects where migraineurs showed a deficit in LN for all spatial frequencies. As suggested in the previous study, this LN reduction could be either caused by a top-down visual attention inhibition or a general visual attention deficit. Results in this study seemed to support the former theory as the LN reduction only appeared in MF. Since subjects 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 has to be further investigated. For instance, an unattended condition of the grating presentation could be introduced in further study. As a result, we would see a clear picture of the role of visual attention in perceiving aversive gratings. Moreover, the current data set can be re-analysed in the frequency domain in order to provide more support to our functional interpretations. Alpha-band oscillatory activities were an obvious direction since it reflected functional inhibition (Jensen & Mazaheri, 2010). For example, a posterior alpha power increase will support our hypothesis that there was a visual inhibitory activity to counterbalance the visual discomfort induced by the gratings.

4.3. Conclusion

Overall, some non-clinical samples were visually more sensitive to medium frequency grating than others. These healthy samples despite not suffering from other clinical conditions, they showed abnormal amplitudes in early and late VEP components. Some current findings on PG group are consistent with migraineurs such as increased in N2 (Oelkers et al., 1999; chapter IV) and reduction in LN (chapter IV). This similarity highlighted the contribution of cortical hyperexcitability to pattern induced visual disturbances.

Chapter VI. General Discussion for the current Thesis

1. Summary of Key Findings

1.1. Elevated Cortical Hyperexcitability Underlies Visual Disturbances

In Chapter II and III, we have examined which types of anomalous visual experience are associated with cortical hyperexcitability. The correlations between *HVSD* and *AHE* with pattern glare appeared to support the notion that heightened visual sensitivity and elementary hallucinatory experiences can be caused by visual cortical hyperexcitation.

1.1.1. Heightened Sensitivity and Discomfort. The correlation between pattern induced symptoms and hyperexcitable cortex is supported by numerous amounts of behavioural and brain imaging research (Aurora & Wilkinson, 2007; Harle, Shepherd & Evans, 2006; Huang et al., 2003; Huang et al., 2011; Marcus & Soso, 1989; Wilkins, 1995). On the other hand, symptoms such as abnormal light sensitivity and the visual discomfort induced by light are found to arise at the early stage of the visual pathway (Aurora & Wilkinson, 2007; Datta, Aguirre, Hu, Detre, & Cucchiara, 2013; Kawasaki & Purvin, 2002; Noseda et al., 2010), while other researches indicate that symptoms of photophobia, including excessive light intolerance due to headache, ocular discomfort and hypersensitivity to light, are associated with cortical hyperexcitability (Denuelle et al., 2011; Drummond, 1986; Silberstein, 1995; Vanagaite et al., 1997; Wilkins, Bonanni, Porciatti, & Guerrini, 2004). Although these literatures provided scattered views of the explanation for increased visual sensitivity and discomfort, there is no contradiction

between the findings of them since their results are, methodologically speaking, not against each other. It is possible that the earlier visual pathway and the visual cortex hyperexcitability both contribute to the photophobia symptoms of an individual.

Our findings appeared to support that visual cortex hyperexcitation is responsible for the photophobia symptoms of migraineurs. One possible mechanism could be that visual cortex hyperexcitability might alter light sensitivity, which could enhance the light-induced activity of the trigeminovascular system, causing the sensation of pain (Noseda & Burstein, 2011, 2013). Although lesions of optic nerve and chiasm or optic neuritis could also lead to hypersensitivity to light and ocular discomfort, we argue that it is not likely the case in our studies since subjects with any forms of ocular and neurological conditions were all excluded from our samples (Kawasaki & Purvin, 2002). It is believed that our results are more likely to be driven by visual cortex hyperexcitability.

1.1.2. Hallucinatory Experiences. Visual hallucinations and illusions are the most common forms of visual symptoms prior to a migraine attack (Russell & Olesen, 1996), which is hypothesized to be associated with a hyperexcitable visual cortex (Aurora & Wilkinson, 2007; Boulloche et al., 2010; Chen et al., 2011; Denuelle et al., 2011; Huang et al., 2003; Wilkins, 1984, 1995; Wilkins et al., 2004). Studies on non-migraine population showing that visual aura-like hallucinations can be triggered by direct stimulation (e.g. light, magnetic or electric field) over retina or visual cortex lend more generalisable support to the above idea (see Antal, Kincses, Nitsche, & Paulus, 2003; Aurora et al., 1999; Marg & Rudiak, 1994; Merabet et al., 2004). For example, visual cortex excitability has been shown to be enhanced by a few minutes of light deprivation, supported by physiological evidence using fMRI and brain stimulation techniques

(Boroojerdi et al., 2000). Merabet and colleagues (2004) also demonstrated that, as a method for manipulating the level of visual cortex excitability, prolonged blindfolding (96 hours) for healthy subjects could induce simple visual hallucinations such as flashes or phosphenes.

These literatures have provided direct evidence for a close association between the background level of cortical hyperexcitability and elementary hallucinatory visual experiences. It is consistent with the CSD theory, which suggests that CSD or CSD-like activities are more easily to arise and propagate over a hyperexcitable visual cortex, generating positive or negative aura symptoms such as fortification, phosphenes and scotomas (Bowyer et al., 2001; Hadjikhani et al., 2001; VanValkenburgh, 2005).

1.2. Different Dimensions of Cortical Hyperexcitability Modulate Migrainoid Symptoms

Pattern glare is found to correlate differently with a distinctive category of anomalous visual experiences, as presented in chapter III. It is believed that different dimensions of cortical hyperexcitability can modulate migrainoid symptoms such as migraine headache, visual aura, interictal hallucinatory visual experiences and heightened visual sensitivity.

1.2.1. Headache and Pain.

First, the CSD theory helps explain how cortical hyperexcitation leads to migraine headache and aura. It has been found that apart from being directly linked with the formation of migraine aura, CSD can highly contribute to the activation of the trigeminovascular system, triggering the meningeal nociceptors to release the signal of pain (Bolay et al., 2002; Noseda & Burstein, 2013; Zhang et al., 2010, 2011). Although CSD is generally agreed to be originated from the visual cortex,

numerous researchers discovered that multiple cortical regions beyond the visual area are also activated throughout a migraine attack (including both the aura and headache phase; Bowyer et al., 2001; Cao et al., 1999; Hadjikhani et al., 2001; Lauritzen, 1994). Neuropsychologists propose, with supporting neuroimaging evidence, that trigeminovascular system can be modulated by the visual cortex and all the associated neural structures such as somatosensory insular cortex and the subcortical regions (e.g. hypothalamus and brainstem), causing migraine headache and photophobia symptoms (see Noseda et al., 2011; Noseda & Burstein, 2013). In addition, if the CSD wave depolarises the cortical regions that process vestibular signals (e.g. posterior insula and temporoparietal junctions), symptoms such as vertigo, dizziness, nausea and motion sickness can be formed (Cutrer & Baloh, 1992; Lempert, Neuhauser, & Daroff, 2009). Collectively, the excitability of any structures within the cortico-subcortical-trigeminovascular network can make an impact on the *HVSD* symptoms. While high PG effect can indicate elevated visual cortex hyperexcitability, it may also imply that the modulation of migraine is based on the excitability of multiple cortical and subcortical areas. We believe that this is likely to be true because the PG effect, in our studies, is strongly associated with the *AHE* in both populations but associates with the *HVSD* differently between migraine and non-migraine populations.

1.2.2. Visual Hallucinatory Experiences. Although the role of cortical hyperexcitability in anomalous visual experience is frequently examined in neurophysiological studies, evidence directly obtained from the non-migraine population has been limited. Results of these studies, when conducted under similar conditions, are generally consistent with the findings obtained in migraine populations, showing a strong association between visual

hallucinations and the hyperexcitability of the visual cortex (including striate and extrastriate cortex). For instance, researchers have found that the severity of Dementia with Lewy bodies patients' visual hallucinations is negatively correlated with their threshold of TMS induced phosphenes (Taylor et al., 2011; Taylor, Firbank, O'Brien, 2016). Also, heavy ecstasy users who reported hallucinatory experiences have a lower TMS phosphenes threshold compared to control and those without hallucinations (Oliveri & Calvo, 2003). On the other hand, rTMS has been developed into an effective therapy to reduce symptoms of hallucination by modulating the level of excitability of a given cortical area (Maeda, Keenan, Tormos, Topka, & Pascual-Leone, 2000; Pascual-Lfeone et al., 1998). This is supported by a wide range of case reports indicating that rTMS treatment can successfully reduce the symptoms of visual and auditory hallucinations of different clinical groups (Hanaway et al., 2016; Hoffman et al., 1999; Merabet, Kobayashi, Barton, & Pascual-Leone, 2003). In general, the literature seemed to support that visual hallucinatory experiences are mainly modulated by the excitability of visual cortex.

1.2.3. Aura. In chapter IV, both of the migraine subgroup - with or without aura showed evidence of elevated cortical hyperexcitability by an N2 deflection. Such neuropathological similarity has been demonstrated in previous studies using VEP and TMS technique (Afra et al., 1998; Mulleners, Chronicle, Palmer, Koehler, & Vredeveld, 2001; Shibata et al., 1998). On the other hand, aura symptoms highlight the key difference between these two types of migraine and how visual aura could be associated with cortical hyperexcitability was discussed in the first chapter (also see Dahlem & Chronicle, 2004 for a computational perspective of aura formation). However, the

naming of these two migraine subtypes is somewhat misleading since the differences between them are beyond aura. For example, the headache experienced by MWOA was reported as longer and more intense than MWA (Rasmessen & Olesen, 1992; Russell, Rasmussen, Fenger, & Olesen, 1996) although there is limited physiological support showing the severity of headache is driven by cortical hyperexcitability. Interestingly, the present research appeared to fill this gap with the biomarker highlighting the difference between MWA and MWOA's VEP responses – C1, was found to be correlated significantly with the HVSD score for a neurotypical sample. Although this finding was rather indirect, and no evidence supports these two signals share the same neural sources, it is still possible that a cortical hyperexcitability mechanism drove such correlation.

1.2.4. Limitations. Despite obtaining results that are consistent with the literature in our behavioural study 2, where PG effect correlated significantly with *AHE* and *HVSD*, we failed to replicate such outcome (with a moderate level of Bayes factor) with a smaller sample size in study 4 (as described in chapter V). We believe the most convincing explanation for such gap in the two studies, rather than attributing responsibility to an effect size issue, is that PG task functions as a state measure of cortical hyperexcitability at a specific time point and *CHi-II* acts as a trait measure. For example, the same subject could show completely different PG effect on different days possibly due to variations in sleep conditions or caffeine/alcohol consumption (Civardi et al., 2001; Scalise et al., 2006; Shapiro, 2007), while *CHi-II* is a trait measure with high test-retest reliability. Therefore, it is not surprising that PG effect and *CHi-II* are sometimes inconsistent. For a similar reason, VEP components as a state measure of cortical hyperexcitability may also show such dissociation with the *CHi-II* factors.

1.3. VEP evidence: Cortical Hyperexcitability leading to visual disturbances

The effect of pattern glare as a result of cortical hyperexcitation has been suggested by Evans and Wilkins (2001), although no study with neurophysiological research method to date has investigated this hypothesis. In our studies highlighted in chapter IV and V of this thesis, we have discovered that an enhanced visual evoked N2 amplitude in viewing high frequency gratings is commonly observed amongst migraineurs and strong pattern glare healthy subjects. Based on the previous literature, such an increased amplitude of visual N2 in migraine patients is expected (Oelkers et al., 1999). Surprisingly, healthy subjects with strong pattern glare also show such an abnormal visual N2 in the experiments, which has never been reported in any previous studies.

Partly contradictory to the pattern glare behavioural responses, the N2 deflection was only visible in the HF condition in which were first proposed as a "baseline" but not in the more critical and intense MF conditions (Evans & Stevenson, 2008). Comparing the VEP results obtained from study 3 and 4, a "phantom" P200, which can be triggered by medium frequency grating, appeared to cancel the effect of N2 deflection. In summary, the N2 can be regarded as an intricate series of component consists of (i) N130, which amplitude increased with cortical hyperexcitability and spatial frequency of the stimuli; (ii) N180, which can be seen for migraine patients in high spatial frequency stimulation (iii) P200, a component strongly associated with visual disturbances in medium frequency. This VEP model provides neurophysiological support to Evans and Wilkins (2001)'s theoretical mechanism of pattern glare.

As shown in Evans and Stevenson (2008)'s research, age of the subjects could play a huge role as they found that young adults could show strong pattern glare effect to HF grating apart from MF. Our experiments, with the young age sample showing strong VEP responses induced by HF gratings, seemed to be consistent with their findings suggesting that cortical hyperexcitability could also be indicated by HF grating. There was evidence showing that age could influence pattern visual evoked potential possibly by structural changes to ocular, cortical or subcortical pathways (Shaw, 1984). As a result, the score of MF or score of (MF - HF) may not be a valid hyperexcitability indicator to some populations. Therefore, a more systematic exploratory study must be carried out to investigate the interactions between age and spatial frequency of patterns.

1.4. Top-down Suppression on Visual Processing

In the experiments covered in chapter IV and V, a top-down visual suppression indicated by late negativity (LN; around 400 – 500 ms) reduction in migraine patients and high PG controls was observed. Such LN suppression has been observed in migraineurs under all three spatial frequency conditions, while only occurs in the MF condition for high PG controls. Consistent with the EEG data, the behavioural response indicates that migraineurs experience stronger visual discomfort/distortions in all three spatial frequencies and high PG controls have substantial visual discomfort/distortions in MF only.

The top-down mechanism could be initiated by forming discomforting memory (induced by gratings). Such memory would be consolidated during repetitive presentations. In each trial, spatial features of the objects were recognised in the early

stage of sensory processing and projected from the primary visual cortex to extrastriate and other visual-related areas (Zani & Proverbio, 2003). This process can constitute a top-down suppressive control in participants who may have, for instance, disengaged their attention from the irritative patterns to counterbalance the hypersensitivity and discomfort induced by the gratings. This cognitive control may influence the amplitudes of early components in the subjects, and partly explain the contradictory findings in VEP studies (Ambrosini & Schoenen, 2006).

However, it is worth noting that the above interpretation may not be applicable in explaining the findings in this thesis because subject attention was manipulated in all our experiments. More specifically, our participants were instructed to keep focus and maintain their attention on the gratings throughout the presentation of them. Therefore, to further investigate this theory and examine whether our current results are originated from attentional control, a new research paradigm with an unattended condition should be introduced, and the attended and unattended late potential should be compared.

1.5. Cortical Hyperexcitability as a Continuum

Previous research often sees cortical hyperexcitation as pathological due to their existence in other psychiatric and neurological conditions. In this thesis, we have proposed that cortical hyperexcitability should be considered as a state of reactivity of the cerebral cortex. Since the measures we used are based on visual modality, one may argue that methodological speaking, our findings only reflect the visual cortex excitability and thus the related interpretations could not be generalised to other types of conditions. However, it should be reminded that patient groups such as Alzheimer's disease, stroke,

schizophrenia (Di Lazzaro et al., 2004; Shimizu et al., 2002; Spencer, Niznikiewicz, Nestor, Shenton, & McCarley, 2009) may have a general cortical excitability dysfunction in motor, auditory and visual area (the inter-region excitability could be correlated). As a result, apart from migraineurs, those patients may also show pattern glare, higher scores in *CHi-II* and high amplitude in VEPs.

Regardless of the medical conditions, all the populations can be placed along that continuum with the migraine patients, high PG subjects and some other patient groups located at the high cortical hyperexcitability end. With higher cortical hyperexcitability, these people would be more susceptible to visual stress and some anomalous visual perceptions. This theory is well-supported by the behavioural and EEG evidence in this thesis.

2. Conclusion

In this thesis, the neural correlates of visual disturbance and pattern glare effect were explored by behavioural and electroencephalography technique in migraine and healthy population. The findings supported that these visual symptoms can be explained by a multi-dimensional cortical hyperexcitability model. To further build on this model, EEG with higher spatial resolution or fMRI is necessary in order to trace the neural sources of the visual evoked responses more accurately. Extending the sample age group and spatial frequency of the stimuli would also benefit the model.

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Appendices

Appendix A – *CHi-II* questionnaire

The Cortical Hyperexcitability index-II (CHi_II)

Jason J Braithwaite, Rachel Marchant, Chun Yuen Fong, Derrick G. Watson, Chie Takahashi

A revised scale designed to provide an index of cortically mediated visual irritability, discomfort and associated visual aberrations / hallucinations. The revisions for this version include; (i) slight altering in wording of some questions; (ii) the complete removal of some questions; (iii) the addition of some new questions. As a consequence, the researcher should be aware that the actual question numbers for the CHi_II will not completely correspond to those from the original CHi. This should be kept in mind when comparing across measures.

Version II = 30 questions.

Responses = 7-point unipolar Likert-scale (0-6), one for Frequency and one for Intensity. Participants must complete both scales (Frequency & Intensity) for each question. Sum the scores from both scales for each question (maximum score of 12 per-question), and then sum all the questions. This provides the index of cortical hyperexcitability (CHi) for each participant (maximum score = 360).

(Pre-screen questions)

Do you have any ocular conditions (e.g., astigmatisms / colour blindness / optic neuritis / accommodation errors)?

Have you ever undergone any form of neurosurgery (including eye surgery)?

Have you been diagnosed with migraine (with or without aura / hallucination)?

Have you been diagnosed with epilepsy (with or without aura / hallucination) or seizures of unknown origin?

Have you ever suffered from a neurological condition / disorder, and taken medication as a form of treatment?

Have you ever suffered from a psychiatric condition, and taken medication as a form of treatment?

1) Do you ever feel that your vision is more sensitive to external sensory information (e.g., light / patterns) than is usually the case?

How frequently?

0 1 2 3 4 5 6

Never All the

How intense?

0 1 2 3 4 5 6

Not at Extremely

2) Do you ever feel overwhelmed by visual information?

How frequently?

0 1 2 3 4 5 6

Never All the

How intense?

0 1 2 3 4 5 6

Not at Extremely

3) Do you ever feel that your visual perception seems heightened or enhanced?

How frequently?

0 1 2 3 4 5 6

Never All the

How intense?

0 1 2 3 4 5 6

Not at Extremely

4) Have indoor lights ever seemed so bright that they have become irritating to you?

How frequently?

0 1 2 3 4 5 6

Never All the

How intense?

0 1 2 3 4 5 6

Not at Extremely

5) Have everyday objects ever looked different in size (e.g., larger / smaller) to you than their typical appearance?

How frequently?

0 1 2 3 4 5 6

Never All the

How intense?

0 1 2 3 4 5 6

Not at Extremely

6) Have you ever experienced transient flashes / spots of white light for no apparent reason?

How frequently?

0 1 2 3 4 5 6

Never All the

How intense?

0 1 2 3 4 5 6

Not at Extremely

7) Do you ever find certain environments to be visually uncomfortable / irritative?

How frequently?

0 1 2 3 4 5 6

Never All the

How intense?

0 1 2 3 4 5 6

Not at Extremely

8) Do you ever see fleeting shapes, even though there is nothing really there?

How frequently?

0 1 2 3 4 5 6

Never All the

How intense?

0 1 2 3 4 5 6

Not at Extremely

9) Do you ever experience flashes of colour, even though there is nothing really there?

How frequently?

0 1 2 3 4 5 6

Never All the

How intense?

0 1 2 3 4 5 6

Not at Extremely

10) Do you ever find that the appearance of objects or people seems to change in a puzzling way (e.g. distorted shapes / sizes)?

How frequently?

0 1 2 3 4 5 6

Never All the

How intense?

0 1 2 3 4 5 6

Not at Extremely

11) Have you ever felt dizzy / nauseous due to strong light levels or the presence of certain visual patterns?

How frequently?

0 1 2 3 4 5 6

Never All the

How intense?

0 1 2 3 4 5 6

Not at Extremely

12) Do you ever have days when lights or colours seem brighter or more intense than usual?

How frequently?

0 1 2 3 4 5 6

Never All the

How intense?

0 1 2 3 4 5 6

Not at Extremely

13) Do you ever experience visual pain / discomfort from looking at certain patterns?

How frequently?

0 1 2 3 4 5 6

Never All the

How intense?

0 1 2 3 4 5 6

Not at Extremely

14) Have you ever had a headache / migraine that you felt was induced by visual information in your immediate surroundings?

How frequently?

0 1 2 3 4 5 6

Never All the

How intense?

0 1 2 3 4 5 6

Not at Extremely

15) Have you ever experienced visual distortions (e.g., shimmer, flicker, bending) when looking around your surroundings?

How frequently?

0 1 2 3 4 5 6

Never All the

How intense?

0 1 2 3 4 5 6

Not at Extremely

16) Does working on a computer for long periods ever irritate your eyes?

How frequently?

0 1 2 3 4 5 6

Never All the

How intense?

0 1 2 3 4 5 6

Not at Extremely

17) Have you ever noticed the presence of perceptual distortions when you have been tired or fatigued?

How frequently?

0 1 2 3 4 5 6

Never All the

How intense?

0 1 2 3 4 5 6

Not at Extremely

18) Does working / reading under fluorescent lights ever induce a feeling of visual irritation / discomfort?

How frequently?

0	1	2	3	4	5	6
Never						All the

How intense?

0	1	2	3	4	5	6
Not at						Extremely

19) Have you had an out-of-body experience, where you were absolutely convinced that you experienced the world from a vantage point completely outside of your physical body?

How frequently?

0	1	2	3	4	5	6
Never						All the

How intense?

0	1	2	3	4	5	6
Not at						Extremely

20) Do you experience visual discomfort / irritation from viewing the headlights of oncoming traffic?

How frequently?

0	1	2	3	4	5	6
Never						All the

How intense?

0	1	2	3	4	5	6
Not at						Extremely

21) Do you experience visual discomfort / irritation from reading certain letter fonts / styles?

How frequently?

0	1	2	3	4	5	6
Never						All the

How intense?

0	1	2	3	4	5	6
Not at						Extremely

22) Have you ever experienced a sudden and unexpected narrowing of your visual field (greying out of peripheral vision / tunnel vision)?

How frequently?

0	1	2	3	4	5	6
Never						All the

How intense?

0	1	2	3	4	5	6
Not at						Extremely

23) Have you ever experienced sudden and unexpected flashes of dynamic moving patterns (e.g., black and white stripes / angular zigzag patterns) superimposed on the visual world?

How frequently?

0	1	2	3	4	5	6
Never						All the

How intense?

0	1	2	3	4	5	6
Not at						Extremely

24) Have you ever experienced a transient, partial loss of vision, like an isolated island of blindness, in your field of vision?

How frequently?

0 1 2 3 4 5 6

Never All the

How intense?

0 1 2 3 4 5 6

Not at Extremely

25) Have you ever experienced a spread of tiny white / black dots resembling the 'static' of a badly-tuned television superimposed across your visual field?

How frequently?

0 1 2 3 4 5 6

Never All the

How intense?

0 1 2 3 4 5 6

Not at Extremely

26) Have you ever experienced perceptions of circular coloured shapes, balls, or coloured circular patterns when nothing was really there?

How frequently?

0 1 2 3 4 5 6

Never All the

How intense?

0 1 2 3 4 5 6

Not at Extremely

27) Have you ever experienced a transient, partial loss of vision (e.g., an island of blindness) that was also surrounded by angular striped zigzag patterns?

How frequently?

0 1 2 3 4 5 6

Never All the

How intense?

0 1 2 3 4 5 6

Not at Extremely

28) Have you ever experienced the illusory perception of a spiral, tunnel or funnel-like shape superimposed on the visual world?

How frequently?

0 1 2 3 4 5 6

Never All the

How intense?

0 1 2 3 4 5 6

Not at Extremely

29) Have you ever experienced transient illusory 'spider-web' type patterns superimposed on the visual world?

How frequently?

0 1 2 3 4 5 6

Never All the

How intense?

0 1 2 3 4 5 6

Not at Extremely

30) Have you ever had the experience where your visual world appears drained of colour and vibrancy, resulting in a flattened and degraded experience of your surroundings?

How frequently?

0 1 2 3 4 5 6

Never All the

How intense?

0 1 2 3 4 5 6

Not at Extremely

To be completed by the researcher.

Total Frequency = _____

Total Intensity = _____

Total CHi = _____

Appendix B – *CAPE* questionnaire

Community Assessment of Psychic Experiences (CAPE)

Participant ID: _____

This questionnaire describes certain feelings, thoughts and mental experiences. Please indicate **how often** you have such experiences and feelings and **how distressed** are those experiences making you feel. If you chose "**never**", please **skip how distressed** you are for the corresponding question. If you chose "sometimes", "often' or "nearly always', please indicate how distressed you are by that experience. Please **circle the most applicable answers** in your case.

1. Do you ever feel sad?

How often?	Never	Sometimes	Often	Nearly always
	0	1	2	3

How distressed?	Not Distressed	A bit distressed	Quite distressed	Very distressed
	0	1	2	3

2. Do you ever feel as if people seem to drop hints about you or say things with a double meaning?

How often?	Never	Sometimes	Often	Nearly always
	0	1	2	3

How distressed?	Not Distressed	A bit distressed	Quite distressed	Very distressed
	0	1	2	3

3. Do you ever feel that you are not a very animated person?

How often? Never Sometimes Often Nearly always

0 1 2 3

How distressed? Not Distressed A bit distressed Quite distressed Very distressed

0 1 2 3

4. Do you ever feel that you are not much of a talker when you are conversing with other people?

How often? Never Sometimes Often Nearly always

0 1 2 3

How distressed? Not Distressed A bit distressed Quite distressed Very distressed

0 1 2 3

5. Do you ever feel as if things in magazines or on TV were written especially for you?

How often? Never Sometimes Often Nearly always

0 1 2 3

How distressed? Not Distressed A bit distressed Quite distressed Very distressed

0 1 2 3

6. Do you ever feel as if some people are not what they seem to be?

How often? Never Sometimes Often Nearly always

0 1 2 3

How distressed? Not Distressed A bit distressed Quite distressed Very distressed

0 1 2 3

7. Do you ever feel as if you are being persecuted in some way?

How often? Never Sometimes Often Nearly always

0 1 2 3

How distressed? Not Distressed A bit distressed Quite distressed Very distressed

0 1 2 3

8. Do you ever feel that you experience few or no emotions at important events?

How often? Never Sometimes Often Nearly always

0 1 2 3

How distressed? Not Distressed A bit distressed Quite distressed Very distressed

0 1 2 3

9. Do you ever feel pessimistic about everything?

How often? Never Sometimes Often Nearly always

0 1 2 3

How distressed? Not Distressed A bit distressed Quite distressed Very distressed

0 1 2 3

10. Do you ever feel as if there is a conspiracy against you?

How often? Never Sometimes Often Nearly always

0 1 2 3

How distressed? Not Distressed A bit distressed Quite distressed Very distressed

0 1 2 3

11. Do you ever feel as if you are destined to be someone very important?

How often? Never Sometimes Often Nearly always

0 1 2 3

How distressed? Not Distressed A bit distressed Quite distressed Very distressed

0 1 2 3

12. Do you ever feel as if there is no future for you?

How often? Never Sometimes Often Nearly always

0 1 2 3

How distressed? Not Distressed A bit distressed Quite distressed Very distressed

0 1 2 3

13. Do you ever feel that you are a very special or unusual person?

How often? Never Sometimes Often Nearly always

0 1 2 3

How distressed? Not Distressed A bit distressed Quite distressed Very distressed

0 1 2 3

14. Do you ever feel as if you do not want to live anymore?

How often? Never Sometimes Often Nearly always

0 1 2 3

How distressed? Not Distressed A bit distressed Quite distressed Very distressed

0 1 2 3

15. Do you ever think that people can communicate telepathically?

How often? Never Sometimes Often Nearly always

0 1 2 3

How distressed? Not Distressed A bit distressed Quite distressed Very distressed

0 1 2 3

16. Do you ever feel that you have no interest to be with other people?

How often? Never Sometimes Often Nearly always

0 1 2 3

How distressed? Not Distressed A bit distressed Quite distressed Very distressed

0 1 2 3

17. Do you ever feel as if electrical devices such as computers can influence the way you think?

How often? Never Sometimes Often Nearly always

0 1 2 3

How distressed? Not Distressed A bit distressed Quite distressed Very distressed

0 1 2 3

18. Do you ever feel that you are lacking in motivation to do things?

How often?	Never	Sometimes	Often	Nearly always
	0	1	2	3

How distressed?	Not Distressed	A bit distressed	Quite distressed	Very distressed
	0	1	2	3

19. Do you ever cry about nothing?

How often?	Never	Sometimes	Often	Nearly always
	0	1	2	3

How distressed?	Not Distressed	A bit distressed	Quite distressed	Very distressed
	0	1	2	3

20. Do you believe in the power of witchcraft, voodoo or the occult?

How often?	Never	Sometimes	Often	Nearly always
	0	1	2	3

How distressed?	Not Distressed	A bit distressed	Quite distressed	Very distressed
	0	1	2	3

21. Do you ever feel that you are lacking in energy?

How often? Never Sometimes Often Nearly always

0 1 2 3

How distressed? Not Distressed A bit distressed Quite distressed Very distressed

0 1 2 3

22. Do you ever feel that people look at you oddly because of your appearance?
How often? Never Sometimes Often Nearly always

0 1 2 3

How distressed? Not Distressed A bit distressed Quite distressed Very distressed

0 1 2 3

23. Do you ever feel that your mind is empty?
How often? Never Sometimes Often Nearly always

0 1 2 3

How distressed? Not Distressed A bit distressed Quite distressed Very distressed

0 1 2 3

24. Do you ever feel as if the thoughts in your head are being taken away from you?
How often? Never Sometimes Often Nearly always

0 1 2 3

How distressed? Not Distressed A bit distressed Quite distressed Very distressed

0 1 2 3

25. Do you ever feel that you are spending all your days doing nothing?

How often? Never Sometimes Often Nearly always

0 1 2 3

How distressed? Not Distressed A bit distressed Quite distressed Very distressed

0 1 2 3

26. Do you ever feel as if the thoughts in your head are not your own?

How often? Never Sometimes Often Nearly always

0 1 2 3

How distressed? Not Distressed A bit distressed Quite distressed Very distressed

0 1 2 3

27. Do you ever feel that your feelings are lacking in intensity?

How often? Never Sometimes Often Nearly always

0 1 2 3

How distressed? Not Distressed A bit distressed Quite distressed Very distressed

0 1 2 3

28. Have your thoughts ever been so vivid that you were worried other people would hear them?

How often? Never Sometimes Often Nearly always

0 1 2 3

How distressed? Not Distressed A bit distressed Quite distressed Very distressed

0 1 2 3

29. Do you ever feel that you are lacking in spontaneity?

How often? Never Sometimes Often Nearly always

0 1 2 3

How distressed? Not Distressed A bit distressed Quite distressed Very distressed

0 1 2 3

30. Do you ever hear your own thoughts being echoed back to you?

How often? Never Sometimes Often Nearly always

0 1 2 3

How distressed? Not Distressed A bit distressed Quite distressed Very distressed

0 1 2 3

31. Do you ever feel as if you are under the control of some force or power other than yourself?

How often? Never Sometimes Often Nearly always

0 1 2 3

How distressed? Not Distressed A bit distressed Quite distressed Very distressed

0 1 2 3

32. Do you ever feel that your emotions are blunted?

How often? Never Sometimes Often Nearly always

0 1 2 3

How distressed? Not Distressed A bit distressed Quite distressed Very distressed

0 1 2 3

33. Do you ever hear voices when you are alone?

How often? Never Sometimes Often Nearly always

0 1 2 3

How distressed? Not Distressed A bit distressed Quite distressed Very distressed

0 1 2 3

34. Do you ever hear voices talking to each other when you are alone?

How often? Never Sometimes Often Nearly always

0 1 2 3

How distressed? Not Distressed A bit distressed Quite distressed Very distressed

0 1 2 3

35. Do you ever feel that you are neglecting your appearance or personal hygiene?

How often? Never Sometimes Often Nearly always

0 1 2 3

How distressed? Not Distressed A bit distressed Quite distressed Very distressed

0 1 2 3

36. Do you ever feel that you can never get things done?

How often? Never Sometimes Often Nearly always

0 1 2 3

How distressed? Not Distressed A bit distressed Quite distressed Very distressed

0 1 2 3

37. Do you ever feel that you have only few hobbies or interests?

How often? Never Sometimes Often Nearly always

0 1 2 3

How distressed? Not Distressed A bit distressed Quite distressed Very distressed

0 1 2 3

38. Do you ever feel guilty?

How often? Never Sometimes Often Nearly always

0 1 2 3

How distressed? Not Distressed A bit distressed Quite distressed Very distressed

0 1 2 3

39. Do you ever feel like a failure?

How often? Never Sometimes Often Nearly always

0 1 2 3

How distressed? Not Distressed A bit distressed Quite distressed Very distressed

0 1 2 3

40. Do you ever feel tense?

How often? Never Sometimes Often Nearly always

0 1 2 3

How distressed? Not Distressed A bit distressed Quite distressed Very distressed

0 1 2 3

41. Do you ever feel as if a double has taken the place of a family member, friend or acquaintance?

How often? Never Sometimes Often Nearly always

0 1 2 3

How distressed? Not Distressed A bit distressed Quite distressed Very distressed

0 1 2 3

42. Do you ever see objects, people or animals that other people cannot see?

How often? Never Sometimes Often Nearly always

0 1 2 3

How distressed? Not Distressed A bit distressed Quite distressed Very distressed

0 1 2 3

Appendix C – *CAPS* questionnaire

Cardiff Anomalous Perceptions Scale (CAPS)

This questionnaire asks questions about sensations and perceptions you may have experienced. Some of the experiences are unusual, some of them are more everyday. We realise circling answers may not always represent your experience as accurately as you might like. However, we would ask you to circle the answers that most closely match your experience and avoid missing any questions out.

We would appreciate it if you could be as honest as possible when giving your answers. *The only experiences we are not interested in are those that may have occurred whilst under the influence of drugs.*

Please read each question and and circle either **YES** or **NO.**

If you circle **NO** please move straight on to the next question.

If you circle **YES** please rate the experience on how **distressing**, **distracting** you found the experience **and how often** it occurs by circling a number between 1 and 5.

Example Question (You do not need to answer this question)

Do you ever notice that lights seem to flicker on and off for no reason?

No **Yes** (if YES please rate below)

Not at all distressing				Very distressing
1	2	3	4	5
Not at all distracting				Completely Intrusive
1	2	3	4	5
Happens hardly at all				Happens all the time
1	2	3	4	5

1. Do you ever notice that sounds are much louder than they normally would be?

No			**Yes** (if YES please rate below)	
Not at all distressing				Very distressing
1	2	3	4	5
Not at all distracting				Completely Intrusive
1	2	3	4	5
Happens hardly at all				Happens all the time
1	2	3	4	5

2. Do you ever sense the presence of another being, despite being unable to see any evidence?

No			**Yes** (if YES please rate below)	
Not at all distressing				Very distressing
1	2	3	4	5
Not at all distracting				Completely Intrusive
1	2	3	4	5
Happens hardly at all				Happens all the time
1	2	3	4	5

3. Do you ever hear your own thoughts repeated or echoed?

No			**Yes** (if YES please rate below)	
Not at all distressing				Very distressing
1	2	3	4	5
Not at all distracting				Completely Intrusive
1	2	3	4	5
Happens hardly at all				Happens all the time
1	2	3	4	5

4. Do you ever see shapes, lights, or colours even though there is nothing really there?

No **Yes** (if YES please rate below)

Not at all distressing				Very distressing
1	2	3	4	5
Not at all distracting				Completely Intrusive
1	2	3	4	5
Happens hardly at all				Happens all the time
1	2	3	4	5

5. Do you ever experience unusual burning sensations or other strange feelings in or on your body?

No **Yes** (if YES please rate below)

Not at all distressing				Very distressing
1	2	3	4	5
Not at all distracting				Completely Intrusive
1	2	3	4	5
Happens hardly at all				Happens all the time
1	2	3	4	5

6. Do you ever hear noises or sounds when there is nothing about to explain them?

No **Yes** (if YES please rate below)

Not at all distressing				Very distressing
1	2	3	4	5
Not at all distracting				Completely Intrusive
1	2	3	4	5
Happens hardly at all				Happens all the time
1	2	3	4	5

7. Do you ever hear your own thoughts spoken aloud in your head, so that someone near might be able to hear them?

No **Yes** (if YES please rate below)

Not at all distressing				Very distressing
1	2	3	4	5
Not at all distracting				Completely Intrusive
1	2	3	4	5
Happens hardly at all				Happens all the time
1	2	3	4	5

8. Do you ever detect smells which don't seem to come from your surroundings?

No **Yes** (if YES please rate below)

Not at all distressing				Very distressing
1	2	3	4	5
Not at all distracting				Completely Intrusive
1	2	3	4	5
Happens hardly at all				Happens all the time
1	2	3	4	5

9. Do you ever have the sensation that your body, or a part of it, is changing or has changed shape?

No **Yes** (if YES please rate below)

Not at all distressing				Very distressing
1	2	3	4	5
Not at all distracting				Completely Intrusive
1	2	3	4	5
Happens hardly at all				Happens all the time
1	2	3	4	5

10. Do you ever have the sensation that your limbs might not be your own or might not be properly connected to your body?

No **Yes** (if YES please rate below)

Not at all distressing				Very distressing
1	2	3	4	5
Not at all distracting				Completely Intrusive
1	2	3	4	5
Happens hardly at all				Happens all the time
1	2	3	4	5

11. Do you ever hear voices commenting on what you are thinking or doing?

No **Yes** (if YES please rate below)

Not at all distressing				Very distressing
1	2	3	4	5
Not at all distracting				Completely Intrusive
1	2	3	4	5
Happens hardly at all				Happens all the time
1	2	3	4	5

12. Do you ever feel that someone is touching you, but when you look nobody is there?

No **Yes** (if YES please rate below)

Not at all distressing				Very distressing
1	2	3	4	5
Not at all distracting				Completely Intrusive
1	2	3	4	5
Happens hardly at all				Happens all the time
1	2	3	4	5

13. Do you ever hear voices saying words or sentences when there is no one around that might account for it?

No **Yes** (if YES please rate below)

Not at all distressing				Very distressing
1	2	3	4	5
Not at all distracting				Completely Intrusive
1	2	3	4	5
Happens hardly at all				Happens all the time
1	2	3	4	5

14. Do you ever experience unexplained tastes in your mouth?

No **Yes** (if YES please rate below)

Not at all distressing				Very distressing
1	2	3	4	5
Not at all distracting				Completely Intrusive
1	2	3	4	5
Happens hardly at all				Happens all the time
1	2	3	4	5

15. Do you ever find that sensations happen all at once and flood you with information?

No **Yes** (if YES please rate below)

Not at all distressing				Very distressing
1	2	3	4	5
Not at all distracting				Completely Intrusive
1	2	3	4	5
Happens hardly at all				Happens all the time
1	2	3	4	5

16. Do you ever find that sounds are distorted in strange or unusual ways?

No **Yes** (if YES please rate below)

Not at all distressing				Very distressing
1	2	3	4	5
Not at all distracting				Completely Intrusive
1	2	3	4	5
Happens hardly at all				Happens all the time
1	2	3	4	5

17. Do you ever have difficulty distinguishing one sensation from another?

No **Yes** (if YES please rate below)

Not at all distressing				Very distressing
1	2	3	4	5
Not at all distracting				Completely Intrusive
1	2	3	4	5
Happens hardly at all				Happens all the time
1	2	3	4	5

18. Do you ever smell everyday odours and think that they are unusually strong?

No **Yes** (if YES please rate below)

Not at all distressing				Very distressing
1	2	3	4	5
Not at all distracting				Completely Intrusive
1	2	3	4	5
Happens hardly at all				Happens all the time
1	2	3	4	5

19. Do you ever find the appearance of things or people seems to change in a puzzling way, e.g. distorted shapes or sizes or colour?

No **Yes** (if YES please rate below)

Not at all distressing				Very distressing
1	2	3	4	5
Not at all distracting				Completely Intrusive
1	2	3	4	5
Happens hardly at all				Happens all the time
1	2	3	4	5

20. Do you ever find that your skin is more sensitive to touch, heat, or cold than usual?

No **Yes** (if YES please rate below)

Not at all distressing				Very distressing
1	2	3	4	5
Not at all distracting				Completely Intrusive
1	2	3	4	5
Happens hardly at all				Happens all the time
1	2	3	4	5

21. Do you ever think that food or drink tastes much stronger than it normally would?

No **Yes** (if YES please rate below)

Not at all distressing				Very distressing
1	2	3	4	5
Not at all distracting				Completely Intrusive
1	2	3	4	5
Happens hardly at all				Happens all the time
1	2	3	4	5

22. Do you ever look in the mirror and think that your face seems different from usual?

No **Yes** (if YES please rate below)

Not at all distressing				Very distressing
1	2	3	4	5
Not at all distracting				Completely Intrusive
1	2	3	4	5
Happens hardly at all				Happens all the time
1	2	3	4	5

23. Do you ever have days where lights or colours seem brighter or more intense than usual?

No **Yes** (if YES please rate below)

Not at all distressing				Very distressing
1	2	3	4	5
Not at all distracting				Completely Intrusive
1	2	3	4	5
Happens hardly at all				Happens all the time
1	2	3	4	5

24. Do you ever have the feeling of being uplifted, as if driving or rolling over a road while sitting quietly?

No **Yes** (if YES please rate below)

Not at all distressing				Very distressing
1	2	3	4	5
Not at all distracting				Completely Intrusive
1	2	3	4	5
Happens hardly at all				Happens all the time
1	2	3	4	5

25. Do you ever find that common smells sometimes seem unusually different?

No **Yes** (if YES please rate below)

Not at all distressing				Very distressing
1	2	3	4	5
Not at all distracting				Completely Intrusive
1	2	3	4	5
Happens hardly at all				Happens all the time
1	2	3	4	5

26. Do you ever think that everyday things look abnormal to you?

No **Yes** (if YES please rate below)

Not at all distressing				Very distressing
1	2	3	4	5
Not at all distracting				Completely Intrusive
1	2	3	4	5
Happens hardly at all				Happens all the time
1	2	3	4	5

27. Do you ever find that your experience of time changes dramatically?

No **Yes** (if YES please rate below)

Not at all distressing				Very distressing
1	2	3	4	5
Not at all distracting				Completely Intrusive
1	2	3	4	5
Happens hardly at all				Happens all the time
1	2	3	4	5

28. Have you ever heard 2 or more unexplained voices talking with each other?

No **Yes** (if YES please rate below)

Not at all distressing				Very distressing
1	2	3	4	5
Not at all distracting				Completely Intrusive
1	2	3	4	5
Happens hardly at all				Happens all the time
1	2	3	4	5

29. Do you ever experience smells or odours that people next to you seem unaware of?

No **Yes** (if YES please rate below)

Not at all distressing				Very distressing
1	2	3	4	5
Not at all distracting				Completely Intrusive
1	2	3	4	5
Happens hardly at all				Happens all the time
1	2	3	4	5

30. Do you ever notice that food or drink seems to have an unusual taste?

No **Yes** (if YES please rate below)

Not at all distressing				Very distressing
1	2	3	4	5
Not at all distracting				Completely Intrusive
1	2	3	4	5
Happens hardly at all				Happens all the time
1	2	3	4	5

31. Do you ever see things that other people cannot?

No **Yes** (if YES please rate below)

Not at all distressing				Very distressing
1	2	3	4	5
Not at all distracting				Completely Intrusive
1	2	3	4	5
Happens hardly at all				Happens all the time
1	2	3	4	5

32. Do you ever hear sounds or music that people near you don't hear?

No **Yes** (if YES please rate below)

Not at all distressing				Very distressing
1	2	3	4	5
Not at all distracting				Completely Intrusive
1	2	3	4	5
Happens hardly at all				Happens all the time
1	2	3	4	5

33. Have you ever had an experience where you have perceived the world from a vantage point outside of your physical body?

No **Yes** (if YES please rate below)

Not at all distressing				Very distressing
1	2	3	4	5
Not at all distracting				Completely Intrusive
1	2	3	4	5
Happens hardly at all				Happens all the time
1	2	3	4	5