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Illusory motion perception in migraine

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Abstract

In between attacks, people with migraine report experiencing both visual discomfort and visual illusions induced by stationary high contrast striped patterns. Since both visual illusion and discomfort have been assessed through largely qualitative self-report, it is unclear how their mechanisms might be related with each other. This thesis aimed to investigate whether subjective reports of visual discomfort in people with migraine are associated with the strength of a motion illusion outside attacks.

To determine the stimulus for motion illusion strength to be quantified, Experiment 1 measured the physical motion speeds that cancelled the illusory motion effect of five variants of the Fraser-Wilcox illusion in people who do not experience headache. The stimulus type that produced the most robust illusory motion was chosen for subsequent experiments.

Experiment 2 compared the motion illusion strength between people with migraine with aura, people with migraine without aura, and non-headache control participants. The relationship between motion illusion strength and self-reported frequency of experiencing visual discomfort in daily life was also investigated. The results indicated that subjective visual discomfort was elevated in people with migraine with aura but that visual discomfort was not accompanied by greater motion illusion strength. These findings suggest that susceptibility to daily visual discomfort is not related to perceived speed of the motion illusion.

Experiment 3 investigated whether motion illusion strength is associated with contrast discrimination threshold and motion sensitivity regardless of migraine status. The results revealed that people with better contrast discrimination, but not motion sensitivity, tended to perceive faster motion illusions.

The findings of this thesis verify previous self-reports of increased visual discomfort in people with migraine. The experiments, however, do not support that this self-reported experience is derived from differences in contrast discrimination or motion sensitivity, for

the types of stimuli used herein. The Fraser-Wilcox motion illusion does not seem to test the same mechanisms as involved in self-reported visual discomfort.

Declaration

This is to certify that:

I. the thesis comprises only my original work towards the MPhil except where indicated in the Preface,
II. due acknowledgement has been made in the text to all other material used,
III. the thesis is fewer than 40,000 words in length, exclusive of tables, maps, bibliographies and appendices.

Chongyue He

Preface

This research received funding from The National Health and Medical Research Council: APP1018174 (McKendrick).

The experiment in Chapter 3 of this thesis has been presented at the following conference:

He, C., Nguyen, B. N., Chan, Y. M., & McKendrick, A. M. (2018). The effects of luminance profile type on the strength of the Fraser-Wilcox illusion. *15th Scientific and 9th Educators meeting in Optometry* (SEMO 2018, April 5-6th 2018), Melbourne.

Clinically qualified optometrists Prof Allison McKendrick and Dr Bao Nguyen assisted with participant screening.

Prof Allison McKendrick assisted with the software development for the motion illusion task.

Amendments suggested by the reviewers are indicated in Appendix 10.

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Chapter 1 Literature review

1.1 Introduction

The earliest record of migraine reputedly appeared in Mesopotamian poems (3000 B.C.), and Hippocrates (460-370 B.C.) is considered to be the first to describe the visual symptoms of migraine (Pearce 1986). Despite migraine being recognised since around 5000 years ago, it is still far from being fully understood. In the interictal period, which refers to the period in between migraine attacks, the quality of living of people with migraine is impaired (Buse et al. 2009). This thesis is interested in interictal visual stimulus induced discomfort, which has been shown through largely qualitative self-report to be greater in people with migraine than people without (Marcus and Soso 1989). A better understanding of visual discomfort could assist in improving the visual environment for people with migraine, as well as contribute to our understanding of migraine pathophysiology.

An optical illusion refers to a phenomenon when perception does not match the physical properties of a visual stimulus. Some studies suggest that the number of illusions that participants report seeing from high contrast striped patterns might be associated with interictal visual discomfort (Wilkins and Nimmo-Smith 1984, Shepherd 2000). However, the link between the number of illusions being reported and their proposed mechanism in the context of migraine (purported to be an imbalance between cortical inhibition and excitation) is still unclear. This thesis aims to determine whether the perceived speed of an illusory motion stimulus can provide a measurable estimate of visual performance that correlates with the strength of visual induced discomfort.

This chapter will briefly introduce some epidemiological studies and the current understanding of the symptoms of a migraine attack. Then, interictal visual discomfort and its relationship with performance on visual tasks that involve contrast and motion processing will be discussed. Subsequently, the Fraser-Wilcox illusory motion stimulus, which was the main visual task quantified in this thesis, will be reviewed. Finally, the literature review will lead to the aims and hypotheses that were examined in this thesis.

1.2 The migraine burden

According to the Global Burden of Disease Survey 2010, which included migraine studies from 43 countries, migraine affects approximately 15% of the global population and is ranked the third most common disease (after dental caries and tension-type headache) in humans (Steiner et al. 2013). Indeed, migraine has been identified as the leading cause of disability among neurological disorders (Steiner et al. 2013) and accounts for substantial loss in productivity and socioeconomic burden worldwide. The age and gender dependency of migraine prevalence (Figure 1-1), in which female and reproductive age are high risk factors, has been consistently shown in a series of survey studies conducted in the USA (Lipton et al. 2001, Bigal et al. 2006, Lipton et al. 2007, Victor et al. 2010). The age-prevalence function in females has been suggested to be related with estrogen levels (Silberstein and Merriam 1991, MacGregor et al. 2006). The bimodal distribution in male prevalence of migraine is also speculated to be related with sex hormone fluctuations (Victor et al. 2010).

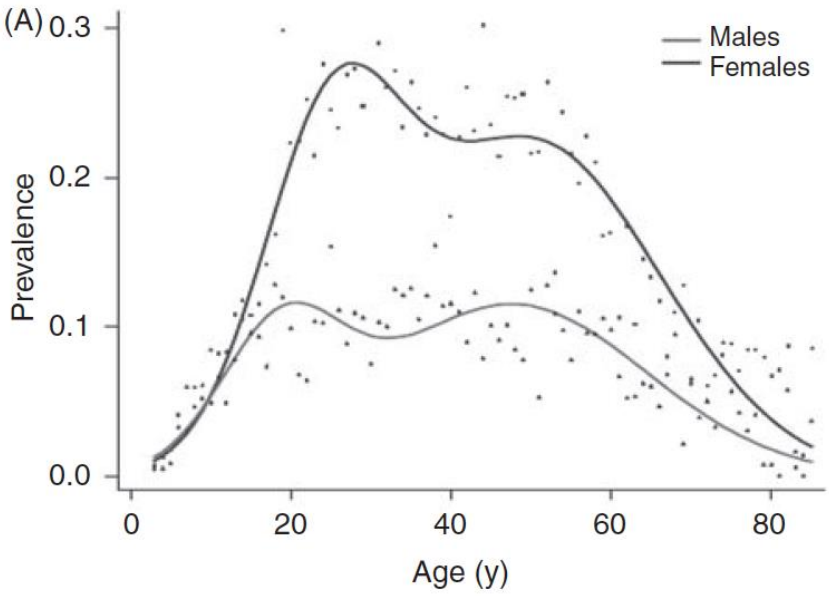

*Figure 1-1 One year prevalence of migraine as a function of age in a US population in 2003. Reprinted with permission by SAGE Publications, from Victor, T. W., X. Hu, J. C. Campbell, D. C. Buse and R. B. Lipton (2010). "Migraine prevalence by age and sex in the United States: a life-span study." Cephalalgia **30**(9): 1065-1072.*

Migraine severity is also different across individuals. To better understand the socioeconomic burden and to provide more personalised treatment, individual variability in migraine severity has been considered. The Migraine Disability Assessment (MIDAS) questionnaire was developed to reflect migraine severity by adding up migraine induced days of absence or loss of productivity from daily activities in the past 3 months (Stewart et al. 2001). The MIDAS score is categorised into 4 grades in which the score range of 0-5, 6-10, 11-20, and more than 20 corresponds to minimal or infrequent disability, mild or infrequent disability, moderate disability, severe disability respectively (Stewart et al. 2001). In a survey conducted in the USA, 63.7% migraine sufferers showed minimal or infrequent disability and 22% had moderate or severe disability (Lipton et al. 2007). Results from two parallel studies in the USA and UK found that people with migraine reported missing household work and reduced productivity at school or work as the highest contributors to the overall MIDAS score (Stewart et al. 1999, Stewart et al. 1999).

1.3 Symptoms of a migraine attack

This section will introduce the symptoms that occur during a migraine attack (the ictal period), which are listed in the diagnostic criteria for the two migraine subclassifications that are included in this thesis - migraine without aura (MO) and migraine with typical aura with headache (MA). Since aura is the key symptom in distinguishing MA from MO, this section will subsequently discuss migraine pathophysiology in general terms and then specifically in the context of the phenomenon of visual aura.

1.3.1 Diagnosis of migraine without aura and migraine with typical aura

The current diagnostic criteria provided by the International Classification of Headache Disorders (ICHD; International Headache Society, 2018) for MO and MA is shown in Table 2-1 (Chapter 2, page 39), which was adhered to in the recruitment of participants for this thesis. This thesis is primarily interested in episodic migraine (i.e. not chronic), where people have clearly defined attacks (ictal period) that are distinguishable from a non-attack (interictal) period.

In this thesis, both MA and MO groups were included, as is typical in many studies of the visual system in people who experience migraine. This experimental choice is typically made because the visual system is involved in the mechanisms of visual aura, which is the most commonly reported aura type (Goadsby et al. 2017). It is possible that the recurrent experience of aura can create subclinical differences in the primary visual cortex, hence, affecting visual processing outside attacks (Chronicle et al. 1995). However, there is still considerable debate in the literature regarding whether the two subclassifications are different in their impact on visual functions (for reviews see O'Hare and Hibbard (2016); Aurora and Wilkinson (2007); Vecchia and Pietrobon (2012)). The findings regarding the visual processing investigated in this thesis will be further discussed later in this review (section 1.5.4).

1.3.2 Common symptoms of MO and MA

The migraine attack is divided into four phases. The premonitory phase is the first phase of a migraine attack, which allows some migraine sufferers to sense an impending migraine up to 72 hours before an attack (Giffin et al. 2003). Through a 3-month prospective electronic diary, 803 migraine attacks were described by 97 participants. The most frequently reported premonitory symptoms were 'tired/weary' (72.5%), 'difficulty with concentration' (51.1%), 'stiff neck' (49.7%) and 'light sensitive' (48.8%) (Giffin et al. 2003). In people who experience migraine headache with aura, aura is defined to be the second phase, occurring with or before the headache (Table 1.1). In the third phase of the migraine attack, the headache is accompanied by at least one of photophobia (sensitivity to light) and phonophobia (sensitivity to sound) or nausea and/or vomiting. The last phase of a migraine attack is the postdrome phase, which is the period just after the headache is relieved when some of the symptoms that are reported in the premonitory phase can still be experienced (Blau 1991, Giffin et al. 2003, Giffin et al. 2016).

The current understanding of migraine pathophysiology, which is incomplete, consists of a neurological and a vascular component. The vascular component originated from the vascular theory in 1940s, which ascribed the headache to an inflammatory reaction caused by vasodilation in the dura and pia mater (Ray and Wolff 1940). Ray and Wolff (1940) suggested headache could be sensed through stimulation of the blood vessels of the dura

mater. However, later evidence suggested that vasodilation is unlikely to be the primary trigger of migraine but perhaps a reflex of trigeminal neural innervation in headache syndromes that are not restricted to migraine (for review see May and Goadsby (1999)). More recent studies suggest that the importance of a vascular contribution to migraine pathophysiology should not be dismissed even though it is more likely to act on the already sensitised nociceptors (pain receptors) rather than being the initiator of an attack (Asghar et al. 2011). Furthermore, certain triptans, which exhibit both anti-inflammatory and vasoconstrictive effects, are effective acute migraine treatments. Attempted triptan treatments which only act on controlling neurogenic inflammation but without the effect of vasoconstriction do not alleviate or prevent migraine headaches (for review see Goadsby et al. (2017)).

Now, migraine is believed to be a neurovascular disorder, in which the ictal symptoms can be explained by the sensitisation of trigeminovascular pathways (see Figure 1-2; for review see Goadsby et al. (2017)). The thalamic projection to cortical regions were proposed to be involved in sensation of a variety of symptoms, for example, the somatosensory cortices (S1 and S1) for headache, the visual cortices (V1/V2) for photophobia, and the auditory cortex (Au) for phonophobia (Goadsby et al. 2017). Potential affected brain regions have been identified using positron emission tomography (PET) during migraine attacks (Weiller et al. 1995, Bahra et al. 2001, Denuelle et al. 2011, Maniyar et al. 2013) and magnetic resonance imaging (voxel-based morphometry) in between attacks (Granziera et al. 2006, DaSilva et al. 2007, Valfrè et al. 2008), by identifying changes in regional cerebral blood flow (rCBF). However, the observed involvement of these brain regions and pathways (Figure 1-2), still, do not explain the primary cause of migraine. For example, structural differences may explain why some people have the potential to initiate migraine attacks, conversely, it is possible that migraine attacks have induced damage to these structures.

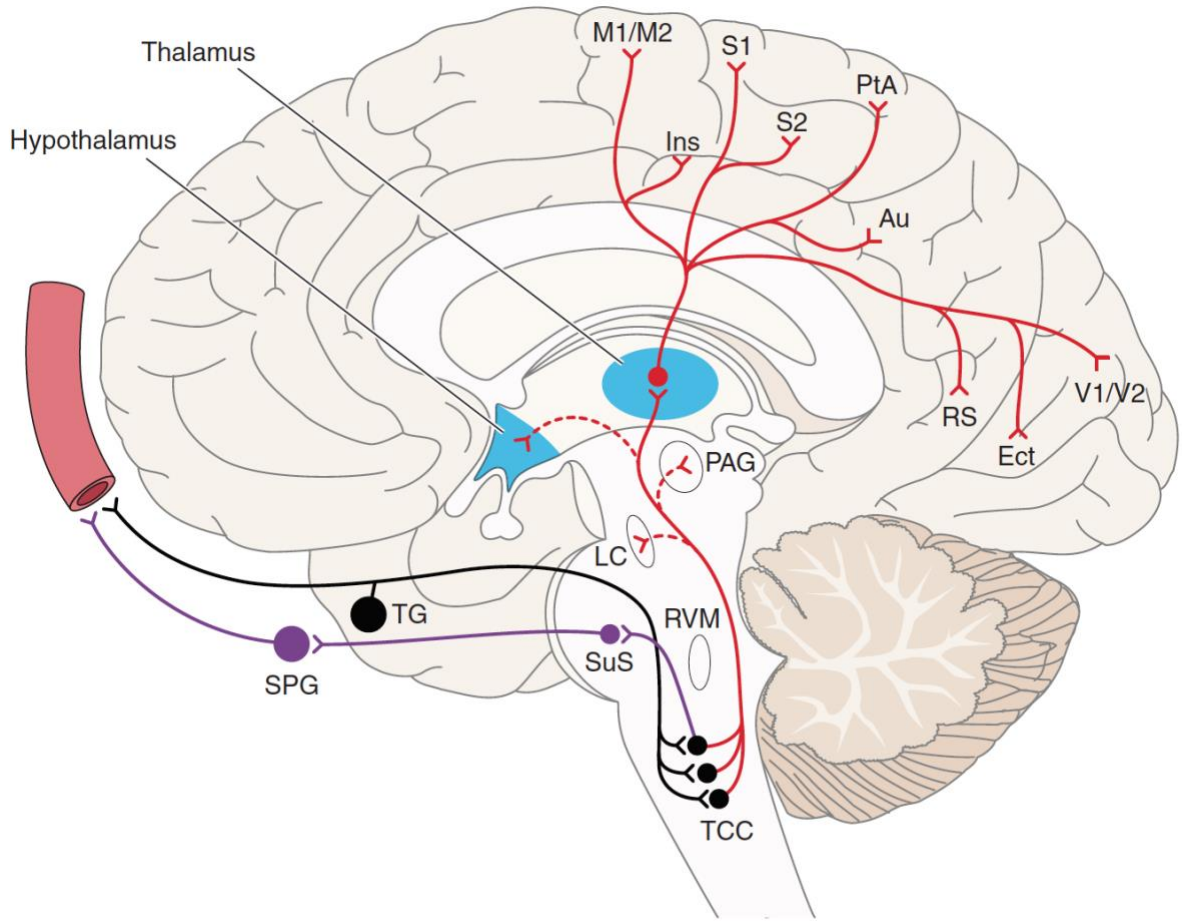

Figure 1-2 Proposed pain pathways after activation of the trigeminovascular system during migraine headache. Black: the trigeminal ganglion (TG) innervate to pial, arachnoid, and the dural blood vessels and the spinal cord trigeminocervical complex (TCC). Red: nociceptive information ascends to thalamocortical neurons via the trigeminothalamic tract and project to cortical regions. Purple: a reflex connection from the TCC and the superior salivatory nucleus (SuS) project parasympathetic outflow to the cranial vasculature via the sphenopalantine ganglion (SPG). Reprinted with permission by Copyright Clearance Center from Goadsby, P. J., P. R. Holland, M. Martins-Oliveira, J. Hoffmann, C. Schankin and S. Akerman (2017). "Pathophysiology of Migraine: A Disorder of Sensory Processing." Physiol Rev 97(2): 553-622

1.3.3 The migraine aura

Animal models have been largely used in the investigation of migraine aura. Genetic mutations in the CACNA1A (Ophoff et al. 1996), ATP1A2 (De Fusco et al. 2003), and SCN1A (Dichgans et al. 2005) have been identified in rare subtypes of MA such as familial hemiplegic migraine. People with familial hemiplegic migraine experience motor weakness in addition to typical aura symptoms, and have at least one first- or second- degree relative experiencing the same migraine condition (International Headache Society, 2018). Cortical spreading depression (CSD) has been proposed to be the neural basis of aura (Leao 1944). The electrophysiological observation of CSD was a spreading membrane potential depolarisation followed by long-lasting hyperpolarisation in neurons and glia cells in rabbit (Leao 1944). Lower induction threshold and faster spreading speed for CSD have been shown in anesthetised CACNA1A mutated mice (van den Maagdenberg et al. 2004). In a single neuron model, spreading depolarisation was proposed to be caused by the increased zonal opening of ion channels, resulting in a large amount of cation influx, which has been associated with high concentration and release of neurotransmitters like glutamate, acetylcholine and γ-aminobutyric acid (GABA) (for review see Dreier (2011)). Increased probability of glutamate release in a P/Q-type calcium channel and enhanced excitatory synaptic transmission have been demonstrated in brain slices of CACNA1A knockin mice (Tottene et al. 2009). Taken together, animal studies suggest an abnormality in the glutamatergic system in migraine.

In humans, aura can manifest as a disruption in 'visual, sensory, speech and/or language, motor, brainstem, retinal' functions (International Headache Society, 2018). Given that over 90% of people with migraine with aura suffer from visual aura (Goadsby et al. 2017), studies investigating aura in human participants have mainly focused on visual aura. Visual aura is observed as a slow progressing scotoma or scintillations spreading at about 3 mm/min in the visual field (Lashley 1941). Examples of aura patterns as drawn by migraine sufferers are shown in Figure 1-3. Using functional magnetic resonance imaging (fMRI) in human, Hadjikhani et al. (2001) demonstrated an initial (~3.3min) increase of blood oxygen level dependent (BOLD) signal followed by a prolonged period (~15min) of suppression of visual stimulation in the occipital lobe within the contralateral side of simultaneous visual aura. The increase of BOLD signal initiated in the extrastriate cortex (V3A) and propagated at a

similar rate (~3.5 mm/min in flattened cortex) as reported by Lashley (1941). Such blood flow change might reflect the increased energy consumption of sodium and calcium pumps as the depolarisation propagates to other regions (for review see Dreier (2011)).

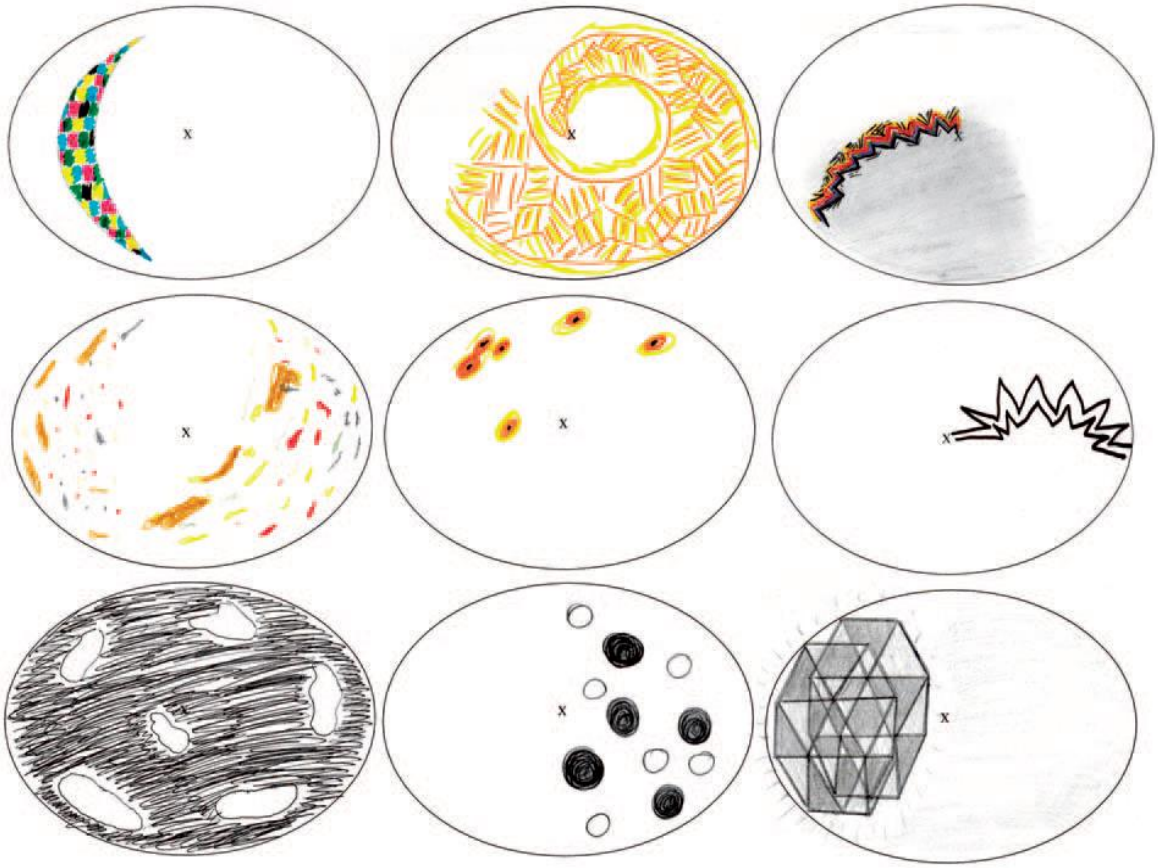

*Figure 1-3 Drawings of visual aura by people with migraine. Reprinted with permission by SAGE Publications, from Queiroz, L. P., D. I. Friedman, A. M. Rapoport and R. A. Purdy (2011). "Characteristics of migraine visual aura in Southern Brazil and Northern USA." Cephalalgia **31**(16): 1652-1658.*

As aura is typically observed within an hour before the headache for MA, whether CSD has a causative role in the initiation of migraine headache is debated. In rat models, CSD has been shown to provoke headache by activating the trigeminovascular system (Zhang et al. 2011). Daily administration of migraine prophylaxis (topiramate, valproate, amitriptyline, DL-propranolol, and D-propranolol) was shown to increase cathodal stimulated CSD thresholds in rats (Ayata et al. 2006). Based on the observation of spreading rCBF reduction after the onset of headache in one MO participant, Woods et al. (1994) proposed that CSD might also occur in migraine without aura attacks despite the absence of obvious typical migraine aura

symptoms. However, since aura without headache and aura starting after headache onset are both commonly observed (Hansen et al. 2012, Viana et al. 2015), any proposed causal link between CSD and migraine headache may not be applicable to all migraine attacks. Goadsby et al. (2017) encouraged future migraine research to consider all the symptoms as one disease rather than focus on whether CSD triggers migraine attack, since there are premonitory symptoms preceding the aura phase, and aura is only one of the symptoms of migraine and not the defining characteristic of the syndrome.

1.4 The interictal period

Given the large genetic heterogeneity of the migraine population and that the diagnostic criterion is tolerant of different combinations of symptoms, the specific cause of the sensitisation of the trigeminovascular pathway may be different for individuals (Vecchia and Pietrobon 2012). Nevertheless, a theory of migraine has attributed the sensitisation of the trigeminovascular system in migraine attacks to constant abnormal interpretations of sensory inputs (Charles 2013, Goadsby et al. 2017). This idea of abnormal sensory processing in migraine has been the basis of studies that have used the visual system to test cortical dysfunction interictally in migraine.

The term cortical hyperexcitability is widely used to refer to the suspected cortical dysfunction in migraine (Aurora and Wilkinson 2007). Interictally, higher cortical excitability in people with migraine has been supported by higher prevalence and lower threshold for transcranial magnetic stimulation induced phosphenes (Aurora et al. 1998, Aurora et al. 1999, Mulleners et al. 2001, Battelli et al. 2002), although this finding is not universal (Áfra et al. 1998, Mulleners et al. 2001, Brighina et al. 2002). In the literature, hyperresponsiveness has also been used as a general term to describe larger responses to visual stimuli observed from brain imaging studies, including greater fMRI BOLD signal, rCBF elevation, and larger visual evoked potential (VEP) amplitudes in response to visual stimuli (for review see Coppola et al. (2007)). Another term, lack of habituation, has been used to describe cortical responses that fail to adapt to constant or repetitive visual stimuli in people with migraine (for review see Brighina et al. (2009)). Typically, the magnitude of the cortical response dampens over time with exposure to a visual stimulus. However, several

visual evoked potential studies demonstrate that the visually evoked cortical response in people with migraine does not become smaller over time, resulting in an overly large response relative to non-migraine control responses. These findings of abnormal visual processing have been proposed to be either primarily caused by enhanced excitatory synapses (Welch et al. 1990) or secondarily caused by weakened inhibitory synapses (Palmer et al. 2000). Therefore, some studies have also suggested an imbalance between excitation and inhibition as a primary cortical abnormality in migraine (for review see Vecchia and Pietrobon (2012)). While these concepts are not mutually exclusive, these terminologies have sometimes been used interchangeably in the literature to describe sensory cortical dysfunction in people with migraine.

Given that it is not the primary aim of this thesis to investigate the exact cortical dysfunction in migraine, the precise neurophysiological mechanism of hyperexcitability and related concepts described above is not further explored here. Nevertheless, there is a general consensus that there are abnormal responses to sensory stimuli in between migraine attacks. Of particular interest to this thesis is the abnormal response to visual stimuli. A frequently reported interictal phenomenon in people with migraine is subjective visual discomfort. As discussed in more detail later in this literature review, interictal visual discomfort may be associated with cortical dysfunction in migraine. Hence, a better understanding of interictal visual discomfort may provide some insight into the pathophysiology of migraine.

1.5 Interictal visual discomfort

Discomfort is abstract and subjective. Visual discomfort has been used by migraine researchers to describe an aversive feeling while viewing certain visual stimuli in the interictal period. In addition to the visual symptoms being involved during migraine attacks, and some reports of migraine being triggered by visual stimuli (Shepherd et al. 2013, Shepherd and Joly-Mascheroni 2017), visual symptoms can exist in the interictal period in people with migraine. When considering discomfort specifically, previous research has largely concentrated on either visual distortions arising from high-contrast striped patterns, or discomfort from light stimulation. These two types of discomfort have distinct potential

mechanisms. Visual distortions induced by high contrast striped patterns have been attributed to cortical hyperexcitability (Wilkins et al. 1984), whereas unpleasant responses to light stimulation are thought to arise from thalamic trigeminovascular neurons (Noseda et al. 2016).

1.5.1 Discomfort induced by non-patterned light stimulation

Assuming that interictal visual discomfort induced by uniform light stimulation might have shared mechanisms to ictal photophobia, previous studies have used interictal light stimulation induced discomfort to study the mechanisms of photophobia during migraine attacks (Woodhouse and Drummond 1993, Main et al. 2000, Boulloche et al. 2010). Noseda et al. (2010) proposed migraine photophobia to be trigeminovascular neuronal activities modulated by signals originating from intrinsic melanopsin (photopigment in the retina) photoactivation, which serves non-image forming functions. It was shown that ictal photophobia can be experienced by blind migraine sufferers if their non-image forming light perception, such as the pupillary light response, is preserved (Noseda et al. 2010). Furthermore, a group of posterior thalamic neurons that are responsive to inputs from both the retina and the dura has been identified in rat models (Noseda et al. 2010). Therefore, Noseda et al. (2010) suggested that abnormal thalamic interaction of nociceptive and photic information drive migraine photophobia.

Boulloche et al. (2010) measured rCBF in the visual cortex in response to heat pain applied to the face, which was proposed to activate the trigeminal system. From 30s before the PET scan, continuous luminous stimulation at low intensities (600 and 1800 cd/m^2) was presented by semi-opaque googles covering the whole visual field (Boulloche et al. 2010). In healthy human participants, rCBF elevation in the visual cortex was only observed when concomitant pain was applied, but not in the light stimulation alone conditions (Boulloche et al. 2010). In interictal migraine participants, such light stimulation could activate the visual cortex even if no pain was applied (Boulloche et al. 2010). In addition, people with migraine also reported cumulative increase of visual discomfort throughout the study. Hence, Boulloche et al. (2010) interpreted their result as a lack of habituation in migraine participants. Using a similar procedure to Boulloche et al. (2010), the visual cortex of

migraine participants was shown to be activated at even lower light intensities (≤300 cd/m^2) during the headache and postdrome phase (Denuelle et al. 2011). It was proposed that the activation of the trigeminovascular system and brainstem are not necessary for photophobia; instead, photophobia thresholds can be lowered due to lack of cortical habituation during migraine attacks (Denuelle et al. 2011).

1.5.2 Attempts to measure pattern induced visual discomfort

Of particular interest to this thesis is the discomfort induced by pattern stimulation, as the visual system is primarily interested in contrast rather than absolute light levels (Thompson 1982). Most commonly, visual illusions induced by achromatic, high contrast striped patterns with spatial frequency of ~3 cpd, 50% duty cycle (Wilkins et al. 1984) have been associated with visual discomfort in both people with and without migraine.

Wilkins et al. (1984) found that the spatial frequency that induced more illusions in one experiment tended to be the least preferred by non-migraine observers in another experiment. Therefore, the total number of illusions seen from striped patterns was proposed to be associated with subjective visual discomfort (Wilkins and Nimmo-Smith 1984). Wilkins et al. (1984) also found that non-migraine headache sufferers reported more illusions than non-headache participants, which has motivated the investigation of stripe pattern induced visual discomfort in people with migraine. Initially, behavioural observations, such as narrowed eyes and head withdrawal, have been used as metrics to indicate that people with migraine are more aversive to high contrast striped patterns (Marcus and Soso 1989). Later studies have calculated the self-reported number of illusions participants observed within stationary high contrast striped patterns as a measurement of visual discomfort in people with migraine as well as other clinical populations (e.g. epilepsy and dyslexia) (Shepherd 2000, Wilkins and Evans 2001).

Studies have attempted to measure pattern sensitivity scores, either through participants describing their visual distortions or choosing items from checklists provided. The items from self-report or checklists include ‘bubbling’, ’checkerboards’, ‘rotation’, ‘motion’, ‘colour’, ‘shape’, ‘depth’, ‘shimmer’, ‘bending of lines’, ‘blurring of lines’, ‘flicker’, ‘fading’, ‘shadowy shapes’, ‘dots stream up and down’, ‘shadowy lines that were not really there’,

'other effects' (Wilkins and Nimmo-Smith 1984, Shepherd 2000, Wilkins and Evans 2001, Harle et al. 2006, Shepherd 2006). A consistent finding is that migraine participants demonstrate higher pattern sensitivity scores compared to non-migraine controls through self-report (Shepherd 2000, Huang et al. 2003, Harle et al. 2006, Shepherd 2006, Shepherd et al. 2013).

Migraine attacks being triggered by high contrast striped patterns has also been considered as an indication of interictal visual discomfort (Evans and Stevenson 2008, Shepherd et al. 2013, Shepherd and Joly-Mascheroni 2017). People with migraine report more visual triggers of migraine attacks than non-migraine headache sufferers (Shepherd et al. 2013, Shepherd and Joly-Mascheroni 2017). It has been suggested that the frequency of migraine attacks can be reduced by alleviating daily visual discomfort (Wilkins et al. 2002). Individualised tinted lens reportedly reduce pattern glare scores (Evans et al. 2002) and migraine attack frequencies (Wilkins et al. 2002). Thus, susceptibility to visual illusions induced by high contrast striped patterns has been linked to severity of daily visual discomfort (Evans and Stevenson 2008). However, it must also be noted that people who saw illusions from the striped pattern did not always find it unpleasant (Shepherd 2000).

An alternate measure of visual discomfort reported in the literature is to estimate the maximum bearable contrast for flicker (10Hz) and grating (3.2 cpd) stimuli (Wilkinson et al. 2008). Such stimuli have been used to demonstrate higher pattern induced visual discomfort in people with migraine. In both tests, the first stimulus presented is a uniform grey screen. Spatial or temporal contrast is then increased (for example, every 5s), and the participants asked to indicate when to stop increasing the stimulus intensity due to self-reported discomfort (Wilkinson et al. 2008). Using the flicker discomfort test, lower tolerable temporal contrast has been shown in people with migraine than non-migraine participants (Wilkinson et al. 2008, Karanovic et al. 2011, Thabet et al. 2013). Similarly, Haigh et al. (2012) showed that migraine participants stopped at a lower spatial contrast when viewing static, drifting, or vibrating grating patterns than migraine-free control participants. Overall, it appears that people with migraine show less tolerance to increasing contrast across a range of different stimuli. However, using this method, participants are

explicitly asked to stop the stimulation if it becomes too uncomfortable, which can prime a person to react in a certain way if they already know that they find visual stimuli aversive.

In the above-mentioned assessments, the existence of increased interictal visual discomfort in people with migraine is supported by differences between migraine and control groups. However, there is still a proportion of people with migraine who report visual discomfort within the control groups, therefore, migraine status cannot be identified based on individual measurement of visual discomfort. Thus, some people with migraine do not experience interictal visual discomfort, and the phenomenon of visual discomfort is not unique to the migraine population.

1.5.3 An indirect path to pattern induced visual discomfort

Other than attempts to understand pattern induced visual discomfort by inquiring about perception for the high contrast grating stimuli, more contextualised questions might be easier for participants to answer. Wilkins and Nimmo-Smith (1984) pointed out that the global pattern of a single-spaced page of text resembles a high contrast square wave grating. They found that customised 'reading aids', which covered lines above and below the line of interest, could alleviate reading induced discomfort for participants who reported greater illusory percept to striped pattern. Therefore, individuals with high visual discomfort might have poor reading efficiency compared to people with low visual discomfort (Wilkins and Nimmo-Smith 1984). However, Conlon et al. (2012) suggested that reading efficiency impairments might involve more higher level processing than visual discomfort.

The association between reading difficulty and visual discomfort motivated the development of the 23-item Visual Discomfort Scale (Table 1-1; Conlon et al. (1999)), which assesses the frequency of experiencing several types of reading distortion (item 6-22). Using this questionnaire, many studies have found higher Visual Discomfort Scale scores in people with migraine compared to non-headache controls (Conlon and Hine 2000, Shepherd et al. 2012, Shepherd et al. 2013, Cucchiara et al. 2015), suggesting that visual discomfort induced reading difficulty is generally greater in people with migraine. The reading impairments in migraine and its association with visual discomfort might be an area worth investigating.

However, given the complexity of visual discomfort in itself, we created a questionnaire aiming to assess visual discomfort more directly.

In summary, there is literature that suggests people with migraine show pattern induced visual discomfort in the interictal period, as demonstrated by more visual illusions perceived from high contrast striped patterns (Shepherd 2000), lower bearable contrast for spatial or temporal repetitive patterns (Wilkinson et al. 2008), and greater reading difficulties (Conlon and Hine 2000) compared to non-migraine observers, as well as self-reports of visual triggers of migraine attacks (Shepherd et al. 2013).

Table 1-1 The 23-item visual discomfort questionnaire. Reprinted from Conlon et al. (1999) with permission from Taylor & Francis.

Items and Original Response Scale Used on the Visual Discomfort Scale

Response categories: Visual Discomfort Scale

0 = Event never occurs
1 = Occasionally. A couple of times a year
2 = Often. Every few weeks
3 = Almost always

|Never|.....|Occasionally|.....|Often|.....|Almost always|

Items used

(1) Do your eyes every feel watery, red, sore, strained, tired, dry, gritty, or do you rub them a lot, when viewing a striped pattern?
(2) Do your eyes every feel watery, red, sore, strained, tired, dry or gritty, after you have been reading a newspaper or magazine with clear print?
(3) Do your eyes every feel watery, red, sore, strained, tired, dry or gritty, when working under fluorescent lights?
(4) How often do you get a headache when working under fluorescent light?
(5) Do you ever get a headache from reading a newspaper or magazine with clear print.
(6) When reading, do you ever unintentionally reread the same words in a line of text?
(7) Do you have to use a pencil or your finger to keep from losing your place when reading a page of text in a novel or magazine?
(8) When reading do you ever unintentionally reread the same line?
(9) When reading do you ever have to squint to keep the words on a page of clear text from going blurry or out of focus?
(10) When reading, do the words on a page of clear text ever appear to fade into the background then reappear?
(11) Do the letters on a page of clear text ever go blurry when you are reading?
(12) Do the letters on a page ever appear as a double image when you are reading?
(13) When reading, do the words on the page ever begin to move or float?
(14) When reading, do you ever have difficulty keeping the words on the page of clear text in focus?
(15) When you are reading a page that consists of black print on white letters, does the background ever appear to overtake the letters making them hard to read?
(16) When reading black print on a white background, do you ever have to move the page around, or continually blink to avoid glare which seems to come from the background?
(17) Do you ever have difficulty seeing more than one or two words on a line in focus?
(18) Do you ever have difficulty reading the words on a page because they begin to flicker or shimmer?
(19) When reading under fluorescent lights or in bright sunlight, does the glare from bright white glossy pages cause you to continually move the page around so that you can see the words clearly?
(20) Do you have to move your eyes around the page, or continually blink or rub your eyes to keep the text easy to see when you are reading?
(21) Does the white background behind the text ever appear to move, flicker, or shimmer making the letters hard to read?
(22) When reading, do the words or letters in the words ever appear to spread apart?
(23) As a result of any of the above difficulties, do you find reading a slow task?

1.5.4 The effect of migraine aura on pattern induced visual discomfort

Some previous studies have attempted to determine whether the presence of aura differentially affects visual discomfort by comparing MO and MA groups. Several studies find no significant difference between MO and MA groups in visual discomfort measured by maximum bearable contrast (Wilkinson et al. 2008, Thabet et al. 2013), visual trigger indices (Shepherd et al. 2013), and Visual Discomfort Scale scores (Shepherd et al. 2012, Shepherd et al. 2013). However, other studies have reported that MA participants tend to see more illusions from high contrast striped pattern than MO participants (Shepherd et al. 2012, Shepherd et al. 2013). Khalil et al. (2011) investigated the effect of lateralisation of aura and headache on pattern sensitivity and contrast detection threshold by presenting stimuli on each half of the visual field. They found that the MA participants with unilateral aura tended to see more illusions on the side of the aura, which was consistent with their previous reports in Khalil (1991), but headache lateralisation was not associated with illusion location (Khalil et al. 2011). On the other hand, Huang et al. (2003) found that aura and illusion locations were not associated with each other when the high contrast striped patterns were presented in the central 13° of the visual field in their 6 MA participants. Among all these measurements of visual discomfort in the literature to date, the only one that seems to be different between MA and MO is the pattern sensitivity score. Hence, it was reasonable in this thesis to *a priori* separate the MA and MO groups, as it is possible that visual discomfort might be different between the two migraine subtypes.

1.6 Attempts to understand pattern induced visual discomfort by objective measurements of visual function

1.6.1 Interictal visual discomfort and its relationship to brain imaging measures

Wilkins et al. (1984) found that the stimulus properties of spatially repetitive high contrast stimuli that were associated with more illusions highly overlapped with those found to induce paroxysmal activity in photosensitive epilepsy patients. Therefore, Wilkins et al. (1984) proposed that a failure of cortical inhibition as a result of intense excitation might underlie visual discomfort. The spatial frequency dependency of square-wave gratings on the subjective rating of visual discomfort and number of illusions reported by observers (Wilkins et al. 1984) has led to the investigation of the effect of the spatial frequency of high

contrast striped pattern on cortical responses. The authors of these studies were interested in whether a similar spatial frequency dependency exists between measurements of cortical responses and that observed for subjective visual discomfort, with the inference that such similarity implies shared mechanisms (Huang et al. 2003, Huang and Zhu 2017).

1.6.1.1 BOLD signal and visual discomfort

Greater striped pattern induced discomfort has been linked to larger amplitude and longer lasting fMRI BOLD signal (Huang et al. 2003, Huang and Zhu 2017). Huang et al. (2003) measured the pattern sensitivity score, self-rated discomfort score, and BOLD signal in the approximate location of primary visual cortex (V1) as a function of grating spatial frequency from 0.3 to 9 cpd for 6 MA and 6 controls. The self-rated discomfort (score of 0-5) was the number of items reported from 'eye ache, queasiness, headache, nausea, or dizziness', after viewing each stimulus for 5s. All three measurements were found to be significantly larger in MA than control participants, whereas both groups showed similar dependence of pattern sensitivity score and BOLD signals on spatial frequency (Huang et al. 2003). However, the spatial frequency at which the BOLD signals peaked (1.2 cpd) was smaller than the 3cpd peak suggested by Wilkins et al. (1984). Huang and Zhu (2017) investigated resting state fMRI while presenting grating stimuli with spatial frequencies of 2.8 cpd and 0.27 cpd in 12 healthy human participants. Grating patterns with the aversive spatial frequency (2.8 cpd) activated the visual cortex for a longer duration than a non-aversive spatial frequency (0.27 cpd). However, Huang and Zhu (2017) used the two spatial frequencies in two separate experiments with different participants (6 people participated both with about 1-year interval between the two experiments), and they did not ask if the participants found 2.8 cpd more uncomfortable than 0.27 cpd.

Huang et al. (2011) studied the impact of tinted lenses for migraine participants (7MA + 4MO) by measuring BOLD signals in V1, V2, V3, V3A, and V4 in response to high contrast striped patterns with spatial frequencies of 0.31, 2.5, and 7.9 cpd under different lens conditions (grey control, coloured control, precision ophthalmic tints). Out of 17 migraine participants who initially participated the fMRI session, effects of tinted lenses on self-rated visual discomfort (scale of 0-10) for the 2.5 cpd pattern were assessed in 10 participants. All three lenses significantly reduced visual discomfort, and the reduced amount was

significantly larger in precision ophthalmic tints than the two control lenses. The authors considered BOLD signal reduction in precision ophthalmic tints condition compare to control conditions to be reflection of reducing visual discomfort. Since the lens effect on brain activation was only observed in the 2.5 cpd stimulus, the other two spatial frequencies were classified as non-stressful patterns. Inconsistent with their previous results (Huang et al. 2003), Huang et al. (2011) found V1 BOLD signals (regardless of lens conditions) peaked at 2.5 cpd for both migraine and control participants. There was also no significant group difference in BOLD signals for stimuli at 0.31 cpd in all areas Huang et al. (2011) have measured, while significantly greater V1 BOLD signals in the MA group, compare to the control group, at 0.3 and 1.2 cpd were shown in Huang et al. (2003).

1.6.1.2 Gamma oscillation measured in magnetoencephalography and visual discomfort

Gamma oscillation is defined as brain rhythms in the 30-90 Hz band which can be detected, through magnetoencephalography or electroencephalogram, in many brain areas where inhibitory interneurons can be found (Buzsáki and Wang 2012). Although the exact underlying mechanisms are not fully understood, the frequency of gamma oscillation is proposed to reflect the sum of local excitation and inhibition activities (Buzsáki and Wang 2012). Adjamian et al. (2004) measured magnetoencephalography recordings and pattern sensitivity score of healthy participants when square wave gratings were presented at different spatial frequencies (0.5-6 cpd). They found a similar dependency on spatial frequency for gamma activity in V1 and pattern sensitivity score, which both peaked at 2-4 cpd. Adjamian et al. (2004) suggested that the greater gamma activity in response to aversive spatial frequencies (2-4 cpd) might reflect greater excitation and lack of inhibition in V1.

1.6.1.3 VEP and visual discomfort

The VEP is an electrical potential measured from the scalp near the visual cortex which is proposed to reflect a sum of local inhibitory and excitatory potentials (Eccles 1951). For transient event-related potential, a typical outcome measure is the amplitude of the waveform in the time domain at approximately 100ms post-stimulus onset (P100 peak). The SSVEP is a periodic VEP elicited by periodic stimuli (Norcia et al. 2015). For periodically

reversed stimuli, where the stimulus luminance contrast in consecutive phases are inverted, instead of switching between stimulus onset and offset, the scalp-measured potentials for the two interleaving phases are identical. Thus, the amplitude at the second harmonic of the reversal rate in the frequency domain, following Fourier transform, is typically reported (Rossion and Jacques 2011). O'Hare et al. (2015) and O'Hare (2017) investigated the relationship in healthy participants between subjective ratings of visual discomfort (score of 0-99; 0 = no discomfort, 99 = maximum discomfort) and VEP amplitudes in 'riloid' stimuli (curved stripes with smaller spatial frequency at turning point) with different spatial frequencies (0.5, 3, 9 cpd) and "waviness" (wavy, medium, straight). Both studies found that the subjective rating of discomfort was the smallest for the highest spatial frequency, and that the curved stimuli were slightly more uncomfortable than the straight stimulus (significantly different between the straight and waviest stimulus). In terms of the physiological response, O'Hare (2017) found that the 3 cpd condition elicited the largest SSVEP peak amplitude, whereas the P100 amplitude was the smallest for the highest spatial frequency (O'Hare et al. 2015). However, there was no association between subjective visual discomfort rating and P100 amplitude (O'Hare et al. 2015), except for a relationship ($\chi^2(1) = 5.507$, $p = 0.0189$) between subjective discomfort rating and the SSVEP response in the 10Hz condition but not in 5Hz condition (O'Hare 2017).

In summary, studies using fMRI, magnetoencephalography, and electroencephalogram have shown that visual stimuli with spatial frequency of ~3cpd can elicit stronger cortical responses than other spatial frequencies. However, these indirect measures of visual cortical neural activity do not necessarily match subjective measurements of visual discomfort in the general population (O'Hare et al. 2015).

1.6.2 Interictal visual discomfort and visual psychophysics

In addition to measuring brain activity and neural responses to visual stimuli indirectly using techniques such as functional brain imaging, visual perceptual studies can provide insight into the cortical processing of visual stimuli. Associations between visual perception and visual discomfort have been studied by finding correlations between psychophysical tasks and subjective measurements of visual discomfort. Hence, the potential mechanisms of

visual discomfort might be inferred from altered visual processing associated with subjective visual discomfort.

1.6.2.1 Contrast perception and visual discomfort

Contrast detection threshold measures the minimum spatial contrast of a grating stimulus or temporal contrast of flicker stimulus that observers can detect. Using the Functional Acuity Contrast Test (Stereo Optical, Chicago, IL, USA), where participants had to correctly identify the orientation (-15°, 0°, or +15°) of a small (1.7°) grating stimuli, an elevation of spatial contrast detection thresholds are present in people with migraine for a wide range of spatial frequencies (1.5-18cpd) (Yenice et al. 2007). Using the Cambridge Low Contrast Gratings test (Wilkins et al. 1988), which requires participants to identify which plate contains a 4 cpd grating among two plates, several studies have demonstrated contrast sensitivity impairments in migraine groups (Shepherd 2000, Shepherd et al. 2012, Shepherd et al. 2013), although this finding has not always been replicated (Singh and Shepherd 2016). In computer based contrast sensitivity tasks, where stimuli were presented for limited durations, the contrast detection threshold for brief (25-1000ms) small (1.6-3°) central targets (3-4 cpd), measured by two-interval forced choice methods, was not significantly different between migraine and control groups (McColl and Wilkinson 2000, McKendrick et al. 2001, Tibber et al. 2006). Elevated contrast detection threshold for mid-periphery targets (eccentricity of 10°) has been shown in people with migraine whose contrast sensitivity was not significantly different from controls for centrally presented targets (McKendrick and Sampson 2009). While, overall, studies suggest contrast sensitivity is impaired in people with migraine, the effect size is small and therefore statistically significant group differences have not always been shown (the above-mentioned studies are summarised in Table 1-2).

Table 1-1 Summary of studies comparing contrast sensitivity between people with and without migraine.

Study	**Stimuli**	**Results**	**Participants**
Yenice et al. 2007	Functional Acuity Contrast Test: Sine-wave grating patch of 1.7°;	Contrast sensitivity significantly lower in	28 people with migraine; 15

	1.5-18 cpd	migraine group in all spatial frequencies: $p < 0.0001$ in Mann-Whitney U tests	non-headache control
Shepherd 2000	Cambridge Low Contrast Gratings test: Square-wave grating; 4 cpd	Significantly lower thresholds in control group: $t(68) = 2.14$, $p = 0.018$	35 people with migraine; 35 non-migraine control
Shepherd et al. 2012		Control group had significantly lower threshold than MA: $t(26) = 2.3$, $p = 0.03$ and MO: $t(26) = 2.4$, $p = 0.02$, 1-tailed	14 MA; 14 MO; 14 non-IHS headache control
Shepherd et al. 2013			
Singh and Shepherd 2016		Non-significant higher contrast threshold in migraine: $t(22) = 1.6$, $p = 0.065$, 1-tailed	12 people with migraine; 12 non-IHS headache control
McColl and Wilkinson 2000	2AFC; Gabor patch of 2°; 3cpd; Duration of 30ms	Non-significant lower contrast threshold in migraine:	25MA; 22MO; 25 non-migraine control

			F(1,69) = 2.80, p = 0.09	
McKendrick et al. 2001	2AFC; Gabor patch of 3.5°; Duration of 1s	0.5 cpd drifting at 16 Hz	No significant group difference for all conditions	15 MA; 15 non-headache control
		4 cpd drifting at 2 Hz		
Tibber et al. 2006	2AFC; Gabor patch of 1.6°; 4cpd; Duration of 25ms		No significant group difference: F < 0.5, p > 0.5	20 people with migraine; 20 non-headache control
McKendrick and Sampson 2009	2AFC; Gabor patch of 2.66°; 0.25-4cpd; Duration of 30ms	central	Non-significant group effect: F(1,27) = 2.68, p = 0.13	12 people with migraine and visual field abnormalities; 17 non-headache control
		10° eccentricity	Main effect of group: F(1,27) = 7.65, p = 0.01	

Chronicle and Wilkins (1996) demonstrated that contrast detection thresholds for letter targets are elevated by superimposing the letters onto high contrast striped patterns in the general population. The experiment measured performance for a range of background pattern spatial frequencies (0.8-12.7 cpd). The contrast threshold as a function of grating spatial frequency demonstrated a similar profile to that of the pattern sensitivity score, with both functions peaking at around 4 cpd. The authors suggested that increased difficulties with letter identification might be associated with the visual illusions induced by the striped patterns. Shepherd (2000) found a statistically significant correlation (r=-0.34, n=35) between pattern sensitivity score and Cambridge Low Contrast Gratings contrast sensitivity in migraine participants. Shepherd (2000) proposed that the impaired spatial contrast detection threshold and the enhanced illusions reported by the migraine group might both be due to increased noise level in the visual system and/or an increased responsiveness to the visual stimulus. However, a later study by the same research group, Shepherd et al.

(2012), did not find a significant correlation between Cambridge Low Contrast Gratings contrast sensitivity and pattern sensitivity score. The inconsistent results might have been affected by the population differences that the participants in Shepherd (2000) (mean±SD: age 40±13 years; mean migraine duration 21±12 years; migraine frequency 14±18 per year) were older and had longer migraine durations than in Shepherd et al. (2012) (age 24.6±8.7 years for MA, 24.6±5.9 years for MO; migraine duration 12.1±8.3 years for MA, 10.4±4.4 years for MO; migraine frequency 12±7 per year for MA, 8±9 for MO). This raises the possibility that characteristics of migraine might influence performance on visual tasks, which is addressed later in this thesis by considering the relationship between visual performance, self-reported visual discomfort and typically reported migraine demographics.

Conlon et al. (2012) grouped their participants in two ways, based on either migraine status or visual discomfort scores, and found that grating contrast sensitivity (spatial frequency within 0.3-8.4 cpd) was only different when the groups were split into those with high and low visual discomfort, but not when split into people with and without migraine. The authors suggested that elevated contrast detection threshold was only specific to people with visual discomfort (i.e. even non-migraine controls) but not for all people with migraine.

Conlon et al. (2012) also measured temporal contrast sensitivity using flicker stimuli of temporal frequency between 2Hz to 33Hz, and only found group differences between MA and control groups but not between high and low visual discomfort groups. Their contrast sensitivity results were consistent with McKendrick et al. (2001), in which the MA group only had higher contrast detection thresholds than the control group for a peripheral (10°) target at 16Hz temporal modulated background, but not for a central target or spatially modulated background (0.5 and 4 cpd). Conlon et al. (2012) suggested that temporal contrast sensitivity impairment was determined by migraine status while spatial contrast sensitivity was associated with visual discomfort. Although it was not quite clear in their description about how different visual discomfort groups were classified, they mentioned that the Visual Discomfort Scale score (Conlon et al. 1999) and 'a measure of sensitivity to pattern obtained from viewing a 4 c/deg striped pattern for 10 seconds' were combined. Therefore, it is possible that the different group effects for spatial and temporal contrast sensitivity

might be influenced by the classification of participants into high and low visual discomfort groups based on a spatial grating rather than a flicker stimulus.

Karanovic et al. (2011) and Thabet et al. (2013) explored the relationship between the visual discomfort score measured by the maximum bearable contrast of a flickering screen (10Hz) and the effect of adaptation on temporal contrast discrimination thresholds of flickering spots (10Hz; diameter of ~2°). Both studies found greater visual discomfort in the migraine participants while temporal contrast detection and discrimination thresholds (reference levels at 10% and 70% Michelson contrast) were not different between groups (Karanovic et al. 2011, Thabet et al. 2013). Hence, temporal contrast discrimination threshold was not correlated with visual discomfort score (Karanovic et al. 2011, Thabet et al. 2013). Effects of adaptation was examined by the change in contrast discrimination thresholds when reference contrast was adapted (180s-preadaptation + 2s-top up between each trial) compare to the no adaptation conditions. Karanovic et al. (2011) found the effects of adaptation (elevation for 10% condition and reduction in 70% condition) to be stronger in the migraine group, and suggested this effect to be explained by increased feedback inhibition according to the model proposed by Wilson and Humanski (1993). By presenting the adapting flicker spots to one eye and testing the detection threshold for the other eye, the detection threshold reduction for high contrast stimulus in migraine group was found to be restricted to the adapted eye while remaining elevated in the fellow eye (Thabet et al. 2013). Thabet et al. (2013) suggested that the visual discomfort to flicker stimulus might be mediated by the non-image forming pathways proposed for photophobia (Noseda et al. 2010), while the stronger adaptation of inhibitory neurons have a pre-cortical locus before monocular information converges in people with migraine.

1.6.2.2 Motion perception and visual discomfort

In the pattern sensitivity test, 'motion' is one of the most common illusory item that is reported (Shepherd et al. 2013). For example, in Shepherd et al. (2013), the number of people reporting seeing 'shape', 'motion', and 'colour' at 3 cpd were 22 (52%), 18 (43%), 9 (21%) out of 42, inclusive of both people with and without migraine. Given that illusory

motion is perceived by people with migraine, it is worth considering whether abnormal motion processing contributes to their enhanced illusory percept.

Random dynamic kinematograms (RDKs) have been used to assess global pooling ability of neurons in the middle temporal visual area (MT) (Newsome and Pare 1988, Britten et al. 1992). In human vision, a common task designed to test this global pooling ability is to measure motion coherence thresholds. The motion coherence task measures the minimum signal (dots move in coherent direction, different signal dots on each frame of the stimulus movie) to noise (dots move in random directions) ratio for participants to correctly identify the direction of coherent motion. Significant but small increases in motion coherence thresholds have been demonstrated in people with migraine compared to healthy controls in many studies with wide range of stimuli with duration of 78ms-456ms, speeds of 2.86°/s-6°/s, and eccentricity up to 20° (McKendrick et al. 2001, McKendrick and Badcock 2004, Antal et al. 2005, Ditchfield et al. 2006, McKendrick et al. 2006, McKendrick et al. 2006, Webster et al. 2011, Shepherd et al. 2012). Based on the assumption that to be able to detect coherent motion, everyone requires a similar signal to noise (external + internal) ratio (Dakin et al. 2005), Antal et al. (2005) suggested that people with migraine have higher internal noise levels and therefore need more signal dots to detect coherent motion amongst noise dots.

Using an N-pass technique (Levi et al. 2007), internal noise can be estimated by the internal consistency of behavioural responses to psychophysical stimuli within individual participants. Using this technique, Webster et al. (2011) did not find a significant difference in internal noise between migraine and control groups, although motion coherence thresholds were significantly elevated in the migraine group. Therefore, Webster et al. (2011) suggested that elevated motion coherence thresholds in migraine were not driven by internal noise, and instead suggested that motion deficits might be related to structural deficits in the motion processing system, e.g. grey matter in areas MT+ and V3A was found to be thicker in people with migraine (Granziera et al. 2006).

Shepherd et al. (2012) suggested that motion deficits in people with migraine might be partially inherited from earlier areas in the visual pathway that have contributed to contrast

deficits. Other than motion coherence threshold, Shepherd et al. (2012) also measured the correct rate for identifying the direction of briefly (50 or 70ms in separate conditions) presented, 100% coherent RDKs, and the minimum speed for motion direction to be discriminated with added static or moving noise dots. In addition, they also measured the Cambridge Low Contrast Gratings contrast sensitivity, pattern sensitivity score, and the Visual Discomfort Scale score (Conlon et al. 1999). Consistent with previous findings (Shepherd 2000, McKendrick and Badcock 2004), Shepherd et al. (2012) found that contrast detection threshold and thresholds for all motion tasks were significantly higher in the migraine groups, and that contrast sensitivity was correlated with all three motion tasks. Furthermore, when contrast sensitivity was considered as a covariate, only motion coherence thresholds remained significantly different between groups, which the authors suggested might be due to altered MT functions (Shepherd et al. 2012).

Haigh et al. (2012) found both migraine and control groups reported lower bearable contrast for vibrating or drifting than static grating stimuli, which suggests that atypical motion processing might contribute to visual discomfort. However, Shepherd et al. (2012) found pattern sensitivity score and the Visual Discomfort Scale score were not correlated with any of the motion tasks, although each measurement alone was significantly higher in the migraine than the control group. Shepherd et al. (2012) suggested that their result might be influenced by their sample being university students instead of a tertiary referral centre for headache patients, and suggested that a different finding may possibly be revealed within a more severe symptom group.

1.6.2.3 After effects and visual discomfort

Motion after effects (MAE) refers to an illusory motion perception in the opposite direction to the displayed stimulus after the real motion has stopped (Adams 1834). The tilt after effect (TAE) is a similar illusory percept of vertical gratings appearing to be tilted to the orientation opposite to previously adapted tilted grating (Gibson and Radner 1937). For both of these after-effects, a proposed mechanism is the release of mutual inhibition to the adjacent neurons who prefer the opposite direction/orientation to the adapted motion/grating (Anstis et al. 1998). Stimulus contrast is important for the MAE as its duration is reduced by reducing the adapting stimuli contrast or increasing the testing

display contrast (Keck et al. 1976). MAE was consistently shown to be longer in people with migraine in a range of stimulus contrast (adapting stimulus ≥30% Michelson contrast; testing stimulus ≤ 30% Michelson contrast), in both static and dynamic testing stimuli (Shepherd 2001, Shepherd 2006, Singh and Shepherd 2016, Shepherd and Joly-Mascheroni 2017). Longer dynamic MAE in migraine might suggest abnormal cortical excitability at later stages of cortical visual processing such as area MT (Shepherd 2006). Longer MAE with static testing display in migraine was proposed to reflect slower cellular recovery speed and long lasting neuronal circuits changes, such as stronger inhibitory connections, at earlier stages such as V1 (Shepherd 2006). A stronger TAE has also been shown in people with migraine, which has been proposed to be due to increased cortical inhibition or reduced excitation (Shepherd 2001, Shepherd et al. 2002).

It has been consistently shown that people with higher pattern sensitivity scores ($0.25 \leq r \leq 0.35$), more self-reported visual triggers of migraine or non-migraine headaches ($0.42 \leq r \leq 0.52$), experience of photophobia during migraine or non-migraine headaches ($0.32 \leq r \leq 0.45$) tended to experience longer MAE across different testing conditions (Shepherd 2001, 2006; Shepherd & Joly-Mascheroni 2017). There was a nonsignificant trend (r=-0.33, -0.49, -0.51 in high, medium, low contrast testing display conditions) of longer MAE being associated with poorer contrast sensitivity in people with migraine (Singh and Shepherd 2016). Given that both motion and contrast processing are thought to contribute to the strength of the MAE, it is possible that abnormal motion or contrast processing in people with migraine may contribute to visual discomfort.

In summary, despite inconsistencies in the literature regarding the nature of contrast sensitivity deficits in migraine, reduced contrast sensitivity has been suggested to contribute to the prolonged MAE and impaired motion perception in people with migraine (Shepherd et al. 2012, Singh and Shepherd 2016, Shepherd and Joly-Mascheroni 2017). Greater pattern sensitivity scores have been linked to altered MAE duration and contrast sensitivity in people with migraine (Shepherd 2000, Shepherd 2006, Conlon et al. 2012). These results suggest that abnormal cortical processing of contrast and motion are involved in inducing visual discomfort, which is an issue explored in this thesis.

1.7 A quantifiable motion illusion

As discussed in the last section (1.6) of this literature review, there are many studies that have investigated the relationship between visual perception, visual cortical responses, and visual discomfort, which may help understand why people with migraine experience interictal visual discomfort. However, the measurement of discomfort is by subjective self-report. The increase in reported number of illusions induced by high contrast striped pattern in people with migraine, relative to control participants, has been used as an index of visual discomfort (Shepherd 2000, Huang et al. 2003, Harle et al. 2006, Shepherd 2006, Shepherd et al. 2013). However, the link between visual discomfort and illusion is still unclear. Thus, illusory vision perception in people with migraine is investigated in this thesis. In the pattern sensitivity test, the most commonly reported illusions are those of 'shape', 'motion', 'colour' (Shepherd et al. 2013). Of particular interest to this thesis is illusory motion, as there has been a long line of work objectively quantifying and investigating the factors that influence the strength of illusory motion.

The rotating snake illusion is an example of a motion illusion which can induce illusory motion perception within stationary images. It has been recently used as a non-invasive tool to study the visual system across different populations and species including infants, older adults, fishes, and macaques (Billino et al. 2009, Kanazawa et al. 2013, Gori et al. 2014, Agrillo et al. 2015). The stimulus was developed by Kitaoka and Ashida (2003) as an enhanced version of the Fraser-Wilcox illusion (1979) also known as the peripheral drift illusion. The strength of the illusion is affected by eye movements, retinal illuminance and retinal eccentricity (Murakami et al. 2006, Hisakata and Murakami 2008). The fact that the illusion can be enhanced in several ways suggests multiple mechanisms are involved. The next section aims to review the proposed mechanisms underlying the Fraser-Wilcox illusion of this nature.

1.7.1 Description of the Fraser-Wilcox illusion

The Fraser-Wilcox illusion (1979) is a static stimulus which is comprised of repetitive segments filled with bright to dark gradient (Figure 1-4). Kitaoka and Ashida (2003)

enhanced the Fraser-Wilcox illusion by splitting one segment into 4 smaller uniform luminance patches and shortening the edges (Figure 1-5). Based on their proposed rule that a motion signal is generated in the direction from black to dark grey and from white to light grey, the right panel of Figure 1-5 typically appears to rotate clockwise and expand towards the circumference. For aesthetic reasons, the shape and colour of the luminance patches can be changed while maintaining the contrast sequence to generate consistent motion signals in the same circular direction (for more artistic variations of the Fraser Wilcox illusion see Akiyoshi's illusion pages: http://www.ritsumei.ac.jp/~akitaoka/index-e.html). Atala-Gerard and Bach (2017) found that 0%-25% contrast for the dark grey and 25%-75% contrast for the light grey can induce the motion illusion in the expected direction, and contrast beyond those ranges can reverse the direction of the illusion.

To quantify the strength of this illusion, a nulling technique was developed by Murakami and colleagues (2006). In this method, real rotation was added to the pattern and observers were required to indicate whether the perceived direction of motion was clockwise or counterclockwise. The cancellation speed, which is typically in the direction opposite to the perceived motion, was determined as the physical rotation speed when observers have a 50% chance of reporting both directions i.e. the pattern appears stationary.

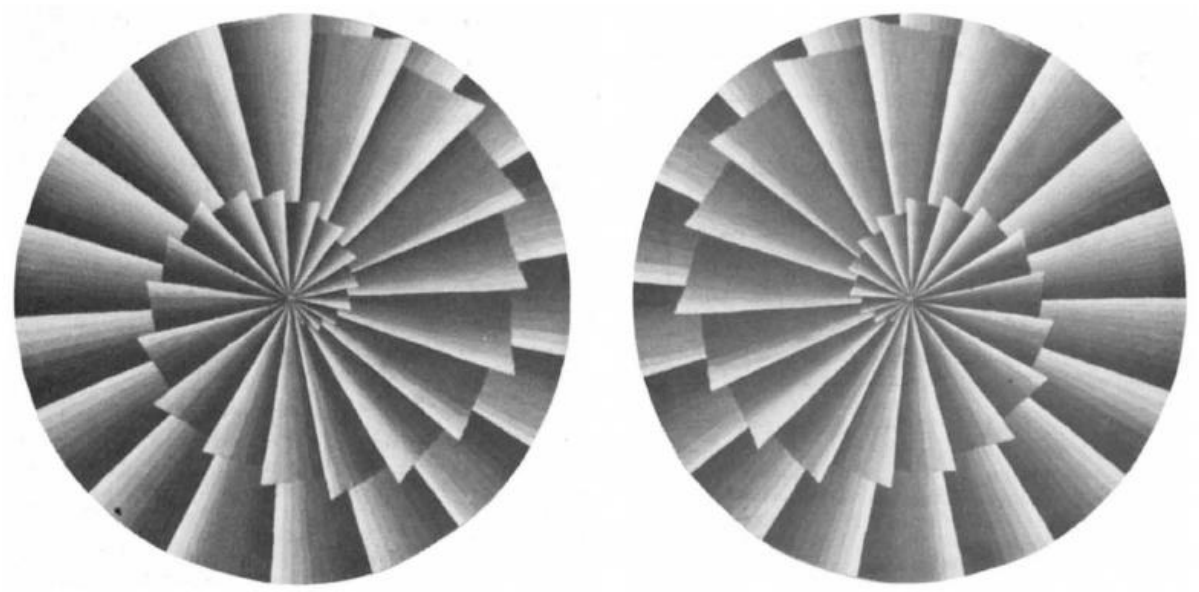

Figure 1-4 The Fraser-Wilcox illusion. Reprinted by permission from RightsLink Permissions Springer Nature Customer Service Centre GmbH: Springer Nature, Perception of illusory movement, Alex Fraser & Kimerly J. Wilcox, Copyright (1979)

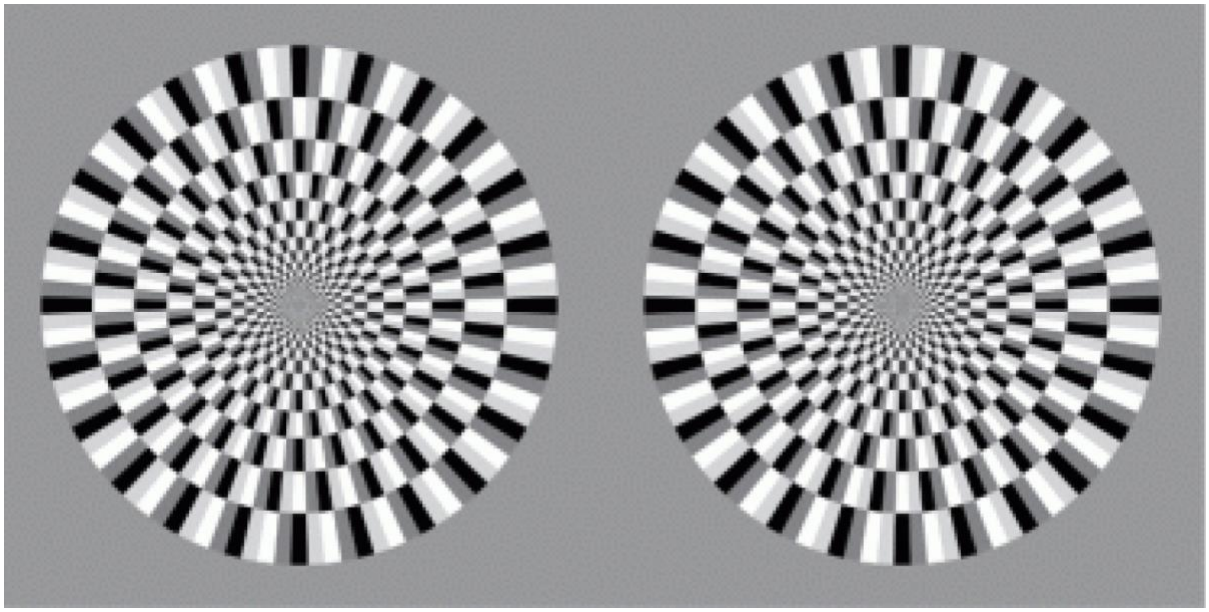

Figure 1-5 The 'Optimised' Fraser-Wilcox illusion. Reprinted from Shapiro, Arthur G. 'The Fraser-Wilcox and its extension' in The Oxford Compendium of Visual Illusions. pp. 504. Copyright (2017) by Oxford Publishing Ltd. Reproduced with permission of the Licensor through PLSclear.

1.7.2 Factors that affect the strength of the motion illusion

The luminance order is the most important feature of the pattern in the context of generating the motion illusion. As the perceived direction is from black to dark grey and white to light grey, Kitaoka and Ashida (2003) proposed a model whereby different neuronal response latencies are generated in response to the change in luminance across the pattern. Support for this interpretation is provided by Conway et al. (2005) who found that the presentation of static pairs of luminance bars (two bars with a shared edge) with similar luminance order as seen in the motion illusion pattern (i.e. black to dark grey, white to light grey) can activate direction selective cells in macaque V1 and MT. Conway et al. (2005) also demonstrated that when single luminance bars were briefly (27ms) presented on a mean grey background, the neural responses in direction selective cells in V1 and MT to high contrast (black and white) bars were 10-20ms prior to neural responses to low contrast

(dark grey and light grey) bars. These results, together, provide physiological evidence for a plausible neural mechanism to underpin a contrast dependent latency hypothesis underlying the Fraser-Wilcox illusion. In addition to this response latency hypothesis, Backus and Oruç (2005) suggested a contribution from a contrast dependent adaptation process. Their model suggests that the response to high contrast elements (relative to mean grey background) reaches its peak faster and adapts earlier than the neural response to lower contrast elements. A prediction of this model is that brief stimulus durations should enhance the perception of illusory motion in these patterns.

There is a correlation between increased cancellation speed and poorer fixation stability (Murakami et al. 2006). Saccadic eye movements also enhance the perception of illusory motion (Kuriki et al. 2008). Eye movements and blinks help refresh the transient signal so that the motion energy generated by luminance dependent responses over time can be repeated (Otero-Millan et al. 2012). Although the overall microsaccade frequency during the observation was not shown to be correlated with cancellation speed (Murakami et al., 2006), the blink and microsaccade rates prior to the report of illusory motion onset was increased (Otero-Millan et al. 2012).

The Fraser-Wilcox illusion is also more pronounced in peripheral vision. Observers are more likely to report the direction of the motion illusion at a larger eccentricity (16.2°) (Naor-Raz and Sekuler 2000). Within the eccentricity range of 0-20°, Hisakata and Murakami (2008) found that the cancellation speed for 2 out of the 4 participants kept increasing as eccentricity is increased. The other 2 participants did not show further increase of cancellation speed for eccentricities beyond 12° (Hisakata and Murakami 2008). However, their measurement of motion sensitivity remained relatively stable for eccentricities up to 12° in all participants (Hisakata and Murakami 2008). Therefore, the previously reported differences in motion sensitivity between peripheral and central vision (Tynan and Sekuler 1982, Baker and Braddick 1985) may not be a dominating factor affecting the motion illusion strength.

Given the above known factors that affect the strength of the motion illusion, the stimulus parameters to be used in this thesis have been chosen to give a relatively strong motion illusion, namely eccentric viewing and brief stimulus presentation. Other critical stimulus factors such as luminance profile will be investigated in more detail in the experimental chapters to determine its effect on the strength of the motion illusion.

1.7.3 Involvement of cortical motion processing areas in the motion illusion

Functional MRI studies in human have suggested that the motion direction for the Fraser-Wilcox illusion may be detected in cortical area MT rather than in V1 (Kuriki et al. 2008, Ashida et al. 2012). Kuriki et al. (2008) demonstrated that area MT showed greater BOLD signals to an illusory stimulus than to a control stimulus (where the order of the four colours in each cycle was reversed between every flanking unit), however, responses in V1 were not distinguishable between these two stimuli. Ashida et al. (2012) measured BOLD signals in several visual areas (V1, V2, V3, V4, V3A, V3B, and MT) in response to the rotating snake illusion after adaptation. The testing and adapting stimuli was presented in either the same or opposite illusory motion directions. Consistent with previous findings, only area MT showed a greater response to the reversed pattern than to the same pattern, which suggested that the direction of illusory motion was not adapted until MT (Ashida et al. 2012).

In summary, the strength of the Fraser-Wilcox illusion relies on several factors including the duration of the stimulus presentation; the presence of eye movements; and the retinal eccentricity of presentation. The strength of these types of illusions can be measured psychophysically as a cancellation speed. Animal neurophysiology suggests contrast dependent responses may be involved in the generation of the illusion (Conway et al. 2005). In humans, it is unclear whether differences in contrast processing, and or motion sensitivity, may predict observed individual differences in illusion strength.

1.7.4 Investigating illusory motion perception in migraine

A recent study has reported greater induced postural sway in migraine participants relative to a control group after viewing the rotating snake illusion, a colourful (blue and yellow)

variant of the Fraser-Wilcox illusion (Imaizumi et al. 2015). The migraine and control groups exhibited significant difference in postural sway (rectangular area) when their eyes were closed during a 30-second interval immediately after viewing a large (29°×29°) rotating snake illusion in a head mounted display, but not when their eyes were opened either during the stimulus presentation or the 30-second interval after stimulus offset. In their second experiment, in which postural sway was measured during the 30-second interval that was 30s after stimulus offset, people with migraine had better postural stability (total path length) than the controls. Assuming that the postural sway measured in the eye closed condition was caused by the MAE to the illusory motion stimulus, Imaizumi et al. (2015) suggested that the improved postural stability in people with migraine by adding the 30-second interval between stimulus presentation and recording of postural sway might be due the decay of MAE. The authors, however, did not directly measure the MAE to the rotating snake illusion.

In addition, Imaizumi et al. (2015) also used a control stimulus (colour sequence reversed in every flanking unit) in their second experiment. The strength of the illusion based on a subjective rating scale (0-10; 0=no illusion, 10=strongest illusion) for the illusory pattern was higher than the control pattern in both migraine and control participants. However, the postural sway after viewing both stimuli was not different. As both the illusory and control stimuli contained the same spatial frequency and contrast, Imaizumi et al. (2015) have alternatively suggested that the postural sway might not be affected by motion illusion strength. Instead, it might be associated with the visual discomfort induced by repetitive patterns, similar in mechanism to the visual discomfort induced by high contrast striped patterns as proposed by Wilkins et al. (1984). To date, no study has considered whether visual discomfort is related to visual performance on a motion illusion task, even though people with migraine report more illusory motion and visual discomfort, separately. Measuring motion illusion strength quantitatively might reveal differences in between people with and without migraine that correlate with self-reported visual discomfort, which has not been systematically explored to date.

1.8 Aims and hypotheses

The main aim of this thesis is to quantitatively compare motion illusion strength in people with and without migraine. The quantitative measure of motion illusion can then be used to investigate the relationship between motion illusion strength and self-reported visual discomfort. This thesis also determines whether abnormal contrast and motion processing contribute to motion illusion strength, if any.

The first experiment, which is a short pilot with 4 observers, aimed to choose the stimulus to be used in experiment 2 among five types of 'optimised' Fraser-Wilcox illusion. A priori knowledge of which type would elicit the strongest illusion is not available. It was hypothesised that

H1: Motion illusion strength will be different between different types of the Fraser-Wilcox illusion.

The aim of the second experiment was to investigate the association between motion illusion and visual discomfort in migraine. More specifically, the two questions asked in this thesis were: a) Is there any difference between migraine with aura (MA), migraine without aura (MO) and controls in motion illusion strength? b) Is motion illusion strength correlated with self-reported visual discomfort scores? The following hypotheses were tested.

H2: Motion illusion strength will be larger in people with migraine.

H3a: People with migraine will report larger discomfort scores.

H3b: Greater strength of motion illusion will be correlated with higher visual discomfort scores.

Pattern illusions that are reported by people with migraine for striped patterns are not considered to result from altered eye movements because no difference in saccadic eye movements or fixation stability has been found between people with migraine and controls(Wilkinson et al. 2006). Therefore, if people with migraine report a different strength of motion illusion, the likely candidate mechanisms are contrast and motion processing abnormalities. As reviewed in this chapter, extensive previous literature points to contrast and motion processing abnormalities in migraine. Therefore, it was hypothesised that:

H4: Contrast discrimination threshold will be different between groups.

H5: Motion sensitivity will be different between groups.

The aim of the third experiment was to investigate what contributes to individual differences in illusion strength, in particular a) Does contrast discrimination threshold contribute to illusion strength? b) Does motion sensitivity contribute to illusion strength? The following hypotheses were tested.

H6: Contrast discrimination threshold will be correlated with illusion strength.

H7: Motion sensitivity will be correlated with illusion strength.

Chapter 2 Participant selection and general methods

2.1 Introduction

This chapter describes the common methods shared in all experiments, including the recruitment and screening process of the participants. Experiment 1 determined the stimulus that was used to quantify motion illusion in Experiment 2. Experiment 2 tested the hypotheses that migraine would affect motion illusion strength and subjective visual discomfort scores. Experiment 3 tested the hypotheses that migraine would affect contrast and motion sensitivity, and that contrast and motion processing would be related to the strength of motion illusion. Further experimental methods specific to each experiment are detailed in their respective chapters, Chapters 3, 4 and 5.

2.2 Participants

2.2.1 Ethics

The experimental protocol was in accordance with the Declaration of Helsinki and approved by the University of Melbourne Human Research Ethics Committee (HREC #1749823.2). All participants gave written informed consent (Appendix 1) after reading a Plain Language Statement (Appendix 2). Each participant attended one session of approximately 2-hours duration and was given a $20 gift voucher to contribute to any out of pocket costs incurred in attending.

2.2.2 Recruitment

Participants were recruited from noticeboard advertisements posted on campus at the University of Melbourne, by invitation to previous participants on the laboratory database, and via electronic advertisements posted on e-noticeboards and mailing lists such as the University of Melbourne Staff News, Melbourne Neuroscience Institute newsletter, My Unimelb student portal notices board, and Headache Australia's 'Participate in research' page.

2.2.3 Eligibility criteria

All participants were required to meet the following inclusion criteria (measured during the vision screening as part of their tests visits): visual acuity better than or equal to 6/7.5;

refractive error within ± 5.00D sphere and less than -2.00D cylinder; clear ocular media as observed during an ophthalmic slit lamp examination; no previous ocular surgery, ocular disease, medications or systemic conditions that can affect vision and cognitive functions (e.g. diabetes, antidepressant use). Control participants had to experience fewer than 4 headaches per year, which were not accompanied by other typical migraine symptoms (e.g. photophobia, phonophobia, nausea and/or vomiting) and were attributable to self-identifiable reasons (e.g. flu and dehydration). Migraine without aura (MO) and migraine with aura (MA) participants satisfied the criteria for 'migraine without aura' and 'migraine with typical aura with headache' according to the International Classification of Headache Disorders 3rd edition (ICHD-3) as described in Table 2-1 (Headache Classification Committee, International Headache Society, 2018). Headache and migraine conditions were assessed through phone interviews before the test visit. Migraine participants were contacted the day before the appointment to check recency of migraine events, which allowed individuals who had experienced a migraine attack within 3 days of the proposed test session to be rescheduled.

2.3 Questionnaires

All participants completed a headache questionnaire and a visual discomfort questionnaire, which were developed in the laboratory to assist in confirming a migraine diagnosis and to characterise the level of visual discomfort associated with headache and migraine. Participants in the migraine group completed an additional Migraine Disability Assessment (MIDAS) questionnaire which assesses migraine induced days of absence and days with reduced productivity at work or school, family, social, leisure activities in the past 3 months (Stewart et al. 2001).

Days since last migraine, age at the first migraine, and number of migraines in the last year of the migraine participants in this study are summarised in Table 2-2. An estimation of lifetime migraine events was calculated by Equation 2-1.

$$\begin{aligned} &Estimated\ numbers\ of\ migraine\ in\ life \\ &= (age - age\ of\ first\ migraine) \\ &\times migraine\ in\ the\ last\ year \end{aligned}$$

(Equation 2-1)

Table 1-1 Inclusion criteria for the two migraine groups included in this study, according to the International Classification of Headache Disorders (3rd edition, ICHD-3), Headache Classification Committee, International Headache Society (2018).

Migraine without aura	A. At least five attacks fulfilling criteria B-D B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated) C. Headache has at least two of the following four characteristics: 1. unilateral location 2. pulsating quality 3. moderate or severe pain intensity 4. aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs) D. During headache at least one of the following: 1. nausea and/or vomiting 2. photophobia and phonophobia E. Not better accounted for by another ICHD-3 diagnosis.
Migraine with typical aura	A. At least two attacks fulfilling criteria B and C B. Aura with both of the following: 1. fully reversible visual, sensory and/or speech/language symptoms 2. no motor, brainstem or retinal symptoms. C. At least three of the following six characteristics: 1. at least one aura symptom spreads gradually over ≥5 minutes 2. two or more aura symptoms occur in succession 3. each individual aura symptom lasts 5-60 minutes 4. at least one aura symptom is unilateral 5. at least one aura symptom is positive 6. the aura is accompanied, or followed within 60 minutes, by headache D. Not better accounted for by another ICHD-3 diagnosis.

Table 1-2 Headache questionnaire

(1)	Do you suffer from headaches? If no, you are not required to answer any further questions.	Yes	No
(2)	Can you sense when you are about to have a headache before the onset of headache pain?	Yes	No
(3)	Does your headache compel you to lie down?	Yes	No
(4)	Do lights and noise bother you close to or with your headache?	Yes	No
(5)	Do you experience nausea or vomiting close to or with the headache?	Yes	No
(6)	Do you have any visual disturbances close to or with the headache? If yes, please describe your visual disturbances (eg. what do they look like, which side of your vision, how long do they last etc)	Yes	No
(7)	Do you take any medications to relieve your headaches? If yes, which medications?	Yes	No
(8)	Have you even been diagnosed by your doctor to have migraines?	Yes	No
(9)	How old were you when you experienced your first migraine?		
(10)	How many migraines have you had in the past year?		
(11)	How long since the end of your last migraine?		

The visual discomfort questionnaire (Table 2-3) was created based on the items used in a series of studies to assess self-reported visual discomfort (Shepherd 2000, Harle et al. 2006, Shepherd 2006). Participants self-reported the frequency of experiencing 1) a migraine, 2) a headache, and 3) discomfort, after viewing the listed types of visual stimuli. Control participants did not respond to the migraine related component. Answers of 'often', 'sometimes' and 'never' were scored with values of 2, 1, and 0 respectively. Three sum scores of migraine, headache, and discomfort were calculated for each participant. These are referred to as 'questionnaire discomfort score', 'questionnaire headache trigger score', and 'questionnaire migraine trigger score' later in this thesis.

Table 1-3 Visual discomfort questionnaire

	1			2			3		
Visual stimuli	migraine			headache (non-migraine)			discomfort		
	often	sometimes	never	often	sometimes	never	often	sometimes	never
direct sunlight									
car headlights at night									
shafts of light coming through trees or venetian blinds									
sunlight on water, snow or modern buildings									
contrasting patterns on materials, wallpapers or pictures									
fluorescent lights									
glare from computer, TV or phone screens									
particular colours									
other visual stimuli									

2.4 Equipment

The experiments were conducted in a room with no lights on. The stimuli were presented on a CRT monitor via a ViSaGe graphics system running in 8-bit depth (Cambridge Research Systems, Kent, UK). Due to ageing of the monitor used for experiment 1 (Sony GDM F-520; refresh rate: 80Hz; resolution: 1232 $\times$ 923 pixels; maximum luminance: 98 cd/m^2), another monitor was used for experiment 2 and 3 (ViewSonic G90fB; refresh rate: 80Hz; resolution: 1232 $\times$ 923 pixels; maximum luminance: 140 cd/m^2). Automated gamma correction was performed using a ColorCal photometer (Cambridge Research System, Kent, UK) interfaced with the inbuilt gamma correction software supplied by Cambridge Research Systems for use with the ViSaGe. The monitor was calibrated approximately once a week to maintain a linear relationship between the output luminance and the electron-gun voltage.

For the experimental testing, responses were collected through a CB6 button box (Cambridge Research Systems, Kent, UK). Participants maintained a working distance of 57cm with a chinrest, and their left eyes were covered by a white plastic opaque eye patch as per Hisakata and Murakami (2008). Refractive correction was provided if required. A small mirror was positioned below the monitor to allow the researcher to manually check participants' fixation throughout the experiment.

2.5 Power analysis

A power analysis was conducted using G*power (Version 3.1.3, Heinrich Heine Universität, Düsseldorf, Germany)(Faul et al. 2007, Faul et al. 2009). Given that the first set of hypotheses were related to differences between migraine and non-headache control groups, and no studies to date have measured motion illusion strength differences between groups, the power analysis was based on previous literature that report group differences in pattern sensitivity scores, as an indicator of visual discomfort (Shepherd et al. 2012). The mean pattern sensitivity score ($\pm$ standard deviation) reported in Shepherd et al. (2012) was 2.5 $\pm$ 1.4 (n=28; 14 MA and 14 MO) for the migraine group and 1.4 $\pm$ 1.5 (n=14) for the control group, which resulted in the effect size of 0.76.

A sample size of n = 23 in each group (migraine, control) achieved a power of 0.81 (alpha = 0.05) with a (moderate) effect size of the group difference of 0.76. As there is conjecture in the literature about whether MO and MA groups perform differently on visual tasks, in this thesis the migraine subtypes were treated as separate groups. Hence, our sample size calculations also took into consideration previous work reporting differences in contrast and motion perception between MO, MA, and non-headache control groups (e.g. 25 control, 22 MO, 25 MA in (McColl and Wilkinson 2000); 21 control, 17 MO, 19 MA in (McKendrick and Badcock 2004)). The sample size for the migraine group in total included 36 participants, consisting of 20 MO and 16 MA participants. The control group included 20 headache free participants.

2.6 Statistical analysis

All analyses were conducted using SPSS Statistics 23 (IBM, NY, USA). Shapiro-Wilk normality tests were conducted for each measure to determine the appropriate statistical tests for between group comparisons and correlations between tasks. Where the data were normally distributed, an analysis of variance (ANOVA) was used. Kruskal-Wallis tests were used to replace a one-way ANOVA for non-normally distributed data. Friedman tests were used as the non-parametric equivalent to repeated measures ANOVA. Dunn-Bonferroni post hoc tests were conducted to determine the significant pairs from Friedman tests. The adjusted significance (adj. sig) was calculated by multiplying the p-values by the number of comparisons being conducted. Data were log transformed when mixed ANOVA was needed for non-normally distributed data. Tukey's post hoc test was used to determine the significant pairs from a mixed ANOVA. Since non-normally distributed data were involved in all correlation tests in this thesis, Spearman correlations were performed to determine the relationships between measurements. A Holm-Bonferroni correction was used to counteract multiple testing. P-values of less than 0.05 were considered significant. Partial omega squared (ω_p^2) was used as a measure of effect size for ANOVA (Equation 2-2). The eta squared (η_H^2) adapted for non-parametric tests was reported as effect size for Kruskal-Wallis tests (Equation 2-3). Degree of concordance (Kendall's W) was reported for Friedman test (Equation 2-4). Unstandardized effect size of significant pairwise comparison was reported as mean difference with 95% confidence interval (95CI) of difference for normally

distributed data, and median difference (within subject) or difference in median (between subject) for non-normally distributed data. Standardised mean difference effect size for within subject design (Cohen's d_{av}; Equation 2-5) was also reported for differences between stimulus condition, since there was only significant main effect of conditions in the mixed ANOVA.

$$\omega_p{}^2 = \frac{df_{effect} \times (MS_{effect} - MS_{error})}{df_{effect} \times MS_{effect} + (N - df_{effect}) \times MS_{error}} \quad (Equation\ 2 - 2)$$

$$\eta_H{}^2 = \frac{\chi^2 - k + 1}{N - k} \quad (Equation\ 2 - 3)$$

$$W = \frac{\chi^2}{N(k-1)} \quad (Equation\ 2 - 4)$$

$$d_{av} = \frac{M_{diff}}{\frac{SD_1 + SD_2}{2}} \quad (Equation\ 2 - 5)$$

df_{effect} = effect degrees of freedom; MS_{effect} = effect mean sum of square; MS_{error} = error mean sum of square; N = sample size; k = number of measurements per subject; M_{diff} = mean of difference between stimulus type; SD = standard deviation

Chapter 3 Choosing the preferred version of the Fraser-Wilcox illusion

3.1 Introduction

In brief, the Fraser-Wilcox illusion consists of patterns with repetitive luminance steps forming a wheel (Fraser and Wilcox 1979). As mentioned in Chapter 1, a range of factors (observer's fixation stability, blink rate, and retinal illuminance; stimulus eccentricity and contrast levels) are known to affect the strength of the Fraser-Wilcox illusion. The order of the underlying luminance sequence (e.g. black – dark grey – white – light grey) is critical for eliciting the motion illusion (Kitaoka and Ashida 2003). Several Fraser-Wilcox illusion versions comprised of different luminance step profiles with the same mean luminance have been reported in the literature (Kitaoka 2017). However, no previous studies have compared their illusion strengths quantitatively. This pilot experiment aimed to determine the luminance profile with the biggest dynamic range of motion speeds, with the intent of then using that stimulus in the group comparison experiments in Chapter 4 (Experiment 2). In this Chapter, cancellation speeds of the five 'optimized' Fraser-Wilcox illusions according to Kitaoka (2017) were compared. It was hypothesised that:

> H1: There will be differences between the motion illusion strengths elicited by the five types of luminance profiles.

3.2 Methods

3.2.1 Participants

Four headache free people participated in this experiment (see Table 3-1 for demographics), and all met the inclusion criteria for control participants as described in Chapter 2.

Table 1-1 Demographics of the participants in Experiment 1.

id	Age	Gender	RE refractive error (dioptre)	VA	Naïve to experimental purpose
A	22	male	-4.50	6/6	Y
B	32	female	-4.25/-1.25×50	6/6	N
C	30	female	plano	6/6	Y
D	19	male	plano	6/4.8-1	Y

3.2.2 Stimuli

Stimuli were produced using custom software written in MATLAB R2010a (The MathWorks Inc., Natick, Massachusetts) using the CRS Toolbox (Cambridge Research Systems, Kent, UK). The equations used to calculate the luminance profiles for each stimulus type that were previously used are not published or available. Hence, for this experiment, the five types of luminance profile classified by Kitaoka (2017) as the 'optimised' Fraser-Wilcox illusion (Figure 3-1) were generated here (Figure 3-2) only to approximate the shapes of the luminance profiles as depicted by Kitaoka.

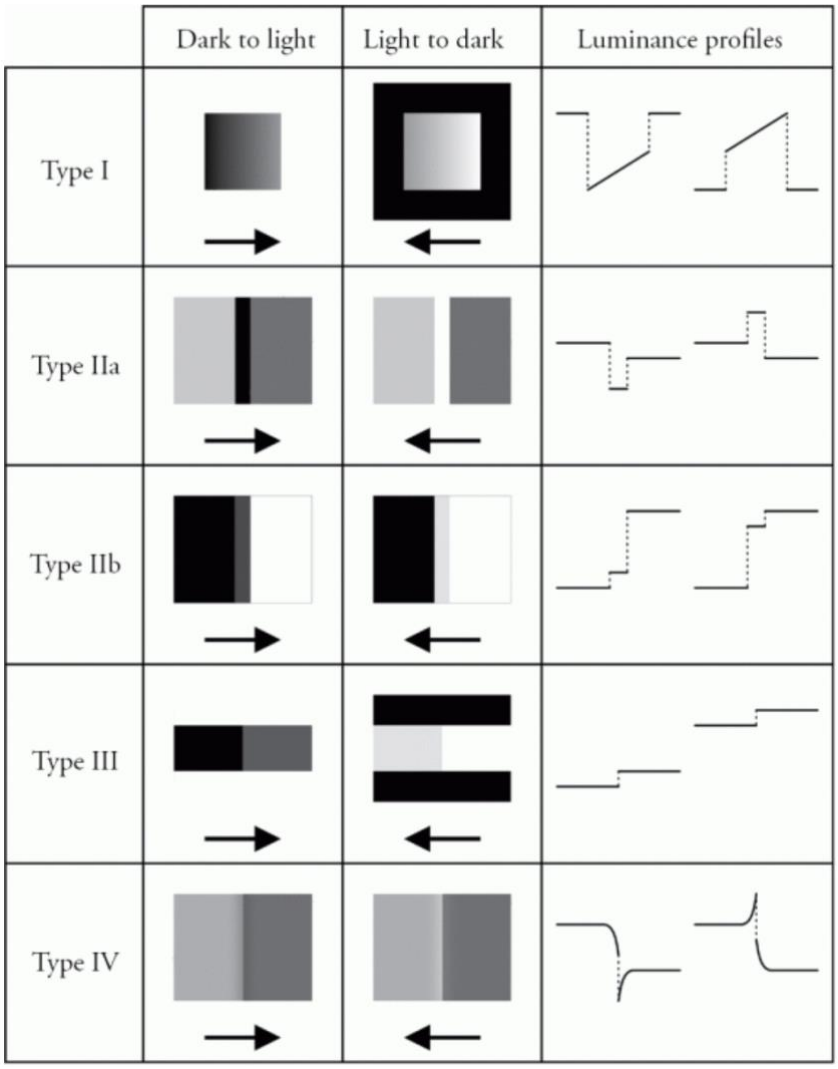

Figure 3-1 Classification of the five types of 'optimised' Fraser-Wilcox illusion. Reprinted from Shapiro, Arthur G. 'The Fraser-Wilcox and its extension' in The Oxford Compendium of Visual Illusions. pp. 504. Copyright (2017) by Oxford Publishing Ltd. Reproduced with permission of the Licensor through PLSclear.

The equations used to generate the luminance profiles (top row, Figure 3-2) are detailed in Appendix 3. Gaussian blur with standard deviation of 4 was applied to the original luminance profiles distributed in 1×256 matrices (Hisakata and Murakami, 2008) to remove zigzag transitions between abrupt luminance steps (second row from top, Figure 3-2).

The smoothed luminance profiles of each type were circularly repeated in two directions to generate either a clockwise or counterclockwise illusory motion in the wheel pattern (Figure 3-3). The outer and inner diameters of the ring shape were 7° and 1° respectively. In each trial, rotatory motion was added to the pattern, which could be either in the same or opposite direction to the illusory motion direction.

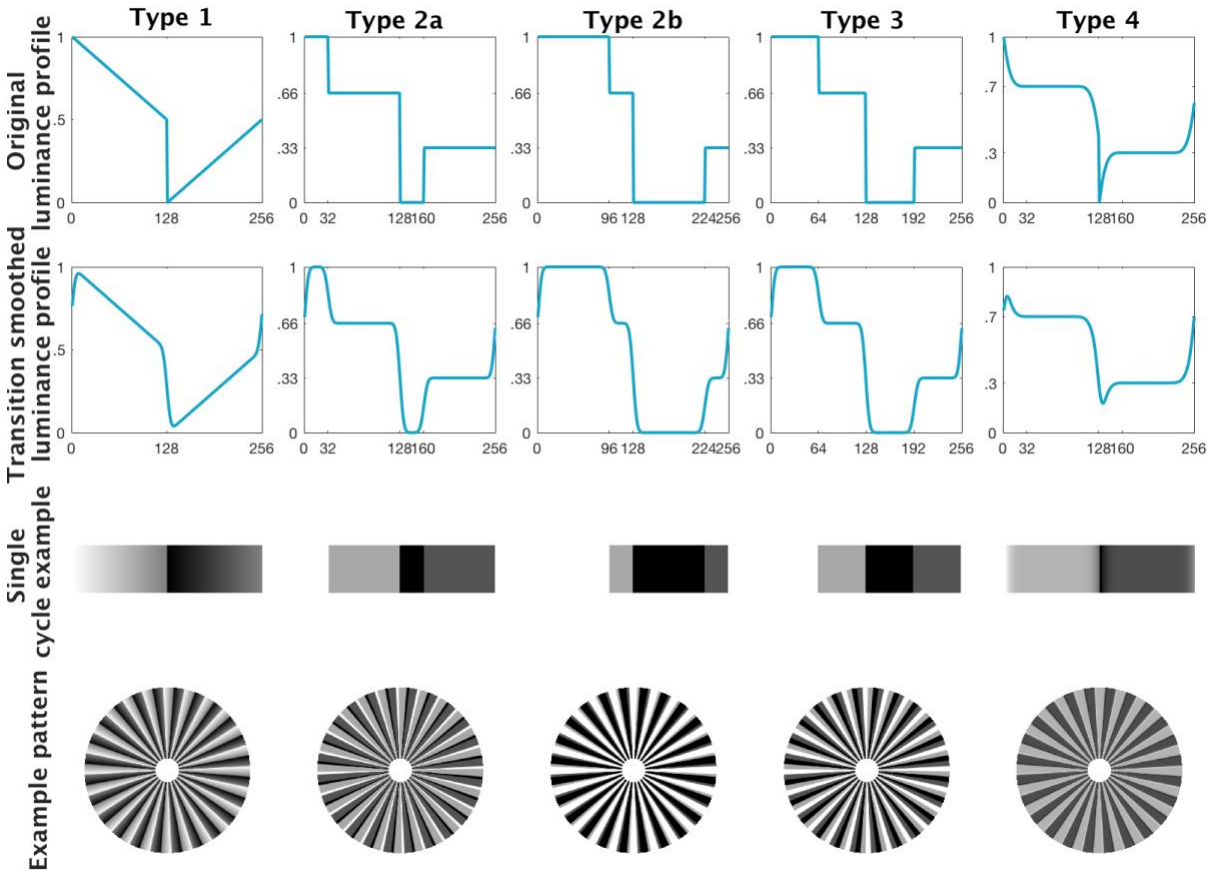

Figure 3-2 Demonstration of the luminance profile and example pattern in clockwise direction of each type of stimulus. The Y-axis represents an arbitrary number proportional to the absolute luminance level, where 1=white, 0=black. X-axis represents locations in the colour lookup table.

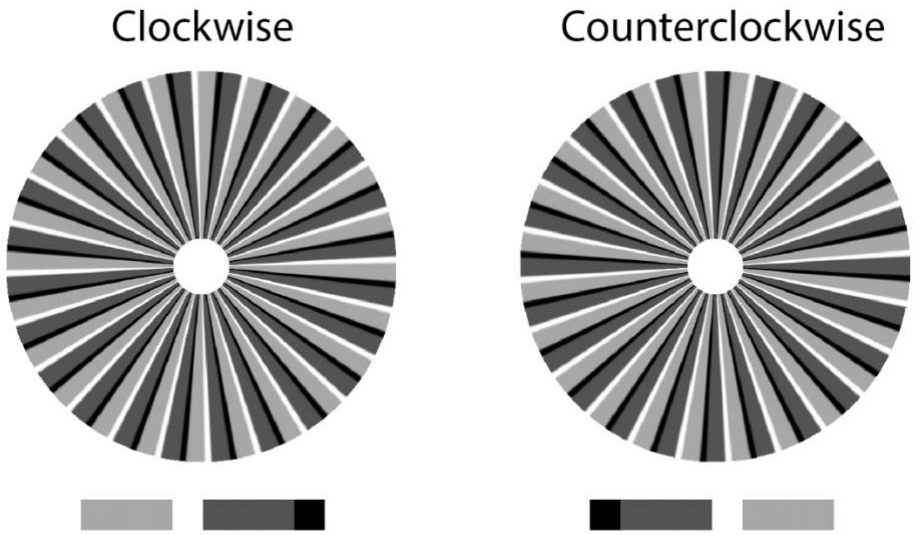

Figure 3-3 An example of the two pattern directions (clockwise and counterclockwise) of the type 2a pattern. The bar below each stimuli indicates the luminance profile steps.

3.2.3 Procedure

A method of constant stimuli with two-alternative forced choice was used to obtain estimates of motion illusion strengths. On each trial, one wheel pattern was displayed for 500ms on a white (98 cd/m^2) background with a black fixation dot (diameter = 0.224°; see Figure 3-4). The target was displayed eccentrically (12°) to enhance the illusion (Hisakata & Murakami, 2008). Participants indicated whether the pattern appeared to rotate in a clockwise (right button) or counterclockwise direction (left button) by pressing a button. They were instructed to balance left and right button presses when they could not decide the rotation direction or did not see any movement. An auditory tone was provided to indicate that a response had been received but no feedback on whether the response was "correct" was provided.

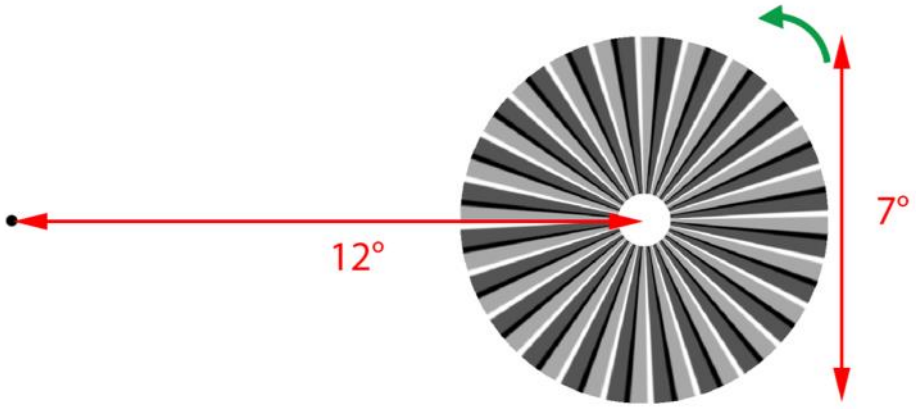

Figure 3-4 Spatial configuration of the motion illusion stimulus.

Performance on the task was measured as a function of speed of rotation. There were 14 conditions for each luminance profile type which consisted of 7 physical rotation speeds of both counterclockwise and clockwise patterns. Five repeats of the 14 conditions were block randomised in each run. Participants were trained on the task and completed at least one preliminary run to familiarise themselves with the task. After training with all types of luminance profile, the final speed ranges for each type were determined based on individual results of practice runs (actual speeds used for each participant are shown in Figure 3-6). Then, a total of 20 runs (4 runs × 5 profile types) were randomly interleaved. For participants A, B, and C, the data were collected from 2 sessions on separate days, and participant D completed the tests within one session. Participants were allowed to take breaks in between runs whenever needed.

3.2.4 Data analysis

To fit the psychometric function, pain-free Bayesian inference (Kuss et al. 2005) were conducted through the 'psignifit 4' MATLAB toolbox developed by Schütt et al. (2016). A cumulative normal function was fit to the probability of choosing counterclockwise as a function of physical rotation speed. Implemented formula are listed in Equations 3-1 to 3-3.

$$\psi(x; m, w, \lambda, \gamma) = \gamma + (1 - \lambda - \gamma)S(x; m, w) \quad \textit{(Equation 3-1)}$$

$$S(x; m, w) = \Phi\left(C\frac{x-m}{w}\right) \quad \textit{(Equation 3-2)}$$

$$C = \Phi^{-1}(.95) - \Phi^{-1}(.05) \quad \textit{(Equation 3-3)}$$

The psychometric function (ψ) is a sigmoid function (S) scaled by upper (λ; the probability of choosing clockwise at infinitely high counterclockwise rotation speed) and lower (γ; the

probability of choosing counterclockwise at infinitely high clockwise rotation speed) asymptotes. In this case, equal asymptotes were assumed ($\gamma = \lambda$). The cumulative standard normal function (Φ) is determined by the stimulus intensity (x; physical rotation speed), the threshold (m; the physical rotation speed at which $S = 0.5$), and the width (w; the difference between rotation speeds at which $S = 0.05$ and $S = 0.95$).

The strength of motion illusion was quantified by the rotation speed of real motion at which the illusory motion in the opposite direction was cancelled. The estimate of the cancellation speed for each luminance profile type was defined by half of the absolute difference between the means of psychometric functions of both patterns (Figure 3-5). The calculation of cancellation is modified from Hisakata & Murakami (2008) in which the mean of the absolute values of the means of the two psychometric functions was calculated.

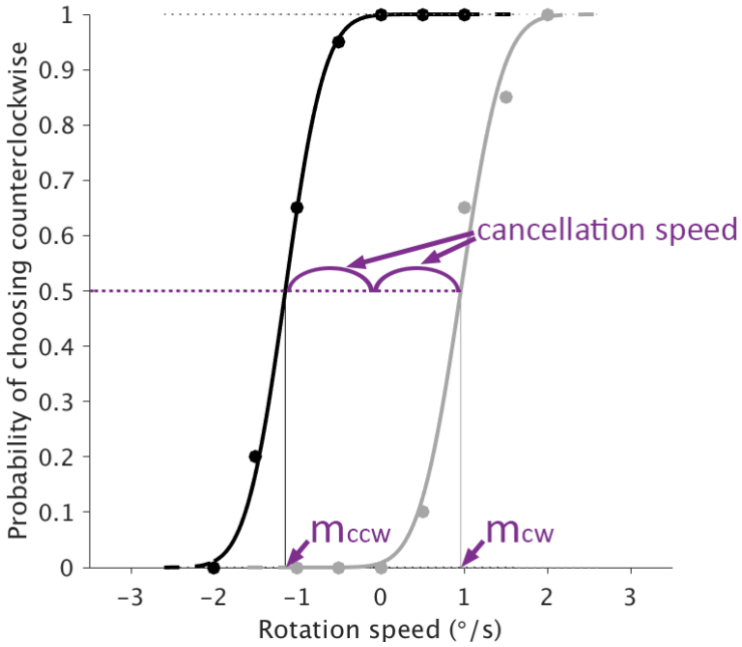

Figure 3-5 Demonstration of calculation of the cancellation speed of one example participant. Grey = clockwise pattern, black = counterclockwise pattern. Positive rotation speed corresponds to counterclockwise. The cancellation speed was calculated as half of the absolute difference between the mean of the psychometic functions of the clockwise (m_{cw}) and the counterclockwise (m_{ccw}) patterns.

3.3 Results

Individual psychometric functions for the five patterns tested are shown in Figure 3-6. The calculated cancellation speeds of the psychometric functions of Figure 3-6 are plotted in Figure 3-7. The hypothesis (H1) that there would be a significant difference in the perceived cancellation speed between different types of luminance profiles was supported (Friedman test; χ^2 (4) = 14.40, p = 0.006, W = 0.9). Dunn-Bonferroni post hoc tests identified significant differences only between the type 2a and type 2b stimulus (adj. sig = 0.02, median of difference = 0.84°/s) and between the type 2a and type 4 stimulus (adj. sig = 0.02, median of difference = 0.90°/s), where type 2a consistently produced the stronger illusion of the pairs. All other comparisons were not significant.

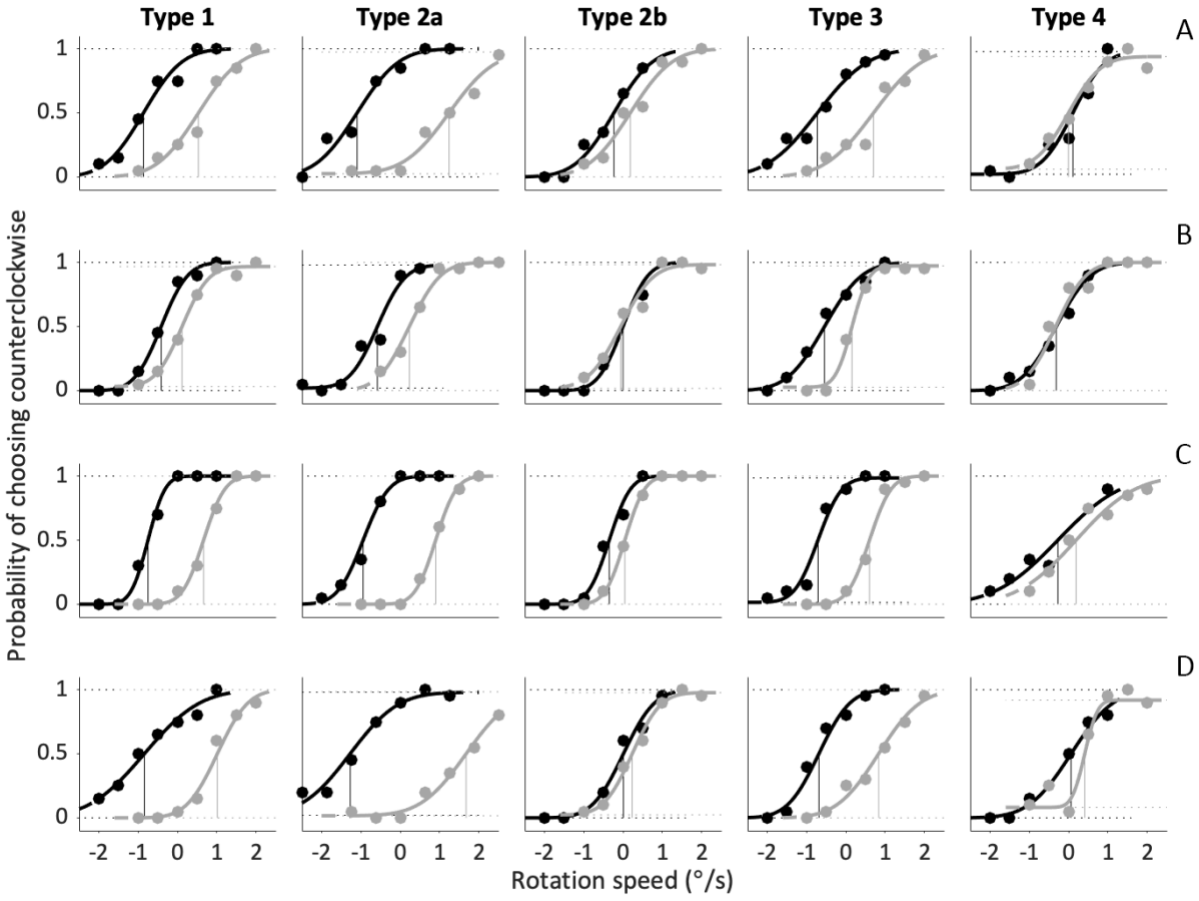

Figure 3-6 Individual results (symbols) for the 5 types of luminance profiles fitted with psychometric functions (solid lines). Each row represents one participant. Grey = clockwise pattern, black = counterclockwise pattern. Positive rotation speed corresponds to counterclockwise.

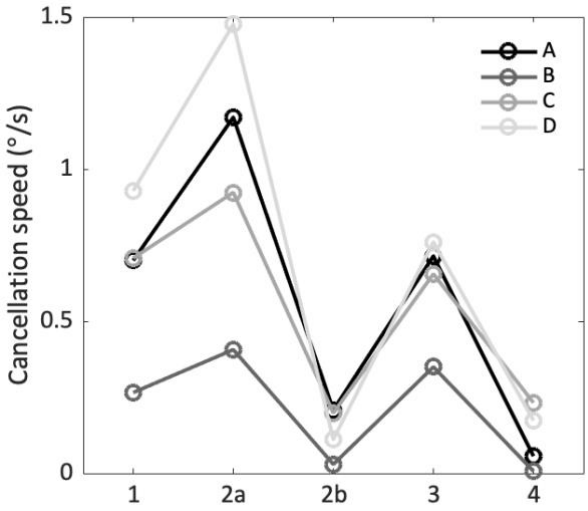

Figure 3-7 Summary plot of the cancellation speed of each participant and luminance profile type. Each shade represents one participant. The higher the cancellation speed, the stronger the illusion.

3.4 Summary

Experiment 1 aimed to identify which of the five classified 'optimised' Fraser-Wilcox illusion (Kitaoka 2017) generates the strongest motion illusion, to be used in the following experiments. Motion illusion strength defined by cancellation speed was compared among the five luminance profiles. Type 2a generated significantly stronger cancellation speeds than type 2b and type 4, however, type 1 and type 3 were not significantly different from any of the other types. The results suggest that type 2a is more likely to produce a stronger and more robust effect. Therefore, type 2a was determined to be the stimulus to be used in experiment 2 (Chapter 4).

Chapter 4 Motion illusion strength, visual discomfort score and migraine

4.1 Introduction

Previous studies have suggested that people with migraine are more susceptible to visual illusions and experience more discomfort induced by visual stimuli in their environment (Harle et al. 2006). Greater postural sway magnitude after viewing the rotating snake illusion has also been reported in people with migraine compared to non-migraine participants (Imaizumi et al. 2015). Imaizumi et al. (2015) suggested that the greater postural sway in migraine participants might reflect greater susceptibility to illusory motion and greater visual stress, which the authors presume is a similar process as the striped pattern induced visual discomfort. However, there was no measurement of visual stress in their study. In this chapter, perceived illusory rotating speed was compared between migraine without aura (MO), migraine with aura with headache (MA), and control groups, and its relationship with a subjective visual discomfort score was measured. The following hypotheses were tested:

H2: Motion illusion strength will be larger in people with migraine.

H3a: The strength of the motion illusion will be positively correlated with visual discomfort scores.

H3b: People with migraine will report more discomfort induced by visual stimuli.

4.2 Methods

4.2.1 Participants

Individual and group age and gender are shown in Figure 4-1. Age range and gender ratio (minimum-maximum; male:female) for each group were: control (19-44 years; 10:10), MO (18-46 years; 7:13), MA (19-42 years; 9:7). Kruskal-Wallis test showed there was no significant difference between the three groups in age ($p = 0.77$) and Pearson chi-square test suggested no significant difference in proportions of gender ratio between groups ($p = 0.41$).

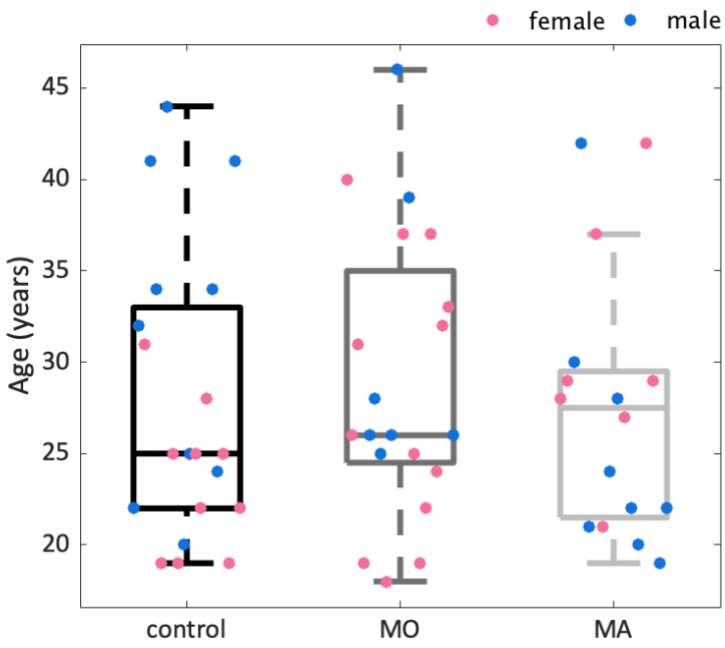

Figure 4-1 Age and gender of individual participants of each group. Pink markers represent female participants, blue markers represent male participants. Boxes describe median, 25th and 75th percentile. Each whisker extends to the data point nearest to 1.5 times the interquartile range.

Migraine participants were tested at least 3 days after a migraine attack to ensure they were not in the postdrome phase. Kruskal-Wallis test showed all three migraine characteristics were not statistically different between the two migraine groups ($p = 0.18$ for estimated numbers of migraine in life, $p = 0.23$ for MIDAS score, $p = 0.42$ for days since last migraine). Group and individual results are shown in Figure 4-2.

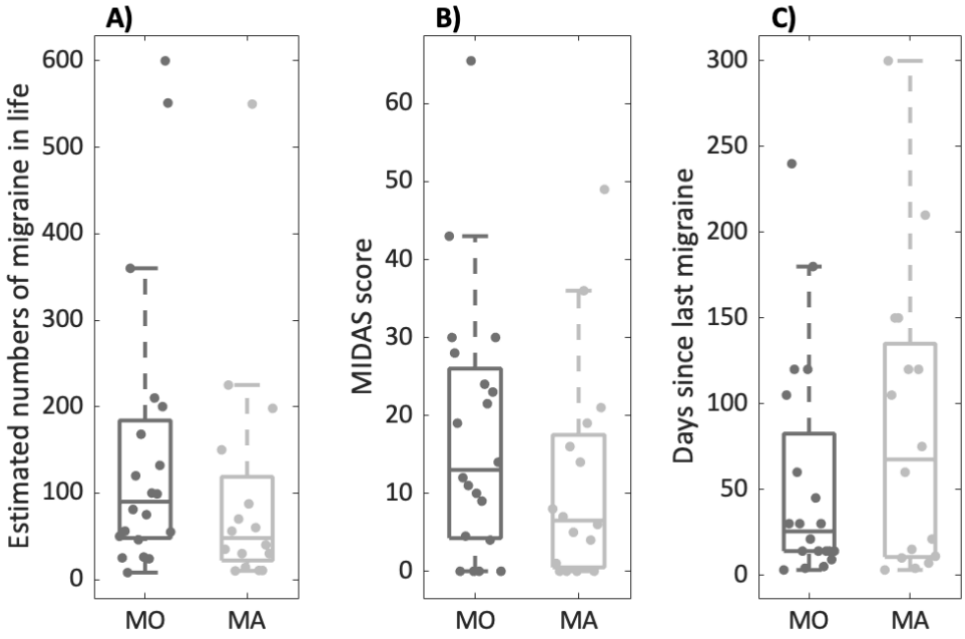

Figure 4-2 Migraine demographics of the two migraine groups. MO(darker) n = 20; MA (lighter) n = 16. Boxes describe median, 25th and 75th percentile. Each whisker extends to the data point nearest to 1.5 times the interquartile range.

4.2.2 Procedure

The methods for this experiment have been detailed in the two previous chapters. In brief, the strength of the motion illusion for a type 2A stimulus (Kitaoka 2017) was measured by cancellation speed (see Chapter 3, page 45). Each participant was given two practice runs to familiarise them with the task and allow determination of a suitable test range of rotation speeds for the actual test. The practice runs consisted of 3 repeats of 9 rotation speeds. The maximum real rotating speed was 3°/s for the first practice run, which was then adjusted based on individual performance. Each participant then performed 4 runs each with 5 repeats of 7 rotation speeds using a fixed speed range. Visual discomfort was measured by questionnaire discomfort score, questionnaire headache trigger score, and questionnaire migraine trigger score using the questionnaire shown in Chapter 2 (Table 2-3; page 41).

4.3 Results

4.3.1 Comparing illusion strength

One-way ANOVA showed there was no significant difference in cancellation speeds between groups ($F(2,53) = 0.52$, $p = 0.60$), which did not support the hypothesis that people with migraine would see a faster illusory motion (H2). The results suggested that people with migraine, regardless of aura status, did not perceive faster illusory motion than the headache free controls. Group and individual cancellation speeds are plotted in Figure 4-3. Individual psychometric functions are shown in Appendix 4. Since the illusion strength was not statistically different between groups, participants were pooled into a single group to run the correlation tests between illusion strength and visual discomfort scores.

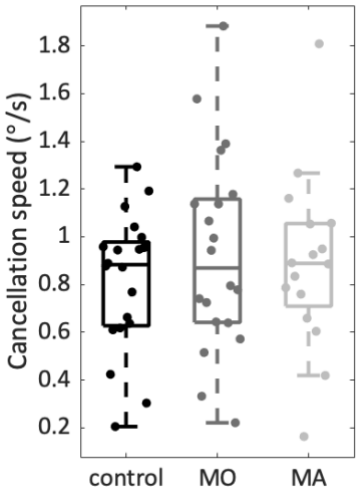

Figure 4-3 Group and individual cancellation speeds. control (dark) n = 20; MO (medium) n = 20; MA (light) n = 16. Boxes describe median, 25th and 75th percentile. Each whisker extends to the data point nearest to 1.5 times the interquartile range.

4.3.2 Visual discomfort questionnaire scores and motion illusion

H3a hypothesised that greater cancellation speed would be associated with more frequent visual stimulus induced discomfort. Cancellation speed as a function of A) questionnaire discomfort score; B) questionnaire headache trigger score; C) questionnaire migraine trigger score are plotted in the top panel of Figure 4-4. H3a was not supported as the cancellation speed was not significantly correlated with questionnaire discomfort score (rho = 0.19, p =

0.16), questionnaire headache trigger score (rho = 0.15, p = 0.25) or questionnaire migraine trigger score (rho = -0.05, p = 0.78). The results suggest that the perceived speed of the motion illusion was not related to self-reported frequency of experiencing visual stimuli induced discomfort, headache or migraine.

H3b hypothesised that people with migraine would experience more visual discomfort. Group and individual questionnaire scores are shown in Figure 4-4-D. Kruskal-Wallis tests showed a significant group difference in questionnaire discomfort score ($\chi^2(2) = 12.69$, p = 0.002, mean rank score of 19.20 for control, 29.93 for MO and 38.34 for MA, $\eta_H^2 = 0.23$), and questionnaire headache trigger score ($\chi^2(2) = 23.68$, $p < 0.001$, mean rank score of 14.88 for control, 35.93 for MO and 36.25 for MA, $\eta_H^2 = 0.43$). The MA and MO groups were not significantly different in questionnaire migraine trigger score ($\chi^2(1) = 3.64$, p = 0.06, mean rank score of 21.45 for MO and 14.81 for MA). Dunn-Bonferroni post hoc tests showed that the questionnaire discomfort score of the control group was significantly lower than that of the MA group (adj.sig = 0.001, difference of median = 4), whereas the MO group was neither significantly different from controls (adj.sig = 0.11) nor from those with MA (adj.sig = 0.36). Therefore, H3b was partially supported. The questionnaire headache trigger score of the control group was also significantly lower than that of the MO (adj.sig < 0.001, difference of median = 4) and MA groups (adj.sig < 0.001, difference of median = 3), but the two migraine groups were not significantly different from each other (adj.sig = 1). The results indicate that the MA participants reported a higher frequency of experiencing visual induced discomfort than headache free controls, while MO was neither statistically different from control nor MA. The self-reported frequency of visual stimuli triggered non-migraine headaches and migraine attacks were both not significantly different between the two migraine groups.

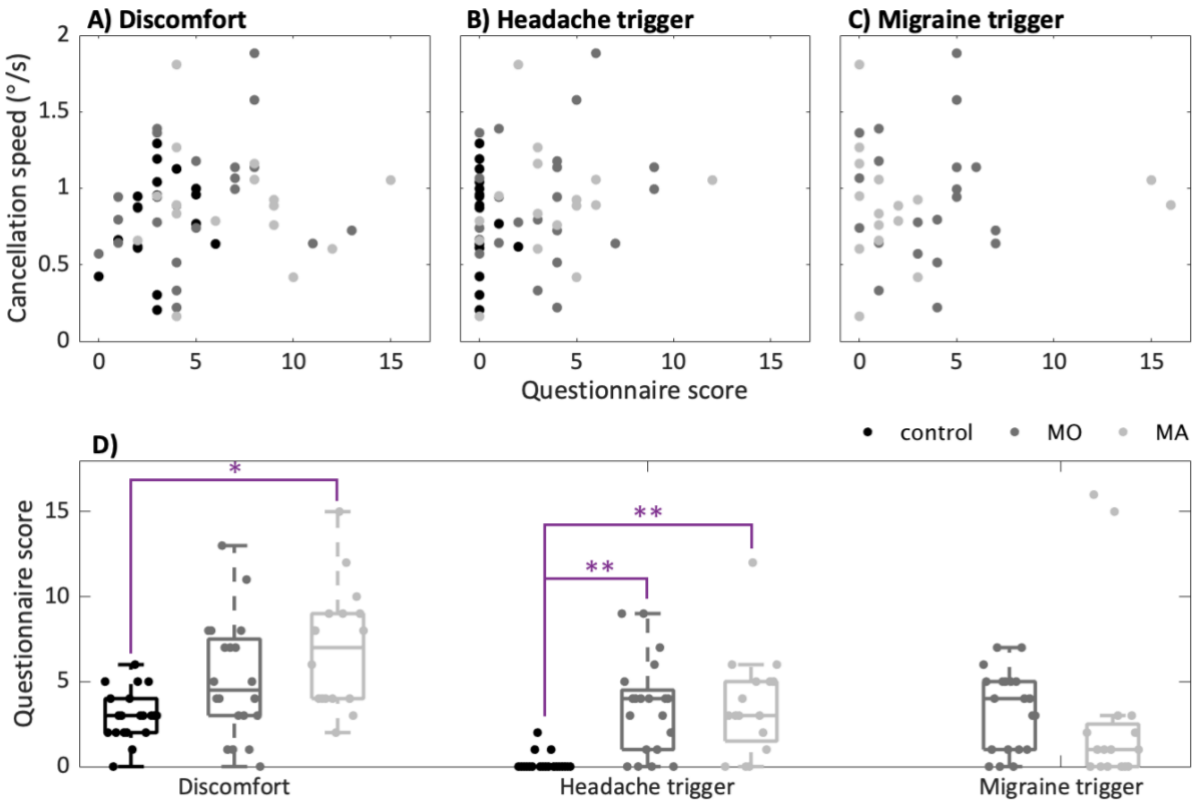

*Figure 4-4 Top panel: Cancellation speeds as a function of questionnaire scores (from the left: n = 56 for discomfort and headache trigger scores; n = 36 for migraine trigger score). Marker shades: darker = control; medium = MO; lighter = MA. Bottom panel: Group and individual questionnaire scores. control (darker) n = 20; MO (medium) n = 20; MA (lighter) n = 16. * indicates the significance level of p < 0.5, and ** indicates the significance level of p < 0.001. Boxes describe median, 25th and 75th percentiles. Each whisker extends to the data point nearest to 1.5 times the interquartile range.*

Percentage positive responses for each option for the individual items of the visual discomfort questionnaire are shown in Figure 4-5. Spearman correlational analysis was conducted to test the relationship between cancellation speed and score for each item. After Holm-Bonferroni correction, none of the scores of individual items was significantly correlated with cancellation speed (for statistical results see Appendix 5).

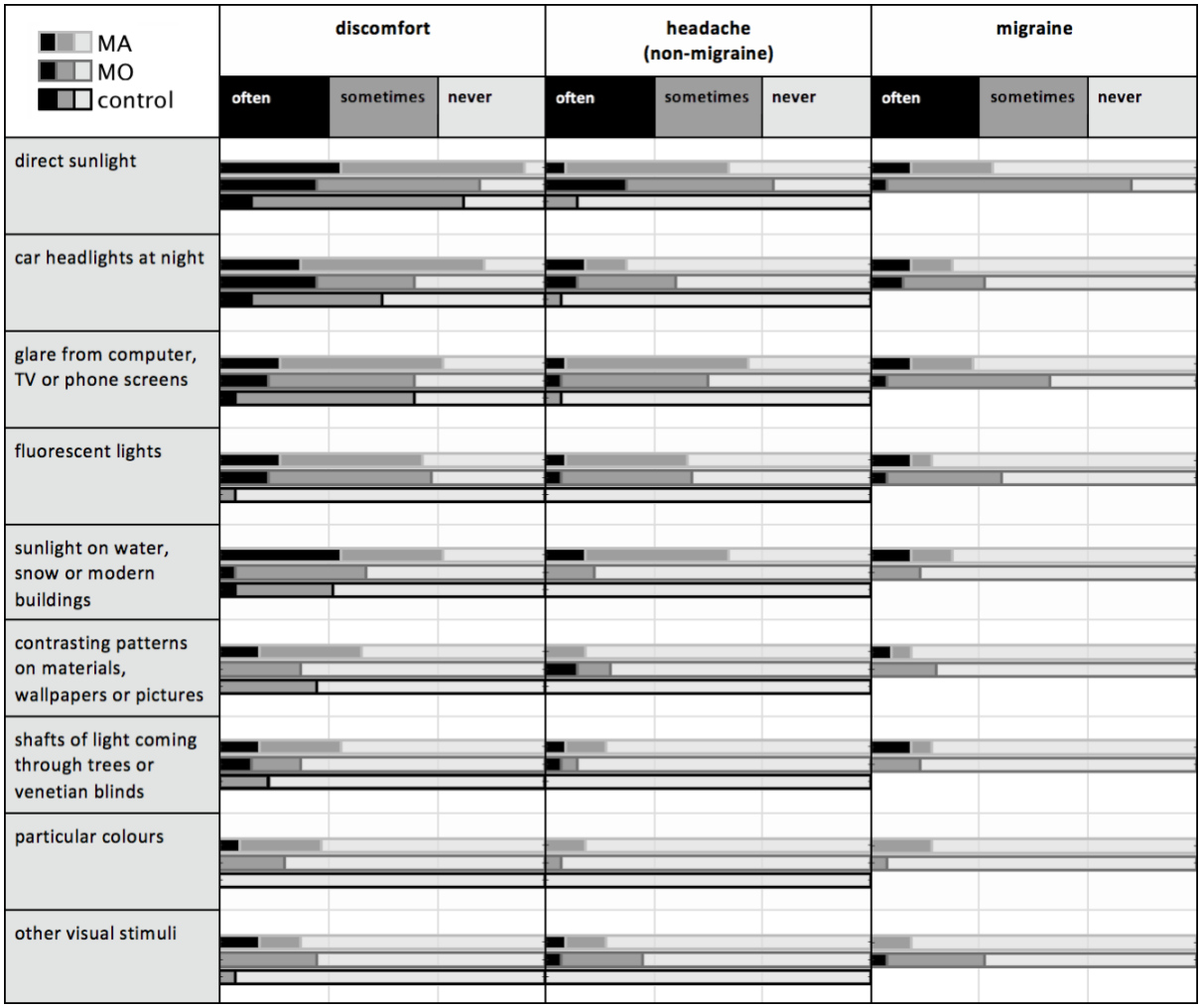

Figure 4-5 Percentage positive response for each item of the visual discomfort questionnaire. Edge shades indicate different group (legend at top left corner): lighter = MA, medium = MO, darker = control. Shading indicates the percentage response for each option (legend in the top row): darker = often, medium = sometimes, lighter = never.

4.3.3 Relationship with migraine characteristics

Cancellation speed was not significantly correlated with any of the self-reported migraine characteristics (MIDAS score, estimated numbers of migraine in life, days since last migraine). After Holm-Bonferroni correction, questionnaire headache score (rho = 0.51, p = 0.001) and questionnaire discomfort score (rho = 0.51, p = 0.002) were still significantly correlated with MIDAS score (Figure 4-6; for all correlational results regarding migraine characteristics see Appendix 6). The results suggested that people who report higher MIDAS scores tended to experience more frequent visual stimuli induced discomfort and triggered headache.

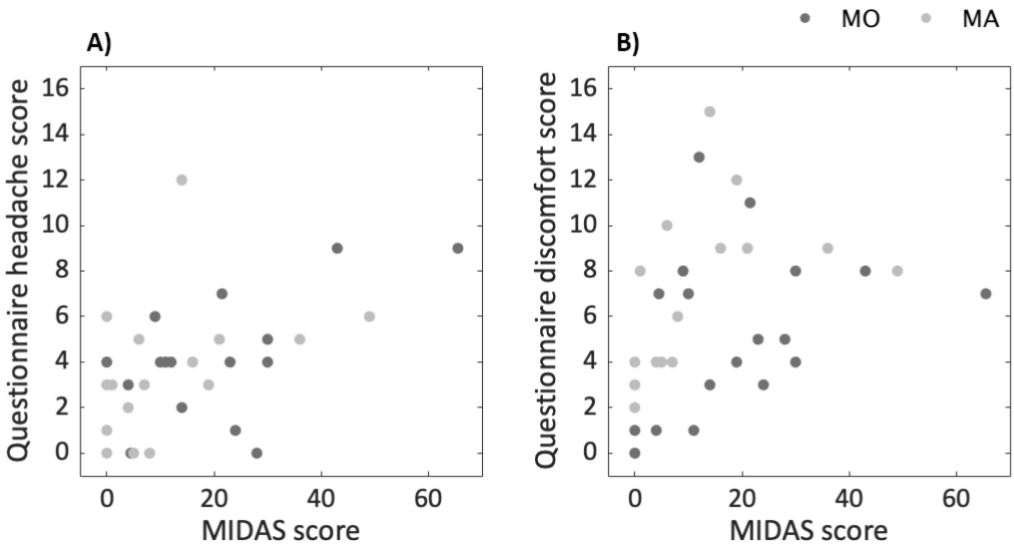

Figure 4-6 Significant correlations between questionnaire scores and migraine characteristics (n = 36).

4.4 Summary

This chapter aimed to determine whether the perceived illusory rotating speed for the specific variant of the Fraser-Wilcox illusion chosen from Chapter 3 would be faster in people with migraine, and whether the perceived illusory rotating speed would be associated with subjective measurements of interictal visual discomfort. While the self-reported frequency of experiencing visual stimulus induced discomfort was higher in MA than control participants, motion illusion strength was not correlated with any subjective measurements of visual discomfort nor different between any groups. These results suggest that migraine status and visual discomfort do not contribute to the measured strength of the motion illusion.

Chapter 5 Potential contributing factors to inter-individual variability in motion illusion strength

5.1 Introduction

As shown in the previous chapter, despite finding no group difference in cancellation speeds, there was significant variability in performance across individuals (cancellation speeds ranging from 0.16-1.88°/s). Although individual differences in the Fraser-Wilcox illusion have been recognised for some time (Fraser and Wilcox (1979), quantitative measurement of the strength of the illusion was not possible until the cancellation technique was developed by Murakami et al. (2006). Using the original cancellation technique, in which the luminance profile was arranged in a ring shape (retinal location at 7.4°-11°) surrounding the fixation point and participants viewed the stimulus binocularly, fixation instability was found to be positively correlated with cancellation speed (Murakami et al. 2006). Murakami et al. (2006) reported a correlation coefficient of 0.425 between variability of horizontal miniature drift eye movements and motion cancellation speed, which suggests that factors other than fixation instability also contribute to individual differences in illusion strength.

The first potential contributing factor considered in this chapter was individual differences in contrast perception. For the particular set of contrast levels featured in the Fraser-Wilcox stimulus, an approximately 10-20ms difference in peak spiking latency between higher (black and white) and lower (dark grey and light grey) contrast (relative to the grey background) has been previously identified in direction selective neurons in macaque V1 and MT, and this latency difference has been proposed to be critical in the generation of motion signals (Conway et al. 2005). Conway et al. (2005) further demonstrated that each pair of the adjacent elements in the illusory motion stimulus alone can elicit directional selective responses consistent with the overall illusory motion direction in both human psychophysical and macaque electrophysiological experiments. Thus, the degree to which responses to the two contrasts levels in each pair of adjacent segments in the illusory motion stimulus are different might affect the illusion strength.

The second factor considered in this chapter was sensitivity to physically moving stimuli. Since the nulling technique used to quantify the illusion involved the addition of real motion to the illusory pattern, individual differences in sensitivity to this real motion might also contribute to differences in measured illusion strength. Using the nulling technique, Hisakata and Murakami (2008) found the cancellation speed increased as stimulus eccentricity increased while the slope of psychometric function did not, which suggested motion sensitivity was not related to cancellation speed. As there were only 4 participants in their study, it is unknown how individual differences in motion sensitivity might affect the illusion strength measured by this technique.

In addition, this chapter aimed to compare contrast perception between control, MO, and MA groups, since abnormalities in contrast processing in people with migraine have been associated with visual discomfort (Shepherd 2000). Motion sensitivity was also compared between groups, as motion processing abnormalities in people with migraine have also been shown in previous studies (McKendrick et al. 2001, Antal et al. 2005). This chapter also aimed to investigate whether abnormal contrast and motion perception contributed to their susceptibility to the motion illusion, if any.

Therefore, this chapter compared contrast and motion perception between control, MO, and MA groups, and investigated how contrast and motion perception might contribute to individual differences in the illusory rotating speed. The following hypotheses were tested:

H4: Contrast discrimination threshold will be different between groups.

H5: Motion sensitivity will be different between groups.

H6: Contrast discrimination threshold will be correlated with illusion strength.

H7: Motion sensitivity will be correlated with illusion strength.

5.2 Methods

5.2.1 Contrast discrimination

5.2.1.1 Stimuli

Contrast discrimination thresholds were measured for the motion illusion stimulus at all four possible combinations of the 2 adjacent contrast steps of the Fraser-Wilcox stimulus.

The four possible types of luminance profiles with their corresponding example patterns are shown in Figure 5-1. The only difference in the patterns compared to those used in the motion illusion task (see Chapter 3, page 47), was the luminance profiles.

In each presentation, a reference pattern and a test (with reduced contrast) pattern were displayed for 500ms simultaneously on a white background (140 cd/m^2) with a black fixation dot. The spatial configuration of task stimulus is described in Figure 5-2. Two wheel patterns (diameter = 7°) were presented in the right hemifield (12° from the fixation dot) at a superior and inferior location (separated 12° apart from the centres).

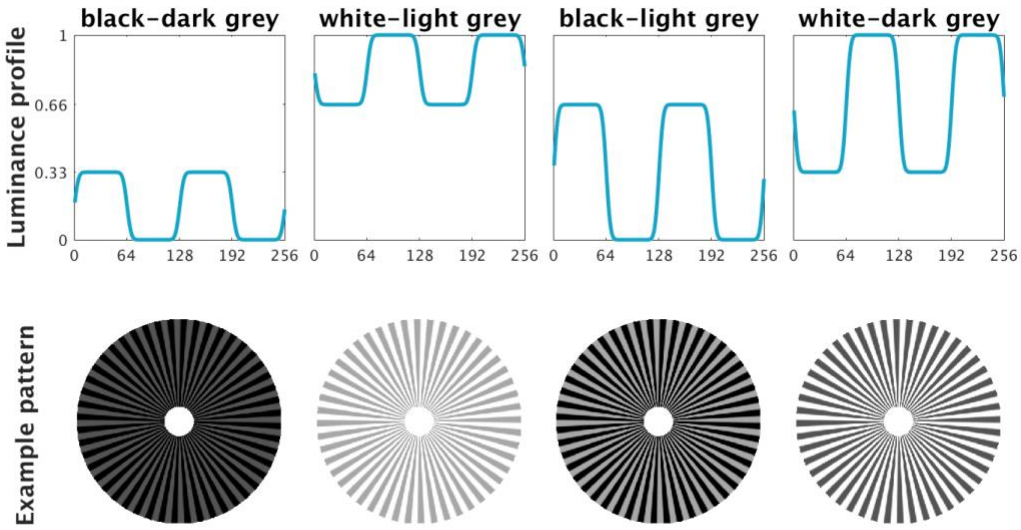

Figure 5-1 Luminance profiles and patterns of the target contrast of the 4 types of contrast discrimination tasks. Y-axis represents an arbitrary number proportional to absolute luminance level, where 1=white, 0=black. X-axis represents locations in the colour lookup table.

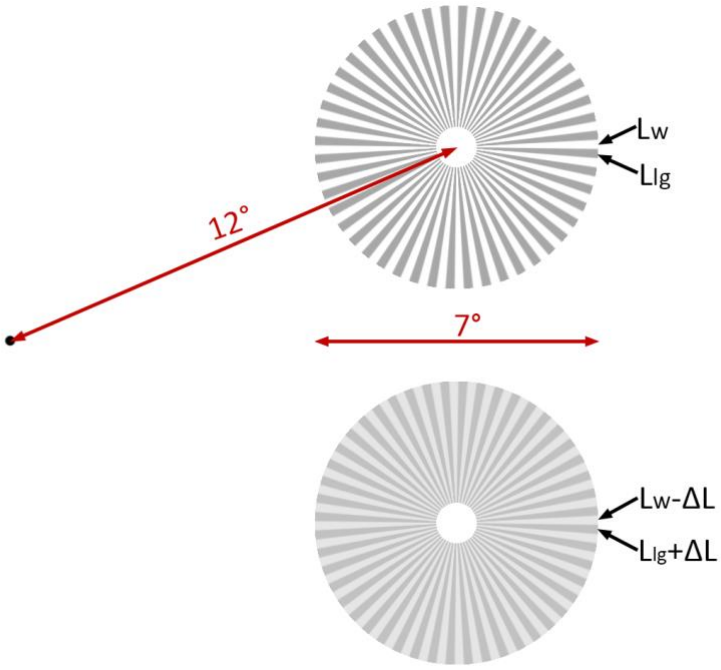

Figure 5-2 Schematic demonstration of the contrast discrimination task, type 2 as an example. The reference pattern on the top consists of the original white (L_w) and light grey (L_{lg}) wedges. The test pattern on the bottom has reduced contrast by reducing white and increasing light grey by the same amount of luminance (ΔL).

5.2.1.2 Procedure

A MOCS with two alternative forced choice was used. The location of the reference and test patterns (superior or inferior) was randomised between trials. Participants indicated whether the higher contrast pattern appeared at the top or the bottom location by pressing corresponding button. The same auditory feedback was provided regardless of whether the response was correct or incorrect; simply to indicate a successful button press. They were instructed that higher contrast refers to a greater difference between the two shades within the pattern and were told that the mean luminance of the two patterns were the same. Their understanding of the task was confirmed by pointing to the correct target pattern of each type on a hardcopy printout of the stimulus depicted in Figure 5-3 prior to commencing the experimental practice.

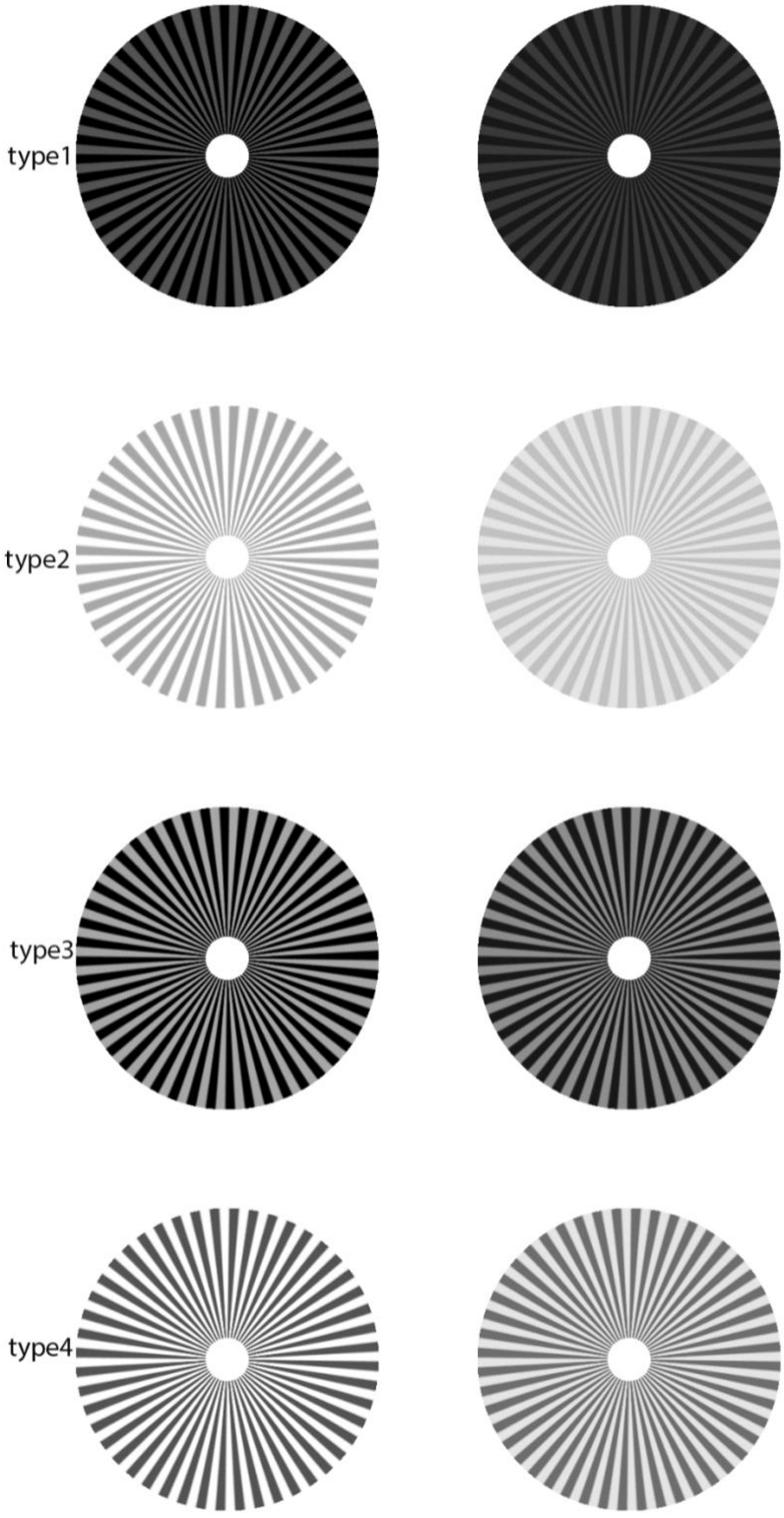

Figure 5-3 Visual aid used to explain the contrast discrimination tasks to participants. Each type (row) shows a reference and a test pattern. In this figure, the reference patterns are shown in the left column. As a practice, the reference pattern was randomised to either the left or right to ensure that the participant understood and could perform the task correctly before commencing the main experiment.

The MOCS contained 7 stimulus intensities (ΔL; see Figure 5-2). Eight repeats of each intensity were block randomised in each run. Half of the reference patterns at each intensity were presented at the top location. Participants completed the first 3 runs for training purposes and to aid in deciding each individual's test range. The first practice run for each participant typically started with a large test range that gradually reduced to a smaller range comprising of smaller step sizes in the two subsequent runs. A suitable contrast range was chosen aiming for the participant to reach 100% correct rate at the maximum ΔL. Then, they performed 3 runs at their individual suitable test range which was used to compute a final threshold (average of the last 3 runs). Individual psychometric functions are shown in Appendix 4. After the total 6 runs of one contrast type were finished, the same process was repeated for the next type. Stimuli were presented in pseudorandom order to counterbalance learning and fatigue effects.

5.2.1.3 Data analysis

The luminance intensity was normalised to 0-1 range (white = 1; black = 0) using linear transformation. The normalised luminance intensity is referred to as luminance ratio (LumRatio). Approximate conversions between ΔL, ΔLumRatio and Michelson contrast are detailed in Appendix 7. Individual data were fitted with cumulative normal functions as presented previously (see Chapter 3, page 49). As the asymptotes and thresholds are defined differently due to the 2-IFC methodology, implemented formula are relisted here. An example of the fitted psychometric functions is shown in Figure 5-4.

$$\psi(x; m, w, \lambda, \gamma) = \gamma + (1 - \lambda - \gamma)S(x; m, w) \quad \textit{(Equation 3-1)}$$

$$S(x; m, w) = \Phi\left(C\frac{x-m}{w}\right) \quad \textit{(Equation 3-2)}$$

$$C = \Phi^{-1}(.95) - \Phi^{-1}(.05) \quad \textit{(Equation 3-3)}$$

The psychometric function (ψ) is a sigmoid function (S) scaled by upper (λ; error rate at infinitely large ΔLumRatio) and lower (γ; the correct rate at ΔLumRatio=0.001) asymptotes. As the tasks were two-alternative forced choice, γ was fixed at 0.5. Parameters of S are the stimulus intensity (x; ΔLumRatio), the threshold (m; the ΔLumRatio at which S = 0.5), and the width (w; the difference between ΔLumRatios at which S = 0.05 and S = 0.95). Contrast discrimination threshold was the ΔLumRatio at which ψ = 0.75.

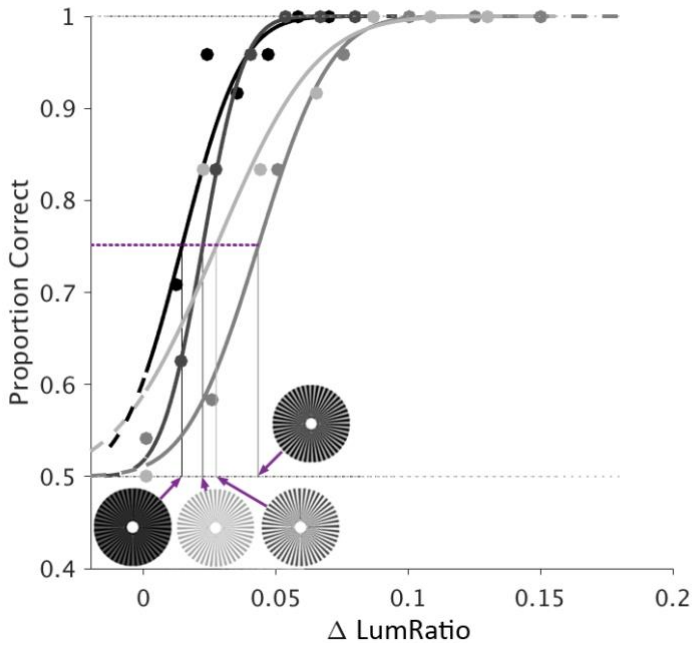

Figure 5-4 Demonstration of contrast discrimination threshold calculated from the fitted psychometric functions of one example participant. Each function represents one stimulus type as indicated on the figure.

The contrast discrimination thresholds for each stimulus condition were ranked in ascending order, resulting in four rank numbers for each participant. The mean of the four ranks was calculated for each participant, which was used to explore the effect of contrast discrimination thresholds on individual differences in illusion cancellation speed.

5.2.2 Motion sensitivity

Motion sensitivity has been quantified by the slope of psychometric functions in Hisakata and Murakami (2008). As suggested by Schütt et al. (2016), here, motion sensitivity is defined as the width of psychometric function (*w*) obtained from the motion illusion task (Chapter 4), where a larger *w* reflects worse motion sensitivity. The parameter *w* was calculated using the same procedure as described in Equation 3-1 to 3-3, Chapter 3 (Page 49). Figure 5-5 shows an example of the calculation of the width of the psychometric functions for an individual.

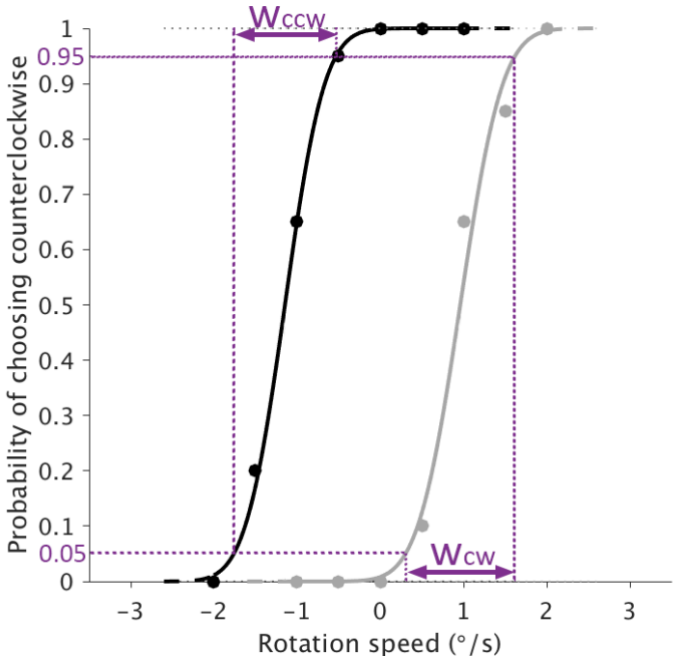

Figure 5-5 Demonstration of calculation of motion sensitivity of one example participant. Grey = clockwise pattern, black = counterclockwise pattern. Positive rotation speed corresponds to counterclockwise. Motion sensitivity was defined by the mean of the width of psychometic functions of the clockwise (Wcw) and the counterclockwise (Wccw) patterns.

5.3 Results

5.3.1 Group comparisons

The hypothesis that contrast discrimination thresholds would be different between groups was not supported (H4). Group and individual contrast discrimination thresholds for each condition are shown in Figure 5-6. A 3 (group: control, MO, or MA) × 4 (conditions: black-dark grey, white-light grey, black-light grey, or white-dark grey) ANOVA on log contrast discrimination threshold showed a significant effect of stimulus type ($F(3, 159) = 54.21$, $p < 0.001$, $\omega_p^2 = 0.747$) but neither main effect of group ($F(2, 53) = 1.60$, $p = 0.21$) nor interaction between group and stimulus type ($F(6, 159) = 1.98$, $p = 0.07$). Tukey's post-hoc tests showed that the contrast discrimination threshold for black-dark grey (type 1) was significantly smaller than white-light grey (type 2; $p = 0.002$, mean difference on log threshold = 0.08, 95CI [0.03, 0.12], $d_{av} = 0.417$); white-light grey (type 2) was significantly smaller than black-light grey (type 3; $p < 0.001$, mean difference on log threshold = 0.13, 95CI [0.09, 0.18], $d_{av} = 0.764$) and white-dark grey (type 4; $p < 0.001$, mean difference on log threshold = 0.15, 95CI [0.11, 0.19], $d_{av} = 0.882$); black-light (type 3) and white-dark grey (type 4) were not significantly different from each other ($p = 1$).

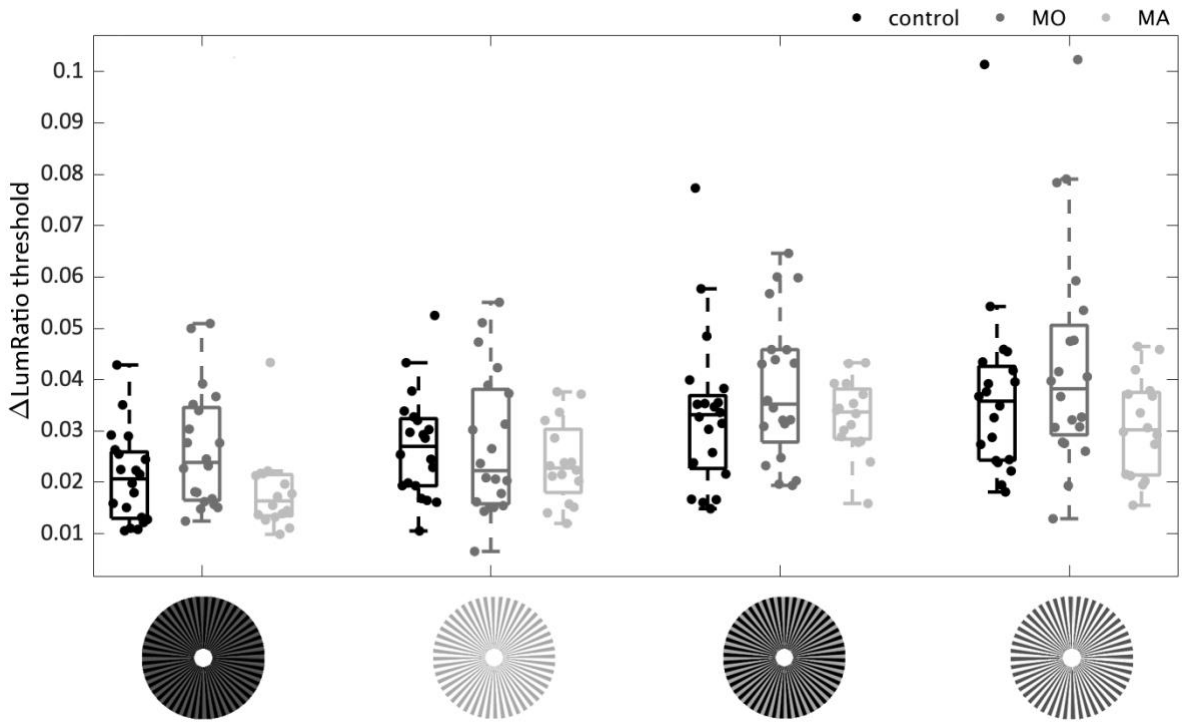

Figure 5-6 Group and individual contrast discrimination thresholds for 4 stimulus types. control (darker) n = 20; MO (medium) n = 20; MA (lighter) n = 16; Boxes describe median,

25th and 75th percentile. Each whisker extends to the data point nearest to 1.5 times the interquartile range.

Group and individual motion sensitivity are plotted in Figure 5-7 (smaller value indicates better sensitivity). The hypothesis that motion sensitivity would be different between groups was not supported (H5). Kruskal-Wallis test suggested that the three groups were not significantly different in motion sensitivity ($\chi^2(2) = 5.64$, $p = 0.06$).

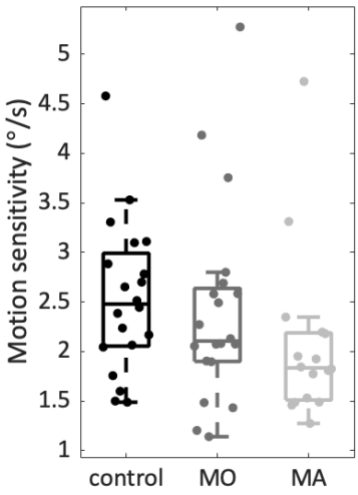

Figure 5-7 Group and individual motion sensitivity. control (darker) n = 20; MO (medium) n = 20; MA (lighter) n = 16; Boxes describe median, 25th and 75th percentiles. Each whisker extends to the data point nearest to 1.5 times the interquartile range.

Given that no significant group difference was found in cancellation speed, contrast discrimination threshold, or motion sensitivity, the relationships between them were investigated across the whole population tested.

5.3.2 Relationship between contrast discrimination and motion illusion strength

The cancellation speeds used in the analysis here were the same data as used in Chapter 4. The correlation between mean rank of contrast discrimination threshold and illusion cancellation speed is plotted in Figure 5-8. The hypothesis that contrast discrimination thresholds would be correlated with motion illusion strength was supported (H6). Spearman correlation showed a weak negative correlation between contrast discrimination threshold and cancellation speed (rho = -0.27, p = 0.04).

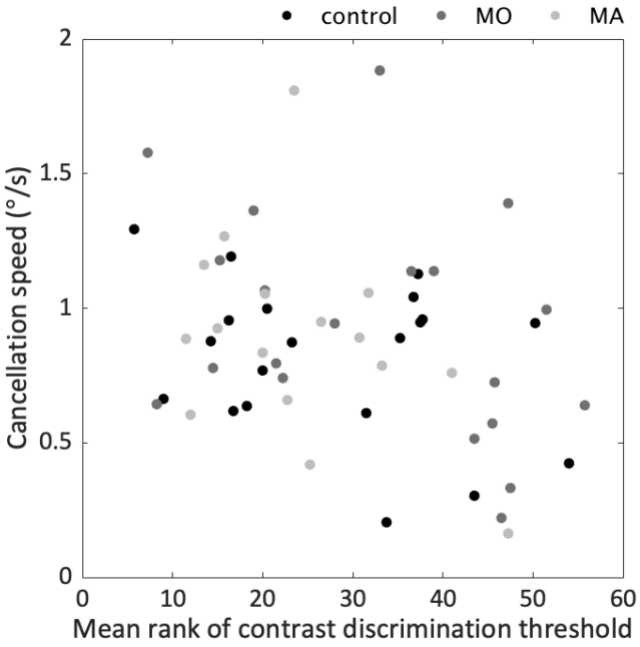

Figure 5-8 Cancellation speeds as a function of with mean rank of contrast discrimination thresholds for all 4 stimulus conditions in participants from all groups (n = 56; marker shades: darker = control; medium = MO; lighter = MA).

5.3.3 Relationship between motion sensitivity and motion illusion strength

Figure 5-9 plots illusion cancellation speed as a function of motion sensitivity, estimated by the width of the psychometric function. Spearman correlational analysis did not support the hypothesis (H7) that illusion strength would be associated with motion sensitivity (rho = -0.12, p = 0.38).

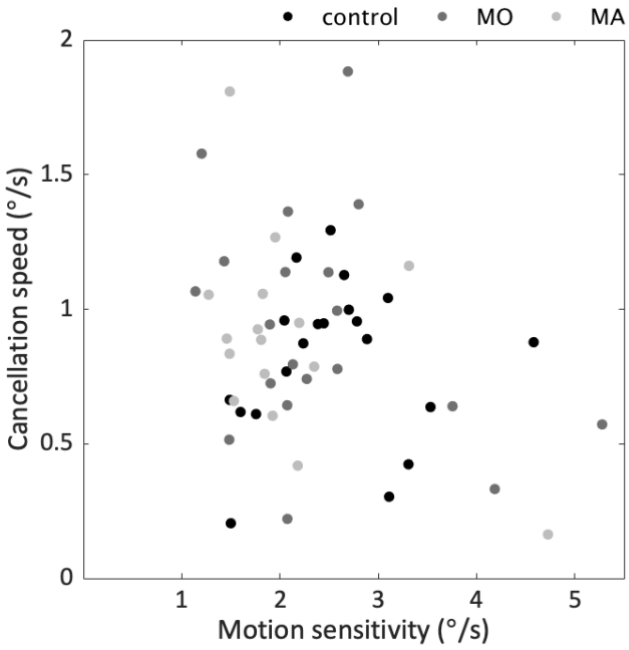

Figure 5-9 Cancellation speeds as a function of motion sensitivity in participants from all groups (n = 56; marker shades: darker = control; medium = MO; lighter = MA).

5.3.4 Relationship with migraine characteristics

Spearman correlational analysis was used to determine if there was any significant correlation between the three migraine characteristics and four contrast discrimination thresholds and motion sensitivity. Given the multiple comparisons, none of the measurements was significantly correlated with migraine characteristics after Holm-Bonferroni correction (for all correlational results regarding migraine characteristics see Appendix 6).

5.3.5 Relationship with visual discomfort

Correlation between the questionnaire discomfort score, questionnaire headache score, and questionnaire migraine score and mean rank of contrast discrimination threshold and

motion sensitivity were also determined. Spearman correlation showed none of the subjective questionnaire scores were significantly correlated with contrast discrimination or motion sensitivity (statistical results are shown in Appendix 8).

5.4 Summary

This chapter aimed to investigate contrast discrimination and motion sensitivity in people with migraine, and whether these two factors contributed to individual differences in motion illusion strength. Contrast discrimination thresholds for each combination of 2 adjacent contrasts in the illusory motion stimulus were measured. Sensitivity to the real motion, which was added to the illusory pattern, was calculated from the same set of data where the motion illusion strength was obtained. The results did not show abnormality in contrast or motion processing in people with migraine, as no group difference was found in contrast discrimination thresholds or motion sensitivity. Stronger motion illusion was significantly correlated with lower contrast discrimination threshold, which supported the hypothesised contribution of contrast perception to individual differences in motion illusion strength. On the other hand, motion sensitivity did not significantly correlate with motion illusion strength.

Chapter 6 Discussion

6.1 Summary of findings

The primary aim of this thesis was to objectively quantify the strength of a motion illusion in people with migraine and to investigate its relationship with interictal visual discomfort. Experiment 1 (Chapter 3) indicated that, of the five variants of the illusion tested, type 2a of the 'optimised' Fraser-Wilcox illusion (Kitaoka 2017) elicited a robust illusion that was suitable to use to compare illusion strength between migraine and control groups. Experiment 2 (Chapter 4) showed that motion illusion strength was not different between MO, MA and control groups, and that motion illusion strength was not associated with self-reported frequency of experiencing discomfort induced by visual stimuli. Finally, Experiment 3 (Chapter 5) suggested that contrast discrimination thresholds, but not motion sensitivity, contributed to individual differences in motion illusion strength regardless of migraine status.

6.2 Is there a link between motion illusion and visual discomfort in migraine?

Motivated by previous findings of more visual discomfort and more illusions experienced by people with migraine, Experiment 2 (Chapter 4) investigated three main measures: the strength of the Fraser-Wilcox motion illusion, the self-reported visual discomfort score, and the relationship between these measures in people with migraine and people without. These three aspects will be discussed in turn below.

6.2.1 Motion illusion strength in migraine

The hypothesis (H2) that motion illusion strength, as quantified by cancellation speed, would be larger in people with migraine was made based on two previous findings: 1) people with migraine reported seeing more illusions when viewing high contrast striped patterns (Harle et al. 2006); 2) people with migraine showed abnormal postural sway, measured in certain conditions (detailed in Chapter 1, page 33), associated with viewing the rotating snake illusion (Imaizumi et al. 2015). However, in this thesis, no significant difference in motion illusion strength was found between the MO, MA, and control groups. Although the previous studies are not directly comparable to this thesis, due to substantial

methodological differences, possible reasons for the discrepant findings are discussed below.

6.2.1.1 Considering our findings in the context of previous stimuli used to test pattern sensitivity and illusory perception

Various stimulus properties of the high contrast grating in the pattern sensitivity test (Wilkins et al. 1984) and the rotating snake illusion used to induce postural sway in Imaizumi et al. (2015) were different from the Fraser-Wilcox illusion used in this thesis.

Firstly, our stimulus duration (0.5s) was much shorter (at least 5s in the pattern sensitivity test; 30s in the postural sway study) (Shepherd 2000, Huang et al. 2003, Harle et al. 2006, Shepherd et al. 2013, Imaizumi et al. 2015). We selected a short duration to be consistent with previous studies using the cancellation method to quantify the strength of the Fraser-Wilcox illusion (Murakami et al. 2006, Hisakata and Murakami 2008). Furthermore, Otero-Millan et al. (2012) found that during a 30s-presentation of two discs of the rotating snake illusion (one at each side of the fixation dot), 8 participants from the general population experienced illusory motion intermittently with stillness. The mean duration for the first illusory period since stimulus onset was 4.1s (ranging from 2s to 8.2s), which was longer than the subsequent shifts of illusory periods (mean duration: 1.5s; ranging from 0.8s to 3.4s). Hence, to quantify the instantaneous motion illusion strength accurately, the stimulus duration is better to be shorter than the duration of the first illusory period.

Previous reports of strong illusions in people with migraine using stimuli with longer durations might be related to a lack of habituation, which was mentioned in Chapter 1 as a potential brain visual processing anomaly in migraine suggested by VEP studies (for review see Coppola et al. (2009)). In habituation studies, 50-100 consecutive responses (each lasting 200-300ms) have typically been averaged to obtain sufficient signal-to-noise to enable quantification of waveform characteristics such as peak amplitude. Amplitudes in the first block of time post-stimulation onset are compared to successive blocks to measure habituation, or a decline in amplitude over time (Schoenen et al. 1995, Afra et al. 1998, Coppola et al. 2007, Coppola et al. 2015). Schoenen et al. (1995) averaged across 50 responses lasting 200ms each, and demonstrated that both MA and MO groups had significantly reduced habituation (i.e. higher amplitudes) in the second 10s-block. Therefore,

the greater postural sway in people with migraine after 30s-presentation of the rotating snake illusion in Imaizumi et al. (2015) could potentially be explained by a lack of habituation. It is not possible in this thesis to determine whether performance on the motion illusion task was related to VEP habituation deficits, but that may be a subject for future investigation.

While the stimuli in previous studies that have measured pattern sensitivity (diameter of at least 6°) and postural sway (diameter of 29°) were both presented centrally in the visual field (Wilkins et al. 1984, Imaizumi et al. 2015), our stimulus (diameter of 7°) was presented at 12° eccentricity, hence our stimulus projected to a smaller area in the visual cortex (Drasdo 1977). This eccentricity was chosen because it has been shown that the Fraser-Wilcox illusion diminishes when it is presented with foveal fixation (Hisakata and Murakami 2008). Wilkins et al. (1984) found that the mean number of illusions reported by healthy participants increased as the percentage of cortical representation stimulated by the striped pattern increased. However, it is unclear whether increasing the total area of stimulated cortical region by displaying multiple wheels as did in Imaizumi et al. (2015) would influence the cancellation speed of the Fraser-Wilcox illusion.

Along with the increased eccentricity, the spatial frequencies of our stimulus were also different from that of the high contrast striped patterns. As Wilkins et al. (1984) has identified, the spatial frequency that generated the most number of illusions for people without migraine was about 3 cpd, close to the peak of the human contrast sensitivity function (Arundale 1978), while our stimulus had a spatial frequency of approximately 1 cpd. It is possible that spatial frequency influences the strength of the motion illusion, but to date this has not been systematically tested. While not a primary aim of this thesis, preliminary data collected in 3 individuals suggests that the Fraser-Wilcox illusion tends to be reduced in strength at a higher spatial frequency (~1.6cpd) than our current stimuli (~1.1cpd) (see Appendix 9). In addition, the spatial frequency we used has been shown by others to induce visual distortions associated with striped patterns. Huang et al. (2003) found an association between greater fMRI BOLD signal in V1 and greater visual illusions induced by high contrast striped patterns within the spatial frequency range of 0.3 to 9 cpd. They found the BOLD signal peaked at 1.2 cpd for both MA and control groups, and the MA

group was only significantly higher than the control group at 0.3 and 1.2 cpd. Perceptually, participants still reported seeing illusions in patterns with spatial frequency less than 1.2 cpd or greater than 3 cpd (Huang et al. 2003, Shepherd et al. 2013). Therefore, the spatial frequency used in the current stimulus seems unlikely to be the key reason for the same motion illusion strength between the migraine and control groups.

In the study assessing postural sway, a key difference in stimulus characteristics from the experiment herein, is that the rotating snake illusion used in Imaizumi et al. (2015) was a blue-yellow version while our stimulus was achromatic. The differences between migraine and control groups in the rotating snake illusion induced postural sway might therefore have been, at least partially, explained by abnormal colour processing. The achromatic stimulus used in this thesis was used to minimise the effect of individual differences in contrast processing of chromatic stimulus, since motion illusion strength has been shown to be dependent on stimulus contrast (Naor-Raz and Sekuler 2000). Several studies have demonstrated S-cone (sensitive to blue light) specific impairments involving colour perception in people with migraine (Shepherd 2005, Shepherd 2006, Tibber and Shepherd 2006). Tibber and Shepherd (2006) found that after adaptation (2 minutes initial adaptation + 7.25s top-up) to neutral light, both colour increment (purple) and decrement (yellow) detection thresholds (from grey) in the S-cone pathway were not different between migraine (n = 32) and non-migraine (n = 32) groups. However, after adaptation to yellow light, increment thresholds but not decrement thresholds were elevated in the migraine group. Tibber and Shepherd (2006) suggested that this might reflect a stronger inhibition through horizontal cells from the L- and M-cone to the S-cone which might be caused by enhanced inhibitory horizontal cell to S-cone synapses and/or enhanced excitatory synapses from the L- and M-cone to horizontal cells. Thus, it is possible that the prolonged presentation (30s) of stimuli, which consisted of repetitive blue, black, yellow, and white elements in Imaizumi et al. (2015), could have induced different responses in people with migraine due to abnormalities in blue-yellow opponent circuitry.

6.2.1.2 Considering our findings in the context of different methods used to quantify pattern sensitivity and illusory perception

Other than stimulus differences, different definitions of illusion measurement are also important to consider when comparing to previous literature. The motion illusion strength being compared in this thesis was measured using a two-alternative forced choice method, in which the physical rotating speed for each participant to cancel the illusory motion was determined. This method was chosen to minimise the possible influence of bias in self-reporting of visual discomfort. In all variations of the pattern sensitivity test (as introduced in Chapter 1, page 12), which might be calculated based on the number of illusions being reported, rating of illusion intensity, probability of reporting each type of illusion from multiple presentations, or within-subject differences in scores between patterns with different spatial frequencies, the scores were obtained purely depending on subjective self-report (Shepherd 2000, Harle et al. 2006, Tibber and Shepherd 2006, Shepherd et al. 2013).

6.2.2 Interictal visual discomfort in migraine

H3b hypothesised that people with migraine would experience more daily visual discomfort. In Experiment 2, the self-reported frequency of experiencing visual stimuli induced discomfort was found to be significantly higher in the MA compared to the control group, while MO was not significantly different from either of the other groups. The frequency of experiencing visual stimuli induced migraine attacks and non-migraine headaches was also assessed in the two migraine groups.

Due to different phrasing used in the questionnaires, the results of the current study and previous investigations (Debney 1984, Shepherd and Joly-Mascheroni 2017) of visual triggers of migraine cannot be compared directly. However, some attempts can be made to relate the items in the current survey to other groupings of symptoms. The proportion of people reporting visual triggers of migraine in our sample is comparable to a previous survey, in which 62%, 53% and 1% of the 344 migraine participants reported ‘glare’, ‘flicker’, and ‘colour’ could trigger their migraine respectively (Debney 1984). In a smaller sample size, Shepherd and Joly-Mascheroni (2017) found 12, 4, 5 out of the 22 migraine participants reported ‘flicker’ (55%), ‘stripes’ (18%), and ‘light and shade’ (23%) as their migraine triggers respectively. In our visual discomfort questionnaire (Figure 4-5; page 59) items potentially

belonging to ‘glare’ were ‘direct sunlight’, ‘glare from computer, TV or phone screens’, ‘car headlights at night’, and ‘sunlight on water, snow or modern building’. When both migraine groups were pooled together, the total percentage responses of ‘often’ or ‘sometimes’ in migraine trigger was 61% (direct sunlight), 44% (glare from computer, TV or phone screens), 31% (car headlights at night), and 19% (sunlight on water, snow or modern building). The only item from our questionnaire that could potentially be interpreted as ‘flicker’ was ‘fluorescent lights’, which ‘sometimes’ or ‘often’ triggered migraine in 31% of the participants. ‘Particular colours’ as a migraine trigger was reported by 11% (compared to 1% in Debney, 1984) of our participants. The ‘contrasting patterns on materials, wall papers or picture’ (17%) and ‘shafts of light coming through trees or venetian blinds’ (17%) are potentially comparable to the ‘stripes’ (18%) in Shepherd and Joly-Mascheroni (2017). Hence, we consider our results to be consistent with previous work measuring subjective visual discomfort, after taking into consideration different groupings of visual stimuli.

There were positive correlations between MIDAS score and frequency of experiencing visual stimuli induced headache and discomfort in our results. The MIDAS score is a measurement of migraine severity based on the ictal period (Stewart et al. 2001). Our customised questionnaire assesses the impact of visual discomfort in the interictal period. Therefore, the correlation might suggest that common factors affecting the disease severity might be shared between the ictal and interictal periods. However, given that no association between any migraine characteristics and motion illusion measurements were found in this thesis, we cannot exclude the possibility that people with more severe migraine conditions are more likely to be aware of potential sources of discomfort, hence reported higher visual discomfort score than people with less severe migraine or without migraine.

No previous studies have tested the relationship between visual discomfort and MIDAS score, but positive correlations between interictal visual discomfort and years of migraine have been found in previous studies (pattern sensitivity score: $r = 0.44$, $p = 0.02$, Shepherd et al. (2012); maximum bearable contrast for flicker stimulus: $r = 0.83$, $p < 0.001$, Karanovic et al. (2011)). In order to compare to previous findings, we conducted additional correlational tests between the questionnaire discomfort score and migraine duration, however, the result was non-significant ($rho = -0.075$, $p = 0.665$). The mean migraine

duration in years in the current thesis is somewhat longer than the two previous studies, but the distributions are generally overlapped (mean migraine duration ± standard deviation in years: MA: 12.1 ± 8.3; MO: 10.4 ± 4.4, Shepherd et al. (2012); MA+MO: 10.71 ± 8.51, Karanovic et al. (2011); MA+MO: 12.7 ± 7.1, the current thesis). If there is an effect of duration of migraine that it is likely a small effect, hence the non consistent findings in the literature.

6.2.3 Motion illusion and visual discomfort

Our hypothesis (H3a) that a stronger motion illusion would be correlated with greater discomfort scores assumed that susceptibility to high contrast striped pattern induced illusions would be positively associated with visual discomfort (Wilkins et al. 1984, Harle et al. 2006) and that people who robustly saw more illusions in high contrast striped patterns would also be highly susceptible to the Fraser-Wilcox illusion. Our results showed that motion illusion strength was not correlated with subjective questionnaire scores about visual stimuli induced discomfort, headache, or migraine, which suggests that motion illusion strength is not indicative of the degree of daily visual discomfort.

Although pattern sensitivity score has been used as a measurement of visual discomfort (Shepherd 2000), it is still unclear how the mechanisms of visual illusion and pattern induced discomfort are related with each other. In previous studies where subjective rating of stripe pattern induced visual discomfort was shown to be greater in people with migraine than non-migraine controls, the stimuli used to induce visual discomfort were all presented centrally and larger than the current stimulus (13° in Huang et al. (2003); 10° in Conlon et al. (2012); not specified in Wikinson et al. (2008) but it was implied that the grating stimulus filled the entire 19-inch screen). In this thesis, it was deliberately chosen to present participants with only one illusory rotating wheel stimulus (7°) at 12° eccentricity to restrict attention to a single location, and to simplify the task. As mentioned in Chapter 1, there are alternative versions of the Fraser Wilcox and 'rotating snakes' illusion that comprise multiple illusory rotating wheels filling out the entire screen. It is possible that our migraine participants might report greater discomfort, or increased illusory motion, for larger full-field stimuli than control participants. Whether the strength of illusion increases with spatial

size, and whether this correlates with subjective self-report of discomfort to the same stimuli, is yet to be tested.

Results of the percentage positive response to individual items in the questionnaire (Figure 4-5; page 55) suggests that the overall questionnaire discomfort scores were mainly contributed by light induced, rather than pattern induced, visual discomfort in all groups. As discussed in Chapter 1, the two types of visual discomfort are proposed to arise from different visual pathways. Although a previous study has shown that self-reported severity of ictal photophobia was associated with visual discomfort scale scores in MA but not MO participants (Cucchiara et al. 2015), the relationship between photophobia and pattern induced visual discomfort needs more investigation and cannot be speculated on here. We can, however, suggest that future work consider treating light induced and pattern induced visual discomfort separately.

Given that previous studies have indicated that interictal visual discomfort is not a universal symptom in all migraine sufferers (Conlon et al. 2012), potential recruitment bias might have contributed to the outcomes of our experiments. As our recruitment depended on voluntary response to advertisements, it was possible that the people who experience more severe visual discomfort were less likely to volunteer for visual psychophysical experiments. Nevertheless, in our cohort, the range of visual discomfort was 0-15 (maximum possible score was 18) for the overall questionnaire score and included a number of participants with scores at the higher end (16 people with migraine scored ≥ 7; all control participants scored between 0 and 6). Hence, it is unlikely that the non-significant correlation between motion illusion strength and interictal visual discomfort was driven by self-selection bias where people chose not to participate due to high levels of visual discomfort.

6.2.4 Future direction

We found that the instantaneous motion illusion strength obtained from a small and achromatic stimulus was not different between migraine and control groups. Several task differences between the current methods and the previous estimates of visual illusions in people with migraine that might contribute to the results have been discussed. Given that

our participants did not do the pattern sensitivity test, as reported by previous studies, we do not know whether the pattern sensitivity score would have been larger in our migraine groups. It is still unclear whether self-reported 'motion' percepts in the static stimuli used in the pattern sensitivity test are perceived through the same mechanisms as illusory motion in the Fraser-Wilcox illusion. Future studies might determine the relationship between the strength of the Fraser-Wilcox illusion and subjective intensity rating of 'motion' in high contrast static striped patterns within the same individuals.

We found that self-reported visual discomfort in daily life was not associated with cancellation speed of the Fraser-Wilcox illusion. One limitation of this study is that we did not ask the participants to rate how uncomfortable they were when viewing the testing stimuli. Therefore, the relationship between the perceived speed of the motion illusion and the subjective discomfort it induced (if any) could not be inferred. Future studies quantifying the illusion strength of the Fraser-Wilcox illusion could also assess the acute discomfort induced by the stimuli. To test whether pattern induced discomfort is dependent on local illusion strength, a future study might also assess subjective discomfort to images with more spatial repetition of the Fraser-Wilcox illusion and quantify illusion strength at each location, compared to a control condition using non-illusory wheels with physical rotation.

6.3 Do people with migraine have altered contrast discrimination and motion sensitivity?

Abnormal contrast and motion processing in people with migraine has been associated with interictal visual discomfort in previous studies (Shepherd 2000, Haigh et al. 2012). Therefore, it was hypothesised that contrast discrimination threshold and motion sensitivity would be impaired in our migraine groups (H4 & H5). In Experiment 3, we found no group difference in either of the two thresholds indicating that migraine and aura status did not significantly affect contrast discrimination and motion sensitivity. The results regarding each task will be discussed separately.

6.3.1 Contrast discrimination in migraine

Contrast discrimination tasks have been used to measure contrast gain control, a form of visual adaptation to local contrast levels (Heinrich and Bach 2001). Our results of Experiment 3 do not suggest altered gain control in people with migraine as there was neither a significant group difference nor interaction between group and stimulus condition in contrast discrimination threshold. Masking effects have also been proposed to assess contrast gain control in people with migraine. Thus, our results might be considered consistent with McColl and Wilkinson (2000) in which the effect of a masking stimulus presented 150ms before the target on contrast detection threshold increase ratio was found to be not significantly different between the migraine (25 MA, 22MO) and control groups. McColl and Wilkinson (2000) suggested that the 150ms delay between the mask and target would allow inhibitory feedback to manage gain control, therefore, the larger threshold shift relative to a no masking condition was assumed to reflect stronger inhibitory contrast gain control. Shepherd et al. (2011) found no group difference (15 MA; 15 MO; 15 non-headache control) in the correct rate of identifying the shape of a central target when a circular mask was briefly (10ms) presented at different timing (ranged $\pm$130ms relative to target onset), which also suggested that inhibitory control localised in V1 was not affected in migraine.

Although the above-mentioned studies seem in agreement with our results in unaltered inhibitory control in people with migraine, these might not reflect the same underlying mechanism given that different tasks were used. Different results on contrast suppression for static and moving stimulus from Battista et al. (2011) suggested that inhibitory functions measured by specific tasks might not be generalisable across all visual functions. Contrast suppression was measured as the magnitude of reduction in perceived contrast of the centre stimulus in the presence of a high contrast surround, and was proposed to reflect the strength of lateral inhibition modulated by feedback excitation (Battista et al. 2011). Battista et al. (2011) have demonstrated significantly higher contrast suppression in migraine groups (12 MA; 14 MO; 20 non-headache control) for a drifting grating stimulus (2 cpd drifted at 2°/s) but not for a static stimulus (4 cpd).

Apart from the task differences in measuring contrast discrimination between the current experiment and previous studies mentioned in the previous paragraph, participant selection might also affect difference in contrast discrimination thresholds between migraine and control groups. The migraine participants recruited in the current thesis were healthy with good vision, and came from the general university community, and not a tertiary headache referral centre for example. Previous work investigating contrast processing in people with migraine have reported impaired visual performance in specific locations of the visual field. In 10 migraine participants who had already been identified to demonstrate impairments on visual field testing, contrast discrimination thresholds measured in the quadrant that exhibited the worst performance in the visual field test were shown to be elevated compared to the healthy control group (McKendrick and Badcock 2003). It was not clear whether the contrast gain anomalies that might be measured interictally as part of the migraine cycle (McKendrick and Badcock 2003) are different to those that might be measured as part of migraine sequalae to the visual system.

6.3.2 Motion sensitivity in migraine

In Experiment 3, we found no significant difference in motion sensitivity between groups, indicating that people with migraine did not have dysfunctional motion processing for the particular stimulus used. In comparison to our motion discrimination task, the motion deficit found in previous studies of global motion coherence thresholds in migraine (McKendrick and Badcock 2004, Ditchfield et al. 2006, Shepherd et al. 2012) might involve more complex processing, such as extraction and integration of signal from noise stimuli. It has been suggested that task performances might only consistently impaired in the migraine cohorts when the tasks required extraction and integration of signals elements from stimuli that were incorporated with noises (Tibber et al. 2014, O'Hare and Hibbard 2016). It is possible to discriminate the direction of our motion stimulus based on local motion information, for example, whether the nearest point (or the radius passing that point) to the fixation dot on the pattern moved upward or downward. Hence, integration over the whole space might not be needed. However, it is unclear which cue, if any, the participants used to perform our task as there was also a global rotatory motion in our stimulus. In the general population, direction of rotatory motion has been shown to be easier to discriminate than translational motion (Lee and Lu 2010). Rider et al. (2016) has recently suggested that local motion

direction is resolved by direction of global rotatory motion rather than being integrated to achieve the perception of global rotation.

Several previous studies found that performance on motion tasks which could be processed based on local motion signals was not impaired in people with migraine. Across a range of stimulus contrast and sizes, Battista et al. (2010) found the average duration threshold for direction discrimination of drifting grating stimulus was not impaired in people with migraine. Using a dot motion stimulus, Webster et al. (2011) found the minimum deviation from circular direction to detect spiral motion was not different between migraine and control groups. Antal et al. (2005) found that people with migraine had better accuracy than control participants at identifying the direction of briefly (48ms) presented 100% coherent translational dot motion stimuli. However, using a similar task to that of Antal et al. (2005), Shepherd et al. (2012) found the percentage correct response was higher for the control group than the MA group. An additional finding of Shepherd et al. (2012) was that the impairments in motion direction detection in their migraine participants could be fully explained by impairments in contrast sensitivity.

Although it was not a planned aim of this thesis, we found a significant correlation indicating that people with lower contrast discrimination threshold tended to have better motion sensitivity (Spearman correlation between mean rank of contrast discrimination threshold and motion sensitivity; n=56; rho = 0.34, p = 0.01). The correlation in our results might be in accordance with the early visual system contribution to motion processing suggested by Shepherd et al. (2012). Hence, the conflict on whether motion sensitivity was impaired in people with migraine between Shepherd et al. (2012) and our results might be because their migraine participants had abnormalities in earlier visual pathways while ours did not. All of our participants underwent a screening by an optometrist to ensure there were no ocular problems that could affect vision, such as intraocular scatter from media opacities that would affect contrast sensitivity, and all were refractively corrected for the specific working distance of the experiment. Alternatively, our correlation between motion sensitivity and contrast discrimination may reflect general factors such as concentration that could result in uniformly lower thresholds across all psychophysical tasks. There was only one participant who participated in experiments 2 and 3 who also participated in

experiment 1. Therefore, we consider learning effects are unlikely to significantly contribute to the correlation found between the different tasks.

6.3.3 Relationship with migraine characteristics

Previous studies have suggested differences in visual processing within migraine groups, depending on migraine duration (Karanovic et al. 2011, Shepherd et al. 2012) and frequency (Shepherd et al. 2011, Shepherd and Joly-Mascheroni 2017, O'Hare 2018). On the other hand, some studies find migraine duration (Shepherd 2000, Battista et al. 2011, Khalil et al. 2011, Shepherd et al. 2011) or frequency (Mulleners et al. 2001, Battista et al. 2011, Karanovic et al. 2011) did not affect their measurements. Performance on some tasks can be affected by migraine cycle effects (Shepherd et al. 2011, Shepherd and Joly-Mascheroni 2017, McKendrick et al. 2018) while other tasks are not (Battista et al. 2011, Nguyen et al. 2014). For the group studied in this thesis, no migraine characteristics (estimated life migraine events, MIDAS score, and days since last migraine) were correlated with the psychophysical results. These non-significant correlations were expected, as these psychophysical measurements were not different between the migraine and control groups in the first place.

6.3.4 Relationship with visual discomfort

Given that previous studies have suggested abnormal contrast and motion processing might contribute to interictal visual discomfort in people with migraine (Conlon et al. 2012, Haigh et al. 2012), correlations between self-reported visual discomfort scores and contrast discrimination threshold and motion sensitivity were tested. It was found that both contrast and motion processing assessed in this thesis were not associated with any subjective measurement of visual discomfort. As previously discussed (in section 6.2.3), the overall visual discomfort scores reported by our participants were mainly driven by photophobic rather than pattern induced visual discomfort. It is possible that had our cohort included more people with high levels of pattern induced visual discomfort, measures of contrast and motion perception might be related to visual discomfort score.

However, it is worth mentioning that in previous studies, where stimuli used to assess subjective visual discomfort and contrast thresholds were closely linked, there was still no significant correlation between the two measurements (Karanovic et al. 2011, Thabet et al. 2013). In the two studies, aversion to flicker (10Hz) assessed by maximum bearable temporal contrast and measurements of temporal contrast adaptation (10Hz) were both significantly different between the migraine and control groups (Karanovic et al. 2011, Thabet et al. 2013). Furthermore, most migraine but none of the control participants reported the testing display for the objective contrast detection task was uncomfortable (Thabet et al. 2013). It was suggested by the authors that the visual information which generated discomfort and that which drove performance on the contrast perception tasks might arise from different visual pathways (Thabet et al. 2013). Their speculation is reasonable based on the available evidence. However, to what extent the processing of contrast detection and visual discomfort are exclusively dependent on particular low level visual pathways is still yet to be solved. It is also possible that their distinction occurred at higher level processing stages. For example, the strength of discomfort might not be significantly affected by lower level visual input even if its early pathways are partly overlapped with that used for performing the contrast detection task.

6.3.5 Future direction

Apart from task differences, the current inconsistency in whether contrast and motion processing is affected in people with migraine might have been contributed by individual differences in migraine participants between studies. As might be the case for visual discomfort (Conlon et al. 2012), group differences between people with and without migraine might be driven by a small set of migraine sufferers that have altered performance, while the remaining are not distinguishable from control participants. It is possible that contrast discrimination and motion sensitivity were impaired in a small group of people with migraine toward the most severe end of the migraine spectrum. However, the link between psychophysical results and self-reported migraine severity is not always found. Migraine characteristics are variable (e.g. not all migraine attacks consist of the same set of symptoms), and vary within a person over their own lifetime (e.g. frequency of attacks changes with age) (Bigal et al. 2008), and is even more variable when fluctuations in the migraine ‘cycle’ is considered (McKendrick et al. 2018). To determine whether visual

abnormalities are affected by migraine severity, more accurate and detailed migraine characteristics may be collected, such as through headache diaries (Nappi et al. 2006, McKenzie and Cutrer 2009).

Previous studies have also suggested that the group differences found in a few studies might not be contributed by migraine per se, instead, they might have happened to include migraine participants with other comorbidities, such as visual discomfort (Shepherd 2001, Tibber and Shepherd 2006, Conlon et al. 2012). This view of migraine and visual discomfort being two parallel conditions was not supported by our results in Experiment 2, in which people with greater visual discomfort also had more ictal phase disability (as indicated by higher MIDAS questionnaire scores). Daily experience of visual discomfort might be considered as one of the migraine characteristics to be assessed in future migraine diaries.

6.4 Factors other than migraine affecting the strength of motion illusion

Apart from the potential applications of motion illusion to investigate visual discomfort, this thesis also provided some understanding of the mechanisms underlying the motion illusion. Perceived motion illusion strength can be affected by stimulus manipulations and individual differences in observers. These two factors will be discussed separately.

6.4.1 Motion illusion experimental parameters

Experiment 1 compared the strength of the five classified 'optimised' Fraser-Wilcox illusion (Kitaoka 2017), with the main finding that type 2a induced a stronger illusion than type 2b and type 4. This suggests that the luminance profile is important for the illusion strength. It is not possible from the current experiment to determine the underlying neurophysiological mechanism for this trend. Nevertheless, we speculate that our findings are related to the magnitude and latency of neuronal responses in visual cortex. Conway et al. (2005) showed that V1 and MT cells had larger peak firing rate (amplitude of contrast response function) and shorter response latency in response to higher contrast (black next to white) stimuli than stimuli of lower contrast (light grey next to dark grey) of the same size. They proposed that the latency difference (10-20ms) in peak firing rate between higher and lower contrast (relative to the background) segments creates the perception of the higher contrast stimuli

moving to the locations of lower contrast stimuli. It is worth noting that the model by Conway et al. (2005) is based on the findings of uniform luminance bars separately presented on grey background. It is unclear whether the relationship between contrast response functions of adjacent segments would remain the same for a brighter background luminance (which was used in the current experiment).

The cancellation speed of the type 3 stimulus in the current experiment was approximately double that reported by Hisakata and Murakami (2008). The only difference between our experiments was the increasing of background luminance to the maximum luminance of the pattern (L_{max}: 98 cd/m^2) which resulted in the increase of contrast difference between three segments of the pattern and the background (and one segments has no contrast cue relative to the background) (Figure 6-1-A), compared to Hisakata and Murakami (2008), which used mean luminance of the pattern as the background (L_{mean}: 48 cd/m^2; Figure 6-1-B). Naor-Raz and Sekuler (2000) found that subjective rating of strength of the Fraser-Wilcox illusion on mean grey background (44.5 cd/m^2) decreased by approximately 50% (estimated from their figure) as decreasing the stimulus contrast from 0.99 to 0.18 Michelson contrast. It is possible that the difference in contrast between the pattern and the background have resulted in the different motion illusion strength between Hisakata and Murakami (2008) and the current study. However, the enhanced illusion strength by altered contrast relationship between two of the segments and the background is not readily explained by the current existing models.

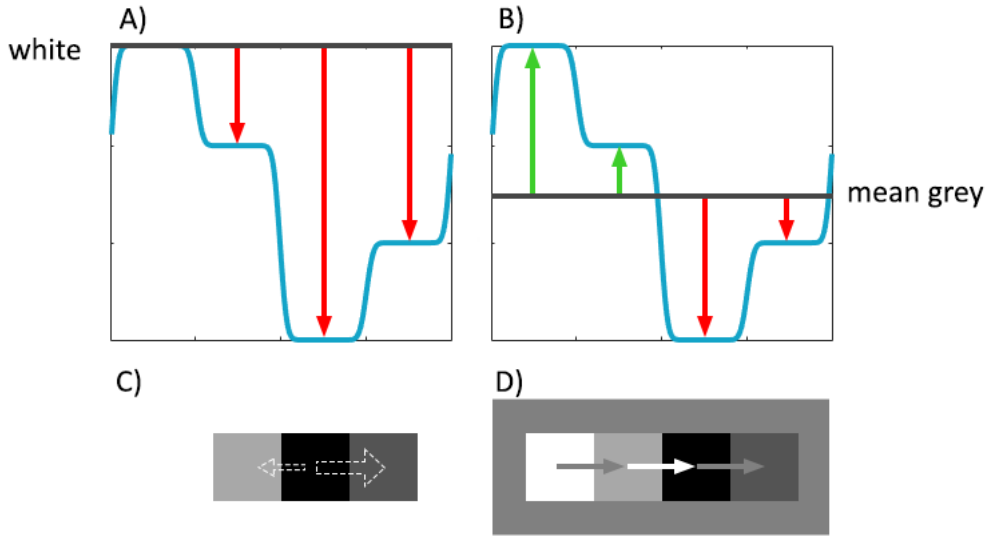

Figure 6-1 Top panels: Contrast relationship between each segment within the pattern the and the background used in A) the current experiment; and B) Hisakata & Murakami (2008). Red arrows indicate luminance decrement; green arrows indicate luminance increment relative to the background. Bottom panels: C) attempt to explain direction of motion signals for the current experiment. Both arrows are predicted by models suggested by Conway et al. (2005) and Backus and Oruc (2005); Larger arrow indicates the observed direction of motion illusion in the current study. D) stimuli used in Hisakata & Murakami (2008) explained by Conway et al. (2005). Grey arrows indicate motion direction predicted by effect of neural latency difference. White arrow is predicted by reverse-phi effect.

Furthermore, the finding that our L_{max} background generates the same illusion direction as the previous L_{mean} background (Hisakata and Murakami 2008) also suggests that the contrast response function explanations of the Fraser-Wilcox illusion may be oversimplified. According to previous models, contrast steps between two adjacent segments within the pattern would generate motion signal in direction from the higher contrast to the lower contrast (relative to background) (Kitaoka and Ashida 2003) or from darker to lighter areas Backus and Oruc (2005). In addition, Conway et al. (2005) suggested that the directions predicted by the two contrast pairs of opposite contrast signs (black to light grey and white to dark grey) relative to their L_{mean} background might have share mechanisms to the reverse-phi motion. Reverse-phi motion refers to an apparent motion stimulus created by two consecutive frames with reversed contrast relationship to the background. Such a

stimulus appears to move in the direction from the location of the second frame to that of the first frame (Anstis and Rogers 1975) (Figure 6-2-D). However, we found that, when three of the segments had contrast decrements, and one did not have contrast to the background, the motion illusion is still generated in the direction of black→dark grey→white→light grey (Figure 6-2-C). If the motion directions predicted by previous models is applicable to the stimulus presented in L_{max} background it is possible that the black→dark grey pair created stronger signal than the black→light grey pair, which resulted in the current observed direction.

In addition, the cancellation speed defined by Hisakata and Murakami (2008) was the physical rotation speed at 50% probability of choosing counterclockwise. They averaged the absolute values of cancellation speed of both pattern directions as the final cancellation speed. However, their measurement was not suitable for participants who may have been biased towards one button which would result in cancellation speeds in the same direction as the illusory motion direction. Looking at the individual psychometric functions between the two studies, the different calculation formula is unlikely to be the key reason for the halved cancellation speed in Hisakata and Murakami (2008).

6.4.2 Individual visual perceptual differences between observers

Experiment 3 demonstrated that contrast discrimination but not motion sensitivity contributed to individual differences in motion illusion strength. Our finding of motion sensitivity being not associated with illusion strength is consistent with Hisakata and Murakami (2008) who found that the motion illusion strength was affected by eccentricity, while motion sensitivity was not.

The independence of illusion strength from motion sensitivity suggests that the cortical processing of illusory motion might be translated into a 'real' motion signal before area MT. Brain imaging studies of the Fraser-Wilcox illusion showed that area MT was activated and adapted to illusory motion in the same way as real motion (Kuriki et al. 2008, Ashida et al. 2012). It has been demonstrated that fish (Gori et al. 2014), cats (Bååth et al. 2014), monkeys (Agrillo et al. 2015), and human infants aged 6-8 months (Kanazawa et al. 2013)

can respond to the rotating snake differently than to its control image. Given the difference in cortical structures in mammalians and the absence of cortex in fish, the perception of illusory motion across species also supports a pre-cortical origin of the motion signals of the Fraser-Wilcox illusion. Other studies (Murakami et al. 2006, Beer et al. 2008) that have investigated human individual differences in strength of the motion illusion also suggest that fixational eye movements are critical in generating the motion illusion. Above all, if motion processing involved in the Fraser-Wilcox illusion is the same as real motion stimuli, it might be reasonable that sensitivity to motion would not make the motion appear faster, but rather, improve how accurately the motion velocity is perceived, just as 'real' motion.

6.4.3 Future direction

In this thesis, based on previous work (Hisakata and Murakami 2008), cancellation speed was estimated based on the stimulus duration of 500ms. Previous studies have suggested that the motion illusion is perceived intermittently with stillness rather than continuous uniform movement (Otero-Millan et al. 2012). According to Conway et al. (2005) the motion signal should be generated at approximately 60-80ms after stimulus onset where the 10-20ms latency difference occurred. If this model is correct, the proposed perceptual positional shift (Kitaoka and Ashida 2003) from high to low contrast segments for our stimulus would be approximately 7.5 degree (24 cycles of the luminance profile in the current stimulus) within 20ms. Backus and Oruc (2005) suggested from their local motion detector model that the contrast response change over time would create a 15-45 degree perceptual rotation in the first 90ms. The instantaneous velocities predicted by both models are much larger than the mean cancellation speed we obtained (~0.9 degree/s), and larger than that measured in previous studies (Murakami et al. 2006, Hisakata and Murakami 2008). The discrepancy between our data and the values predicted by previous models indicates that the proposed models for motion illusion strength require refinements with the current empirical findings considered.

Our results, for the first time, provided quantitative evidence of motion illusion strength being affected by observer's contrast processing in humans. However, the weak (rho = -0.271) association between contrast discrimination threshold and motion illusion strength might suggest either contrast response function makes a small contribution to illusion

strength or the contrast discrimination thresholds is not a suitable parameter to represent the contrast processing that is critical in generating the illusion. Using a noise transform paradigm, Taylor et al. (2006) demonstrated that median reaction times to the appearance of targets as a function of its contrast can be transformed into a linear relationship. To determine a more precise relationship between contrast dependent response latency and motion illusion, future studies could measure the contrast response function as described by Taylor et al. (2006) and its relationship with cancellation speed. Furthermore, given that fixation instability was shown to be associated with motion illusion strength (Murakami et al. 2006, Kuriki et al. 2008), to better understand the mechanisms of the motion illusion, eye movements and contrast response should be considered in one model in future studies.

6.5 Conclusion

Interictally, people with migraine with aura report greater visual discomfort than non-headache controls. The positive association between interictal visual discomfort and disability induced by migraine attacks suggests that interictal visual discomfort might be an informative assessment of individual migraine severity. However, in this study, measures of motion illusion strength, contrast discrimination, and motion sensitivity did not differ between those with migraine and non-headache controls. Motion illusion strength was not affected by migraine status, severity of daily visual discomfort, nor motion sensitivity. However, individuals with better contrast discrimination tended to see stronger motion illusions. The results of this thesis suggest that the Fraser-Wilcox motion illusion, quantified using psychophysical methods, does not seem to test the same mechanisms as involved in self-reported visual discomfort.

Appendices

Appendix 1 Consent form

Consent Form

Department of Optometry and Vision Sciences

Project: Visual perception in migraine
Ethics ID: 1749823.2

Primary Researcher: Prof Allison McKendrick
Additional Researchers: Dr Bao Nguyen (Co-researcher), Dr Yu-Man (Janet) Chan (Co-researcher), Ms Chongyue He (Masters student)

Name of Participant: _____

1. I consent to participate in this project, the details of which have been explained to me, and I have been provided with a written Plain Language Statement to keep.

2. I understand that the purpose of this research is to investigate *differences in visual perception between people with and without migraine*

3. I understand that my participation in this project is for research purposes only.

4. I acknowledge that the possible effects of participating in this research project have been explained to my satisfaction.

5. In this project I will be required to *undergo a screening eye examination, complete migraine related questionnaires, and computerised tests of vision.*

6. I understand that my participation is voluntary and that I am free to withdraw from this project anytime without explanation or prejudice and to withdraw any unprocessed data that I have provided.

7. I understand that the data from this research will be stored at the University of Melbourne for at least 5 years.

8. I have been informed that the confidentiality of the information I provide will be safeguarded subject to any legal requirements; my data will be password protected and accessible only by the named researchers.

9. I understand that after I sign and return this consent form, it will be retained by the researcher.

Participant Signature: _____ **Date:** _____

Appendix 2 Plain language statement

Plain Language Statement

Department of Optometry and Vision Sciences

Project: Visual perception in migraine
Ethics ID: 1749823.2

Prof Allison McKendrick (Responsible Researcher)
Tel: +61 3 90359979 Email: allisonm@unimelb.edu.au

Dr Bao Nguyen (Co-researcher) Email: bnguyen@unimelb.edu.au
Dr Yu-Man (Janet) Chan (Co-researcher) Email: yu.chan@unimelb.edu.au
Ms Chongyue He (Masters student) Email: chongyueh@student.unimelb.edu.au

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Introduction
Thank you for your interest in participating in this research project. The following few pages will provide you with further information about the project, so that you can decide if you would like to take part in this research.

Please take the time to read this information carefully. You may ask questions about anything you don't understand or want to know more about.

Your participation is voluntary. If you don't wish to take part, you don't have to. If you begin participating, you can also stop at any time.

What is this research about?
Migraine is a primary headache disorder affecting about 15% of the population. The visual symptoms reported by people with migraine, such as discomfort with normal light, suggest that the abnormal changes that contribute to a migraine attack are somehow related to the visual system. This research aims to improve our understanding of the visual symptoms of migraine by investigating how visual information is interpreted by people who experience migraine.

We are seeking 40 participants with migraine and 20 participants who do not regularly suffer from headaches. People between ages of 18-45 are invited to participate.

What will I be asked to do?
Should you agree to participate, you will be asked to complete the following…

1) Screening optometric eye examination

We will conduct a short series of tests to determine whether you are eligible to participate in the study. All tests to be performed in these sessions are routine optometric tests and will be performed by a qualified optometrist. This will include general questions about your vision and ocular and general health, measuring your ability to read letters on a chart, spectacle prescription (if any), and examining the health of your eye.

2) Headache/migraine related questionnaires

All participants will be asked to complete a headache questionnaire to ensure their migraine or migraine free status, a questionnaire about your response to visual stimuli, and a Migraine Disability Assessment (MIDAS) questionnaire to assess the impact of migraine on your life.

3) Computerised tests of vision

You will be asked to sit in a dimly lit room, observe visual patterns shown on a computer monitor and make judgements about the features of the patterns (e.g. contrast, direction or presence of motion) by pressing a key in a computer keyboard, or by clicking a mouse button, or by pressing a particular button in a custom-made button box. Each individual test will take no longer than 10 minutes. You will be free to take rest breaks in between each test as required. These computerised tests of vision do not involve any invasive or painful procedures and pose no greater risk than working on a personal computer in the office or the home.

Participants will be asked to attend up to three sessions that will each take up to 2 hours. After each session, migraine participants will be followed up (via email or phone) to find out when their next migraine attack occurred relative to the date of testing.

What are the possible benefits?

This research aims to improve our understanding of the visual experience of people with migraine. The broader benefits of the research to society are to contribute to knowledge regarding the symptoms and possible mechanisms involved in migraine events. Our research may assist in informing new methods of measuring migraine symptoms, and therefore may be useful for evaluating new therapies and treatments.

To contribute to any out-of-pocket expenses incurred in attending, each participant will be given a $20 giftcard per session.

What are the possible risks?

Possible risks associated with the eye examination:

The screening eye examination does not constitute a full eye examination. If abnormal findings are discovered on the screening eye examination, the attending optometrist will advise that you have failed the screening and recommend that you attend your regular eyecare provider for a full examination. If you do not have an existing regular eye care practitioner, the optometrist can assist with referral to a relevant optometric practice.

Possible risks for migraine participants:

We do not know what triggers a migraine event in people, as they occur spontaneously. Some people with migraine find certain visual patterns discomforting, so there is a chance that in susceptible individuals who have migraine attacks, a visually presented stimulus may provoke a migraine event. Alternatively, as we are testing susceptible individuals, a migraine event may occur coincidentally on the day of testing. If you feel uncomfortable viewing the stimuli, we will cease testing. If a migraine attack occurs, all testing will be postponed and you can withdraw permanently from the study, or until the migraine symptoms subside and another visit will be scheduled, if you consent. We can assist in arranging transport home by calling a taxi, friends or family.

Do I have to take part?

No. Participation is completely voluntary. You are able to withdraw (quit) at any time. You are free to withdraw any data already collected from or about you.

Will I hear about the results of this project?
A written summary of the findings will be available if you request after the study has been completed. We will also send you an annual end-of-year update of the lab research.

What will happen to information about me?
We intend to protect your anonymity and the confidentiality of your responses to the fullest possible extent, within the limits of the law. All records taken as a part of this study will remain confidential. Any information supplied and data collected will be added to our internal database of previous participants. The data are kept in a password-protected computer or in a locked drawer. Your name will not appear in any publications or reports arising from this study, and if needed you will be referred to by a pseudonym. We will remove any references to personal information that might allow someone to guess your identity. The data will be kept securely in the Department of Optometry and Vision Sciences for a minimum of 5 years from the date of the last publication arising, before being destroyed.

Is there any potential conflict of interest?
If you are a student in the Department of Optometry & Vision Sciences, your decision of whether to participate in the experiment will not affect your academic results or the way you are treated by the relevant researchers.

Who is funding this project?
This project is funded by an NHMRC grant (App 1081874).

Where can I get further information?
If you would like more information about the project, please contact the responsible researchers: Prof Allison McKendrick Email: allisonm@unimelb.edu.au

Who can I contact if I have any concerns about the project?
This research project has been approved by the Human Research Ethics Committee of The University of Melbourne. If you have any concerns or complaints about the conduct of this research project, which you do not wish to discuss with the research team, you should contact the Manager, Human Research Ethics, Research Ethics and Integrity, University of Melbourne, VIC 3010. Tel: +61 3 8344 2073 or Email: HumanEthics-complaints@unimelb.edu.au All complaints will be treated confidentially. In any correspondence please provide the name of the research team or the name or ethics ID number of the research project.

Appendix 3 Equations to generate luminance profiles for Chapter 3

The luminance profile of types as shown in Figure 3-2 in Chapter 3 are listed in Equation A3-1 to Equation A3-5.

$$LumRatio_1 = \begin{cases} 1 - \frac{x}{256}, & 0 < x \leq 128 \\ \frac{x-128}{256}, & 128 < x \leq 256 \end{cases} \quad \textit{(Equation A3-1)}$$

$$LumRatio_{2a} = \begin{cases} 1, & 0 < x \leq 32 \\ 0.66, & 32 < x \leq 128 \\ 0, & 128 < x \leq 160 \\ 0.33, & 160 < x \leq 256 \end{cases} \quad \textit{(Equation A3-2)}$$

$$LumRatio_{2b} = \begin{cases} 1, & 0 < x \leq 96 \\ 0.66, & 96 < x \leq 128 \\ 0, & 128 < x \leq 224 \\ 0.33, & 224 < x \leq 256 \end{cases} \quad \textit{(Equation A3-3)}$$

$$LumRatio_3 = \begin{cases} 1, & 0 < x \leq 64 \\ 0.66, & 64 < x \leq 128 \\ 0, & 128 < x \leq 192 \\ 0.33, & 192 < x \leq 256 \end{cases} \quad \textit{(Equation A3-4)}$$

$$LumRatio_4 = \begin{cases} 0.7 + 0.3\frac{(x-32)^4}{31^4}, & 0 < x \leq 32 \\ 0.7, & 32 < x \leq 96 \\ 0.7 - 0.3\frac{(x-97)^4}{31^4}, & 96 < x \leq 128 \\ 0.3 - 0.3\frac{(x-160)^4}{31^4}, & 128 < x \leq 160 \\ 0.3, & 160 < x \leq 224 \\ 0.3 + 0.3\frac{(x-225)^4}{31^4}, & 224 < x \leq 256 \end{cases} \quad \textit{(Equatio A3-5)}$$

The luminance ratio for each type ($LumRatio_1$, $LumRatio_{2a}$, $LumRatio_{2b}$, $LumRatio_3$, $LumRatio_4$) calculated from location in colour lookup table (x).

Appendix 4 Individual psychometric functions for Chapters 4 and 5

This section shows individual raw data and fitting of psychometric functions. Results of the motion illusion (Chapter 4) and contrast discrimination tasks (Chapter 5) are shown in the same row to indicate a general data quality of each participant. There were 20 trials per dot for the motion illusion task, and 24 trials per dot for the contrast discrimination task.

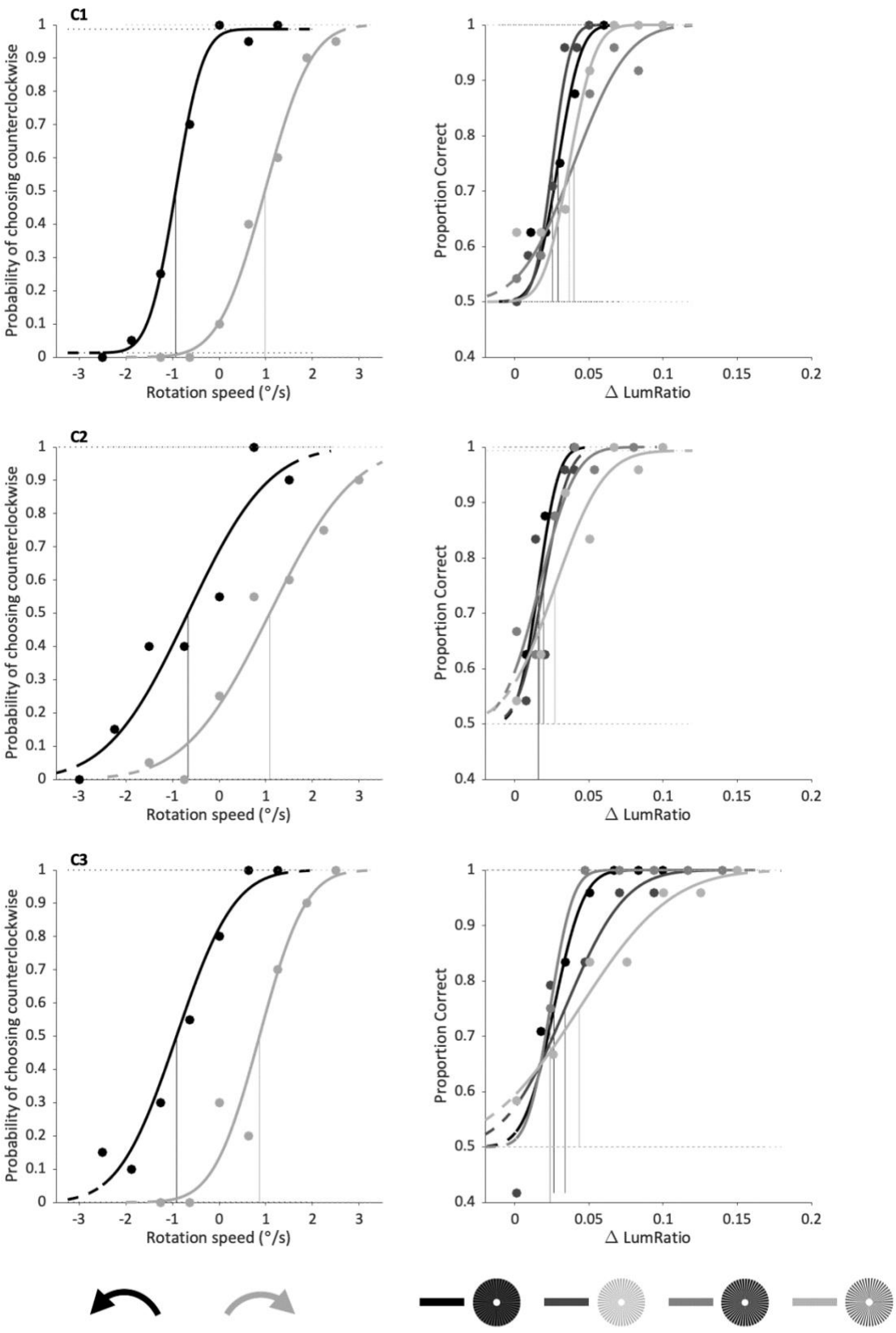

Figure A. 4-1 Data of control participants 1-3.

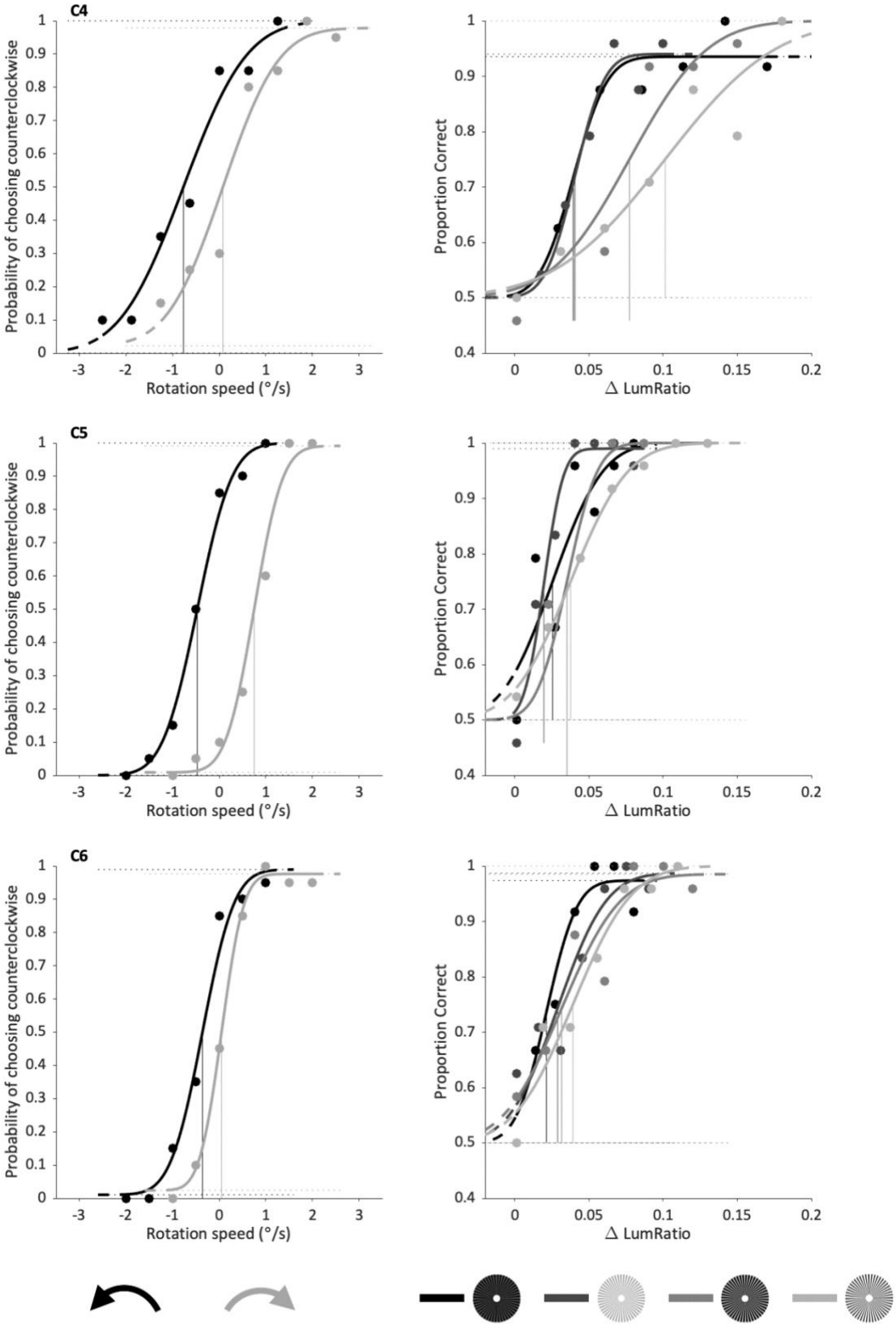

Figure A. 4-2 Data of control participants 4-6.

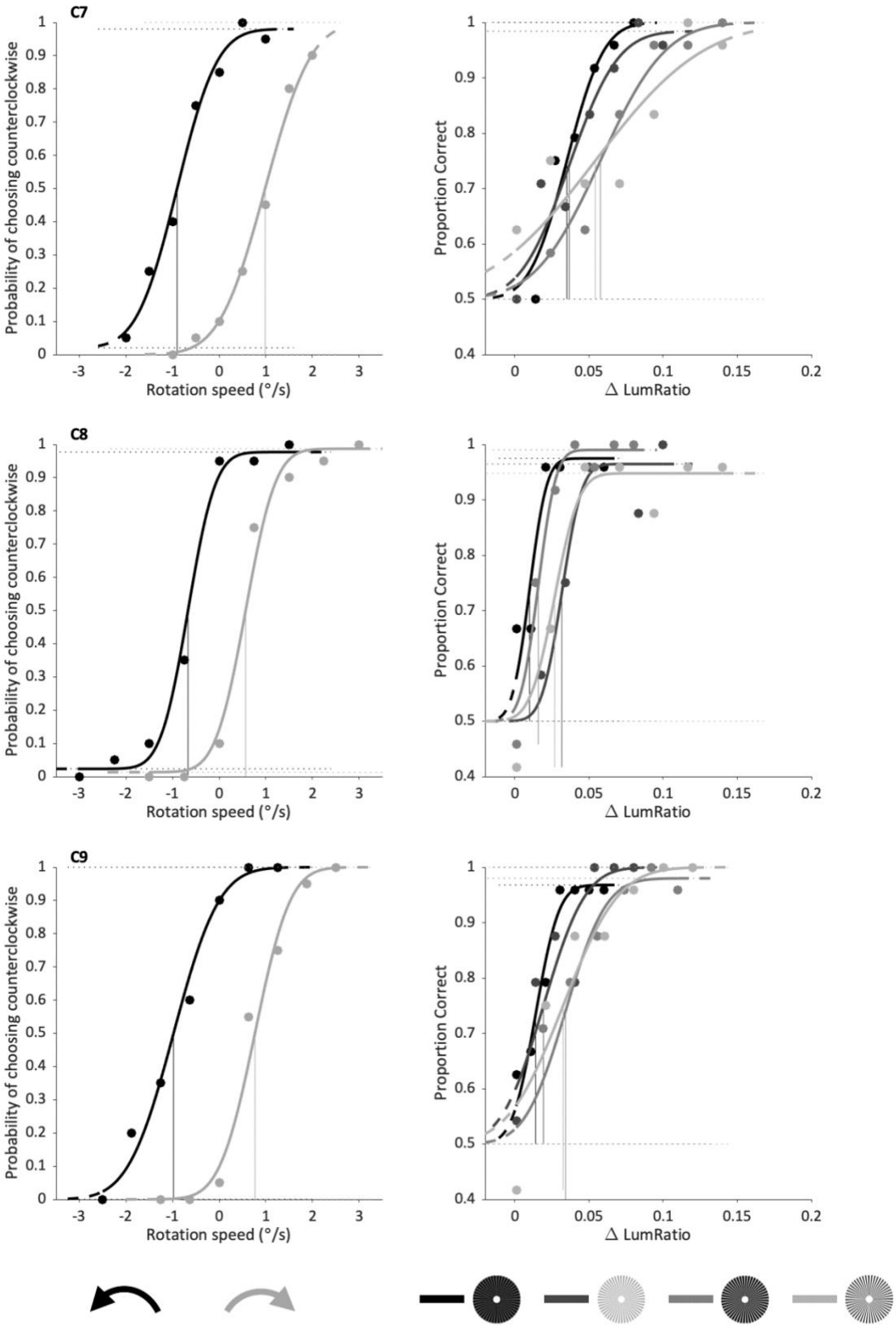

Figure A. 4-3 Data of control participants 7-9.

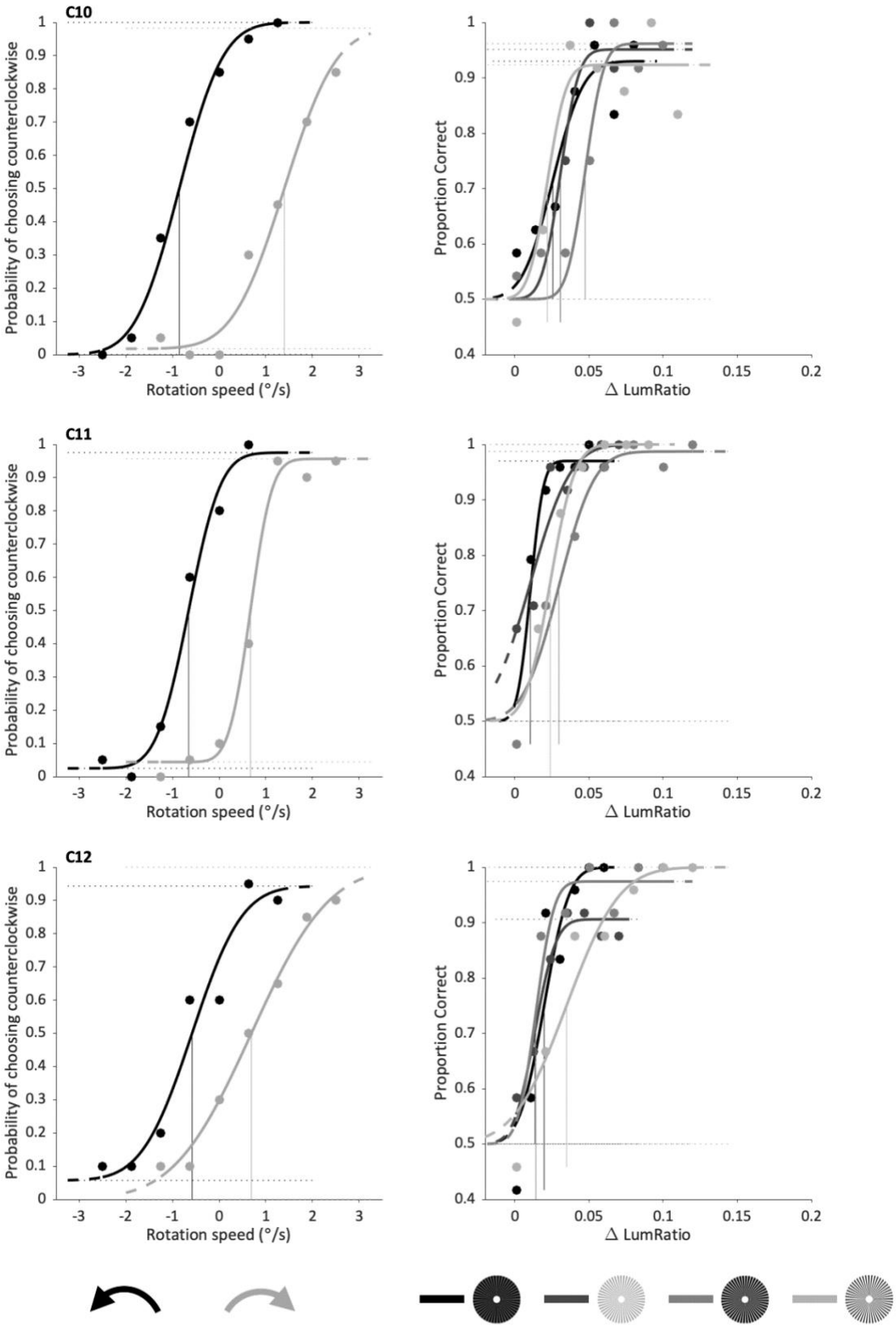

Figure A. 4-4 Data of control participants 10-12.

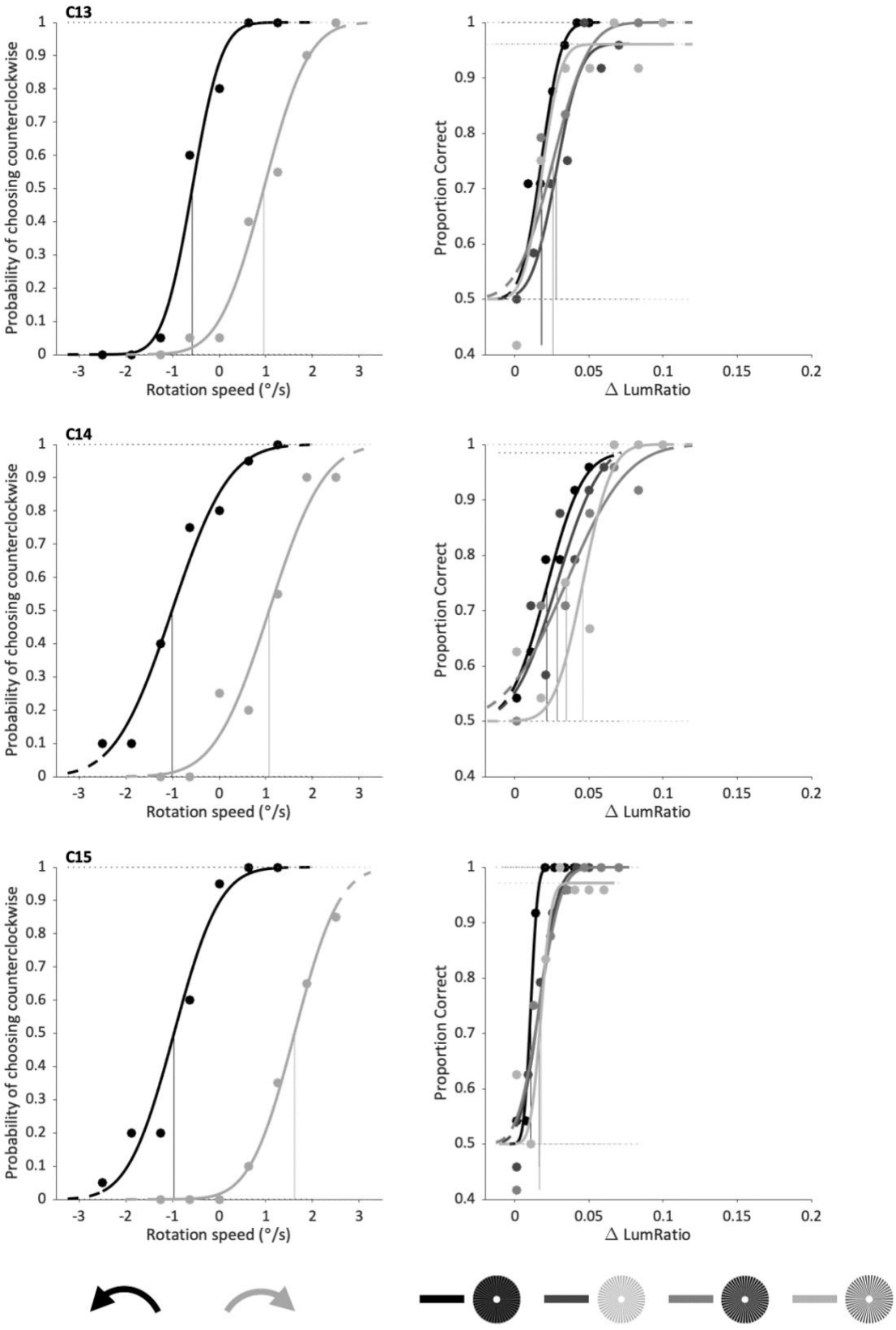

Figure A. 4-5 Data of control participants 13-15.

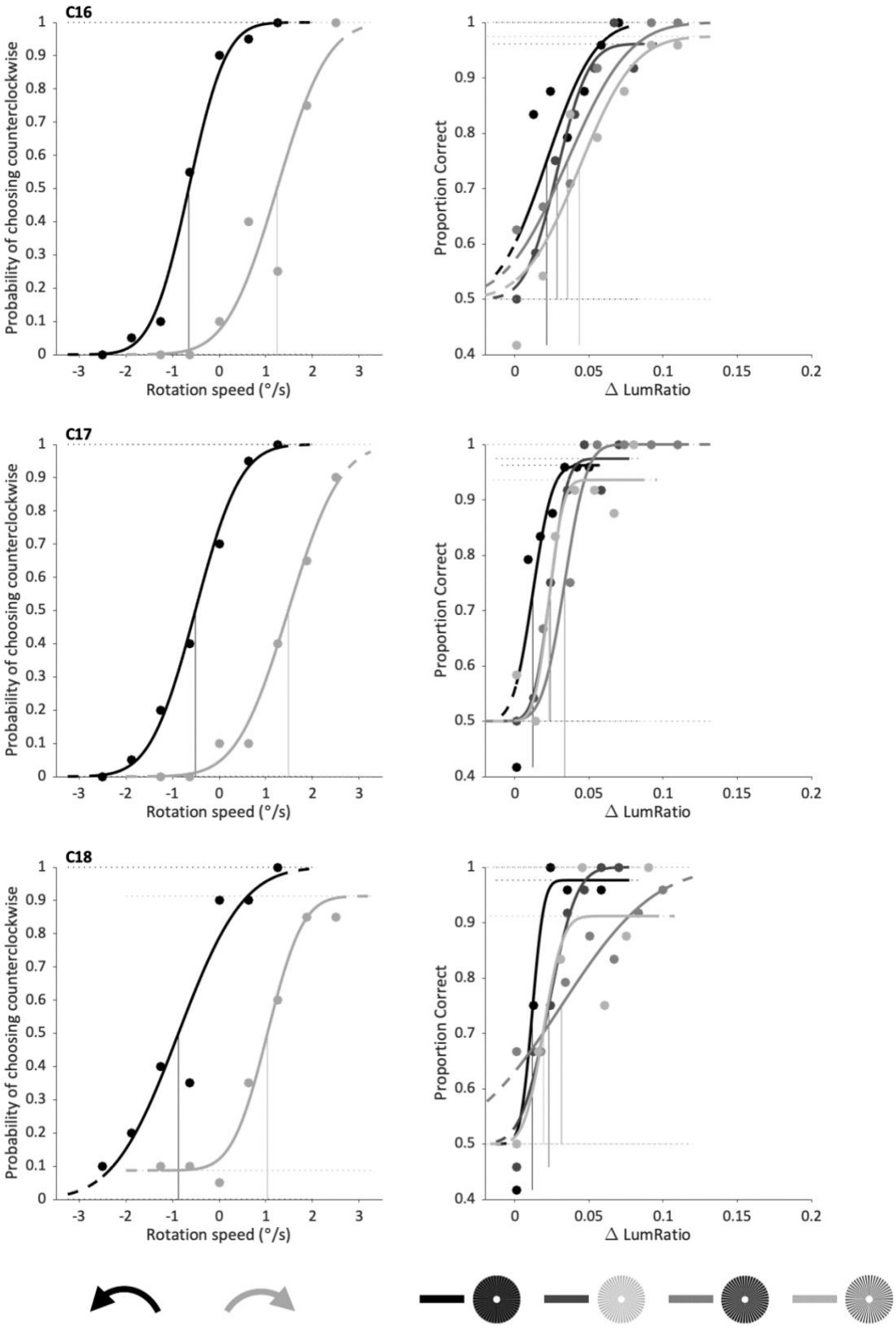

Figure A. 4-6 Data of control participants 16-18.

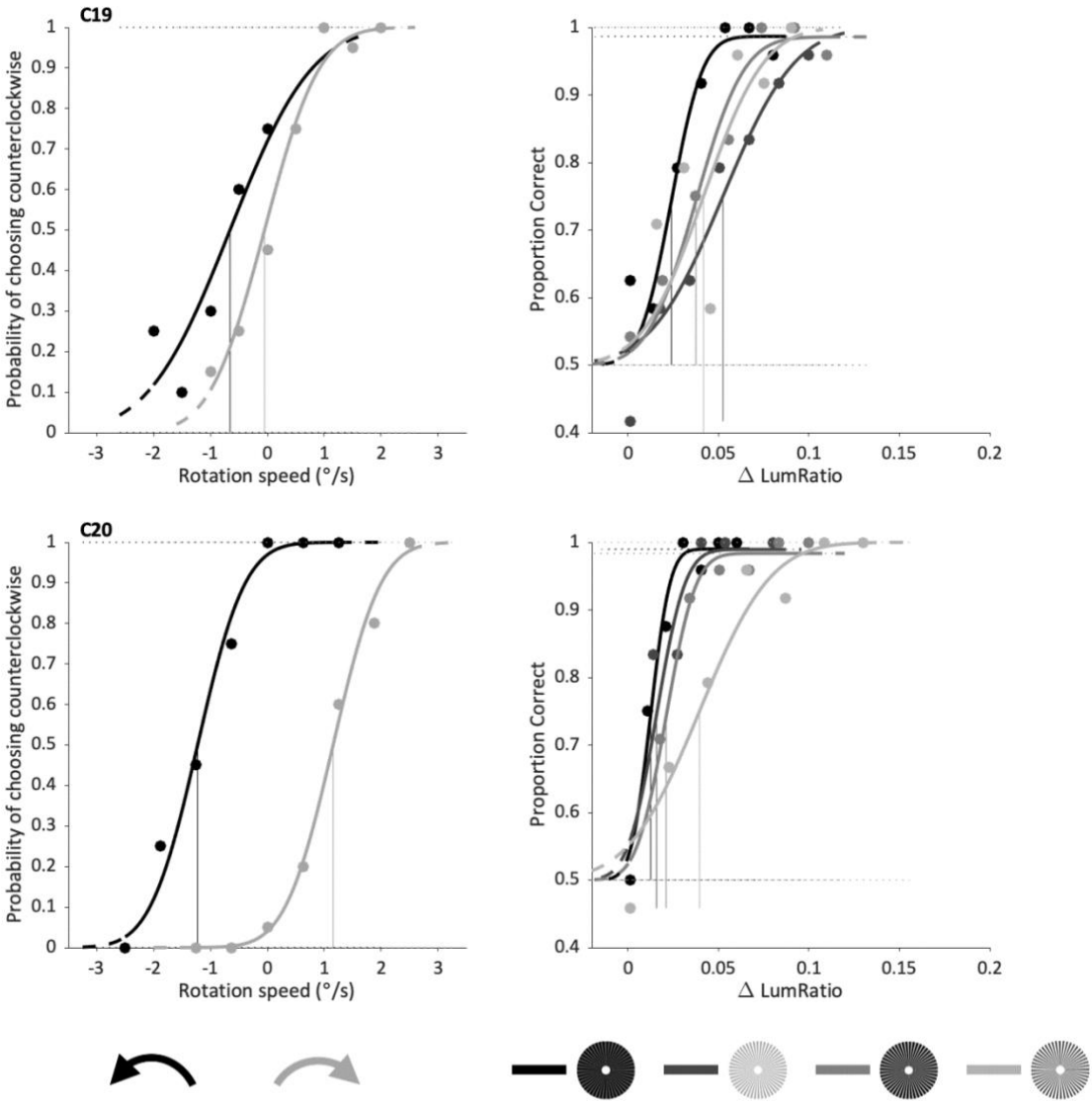

Figure A. 4-7 Data of control participants 19-20.

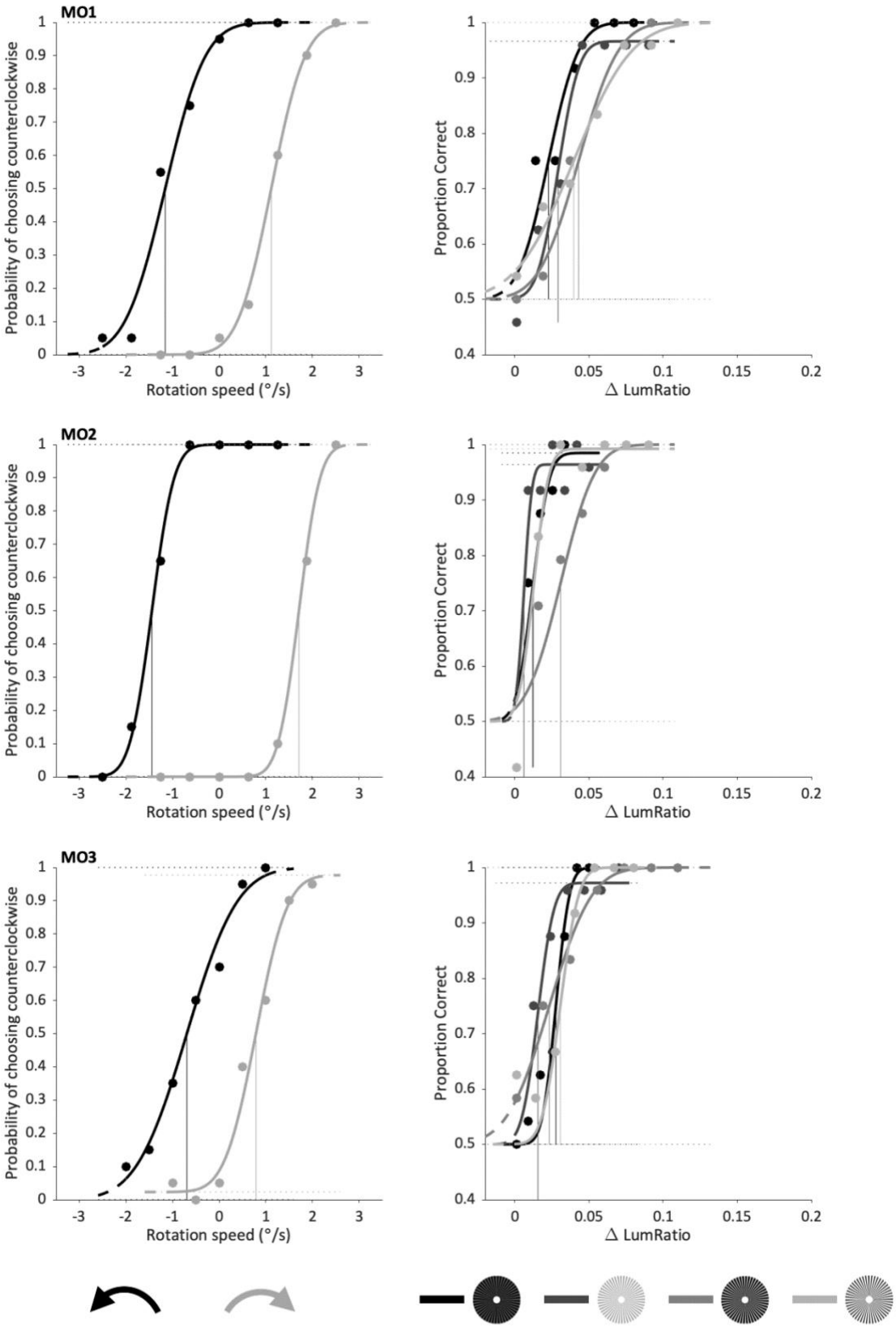

Figure A. 4-8 Data of MO participants 1-3.

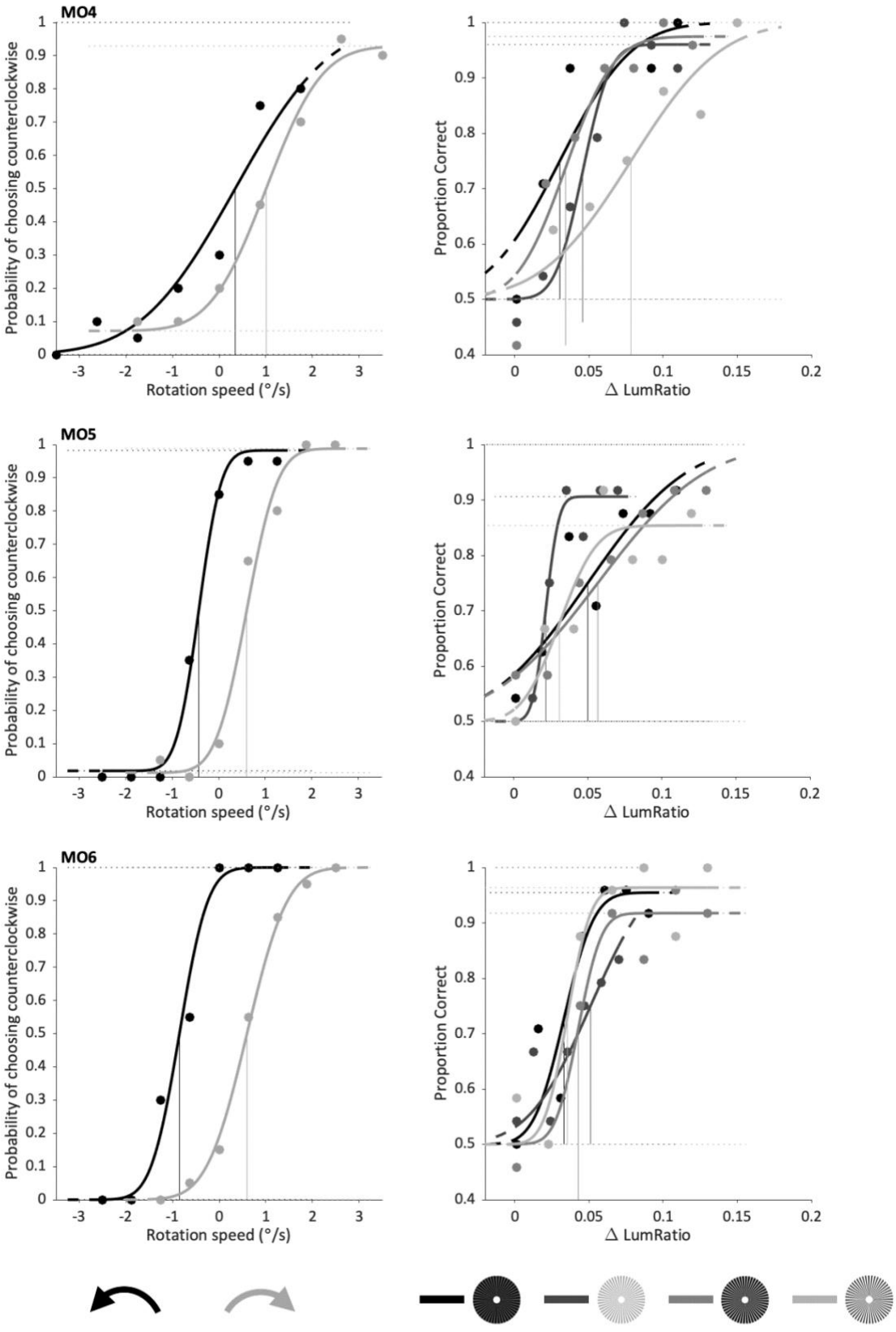

Figure A. 4-9 Data of MO participants 4-6.

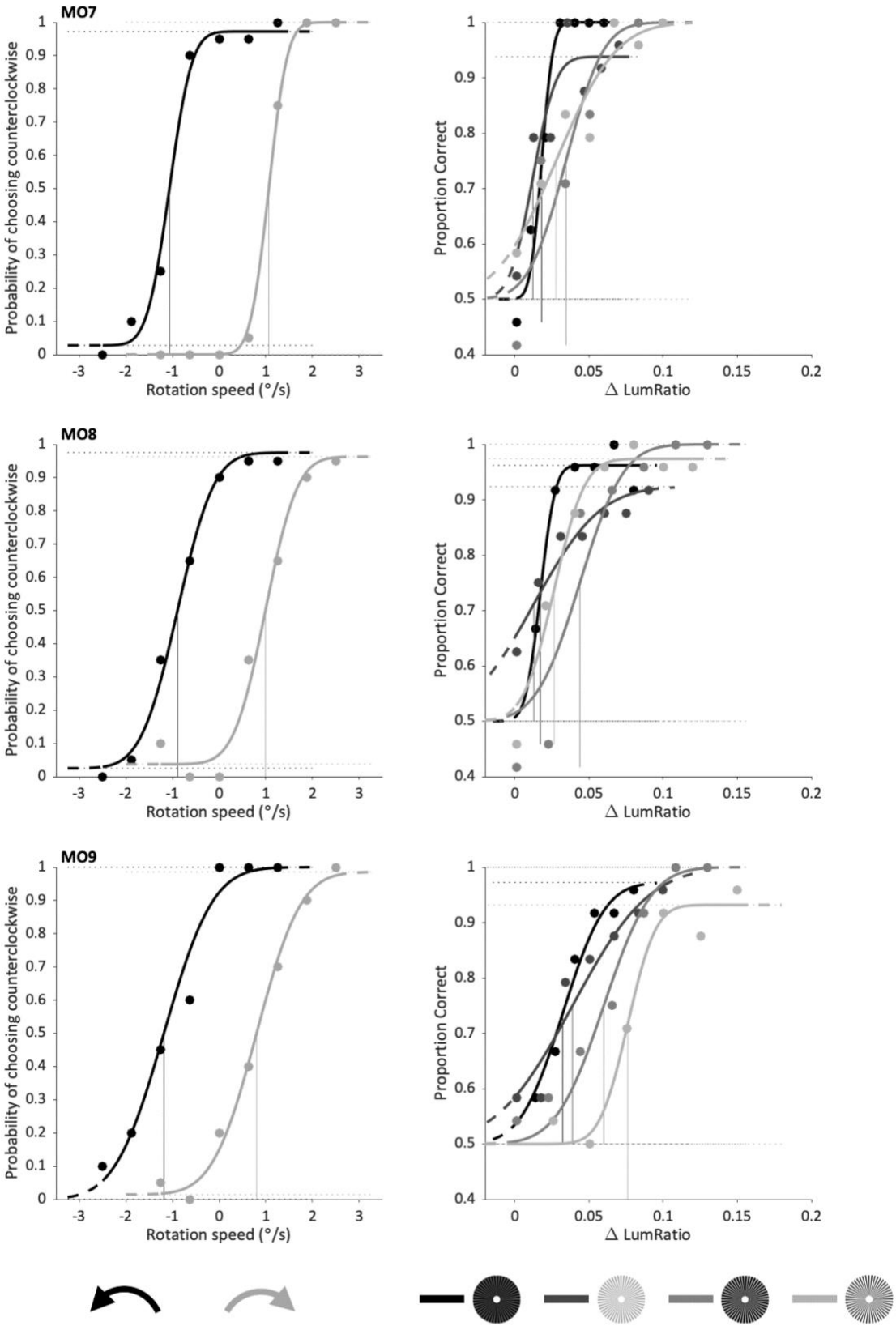

Figure A. 4-10 Data of MO participants 7-9.

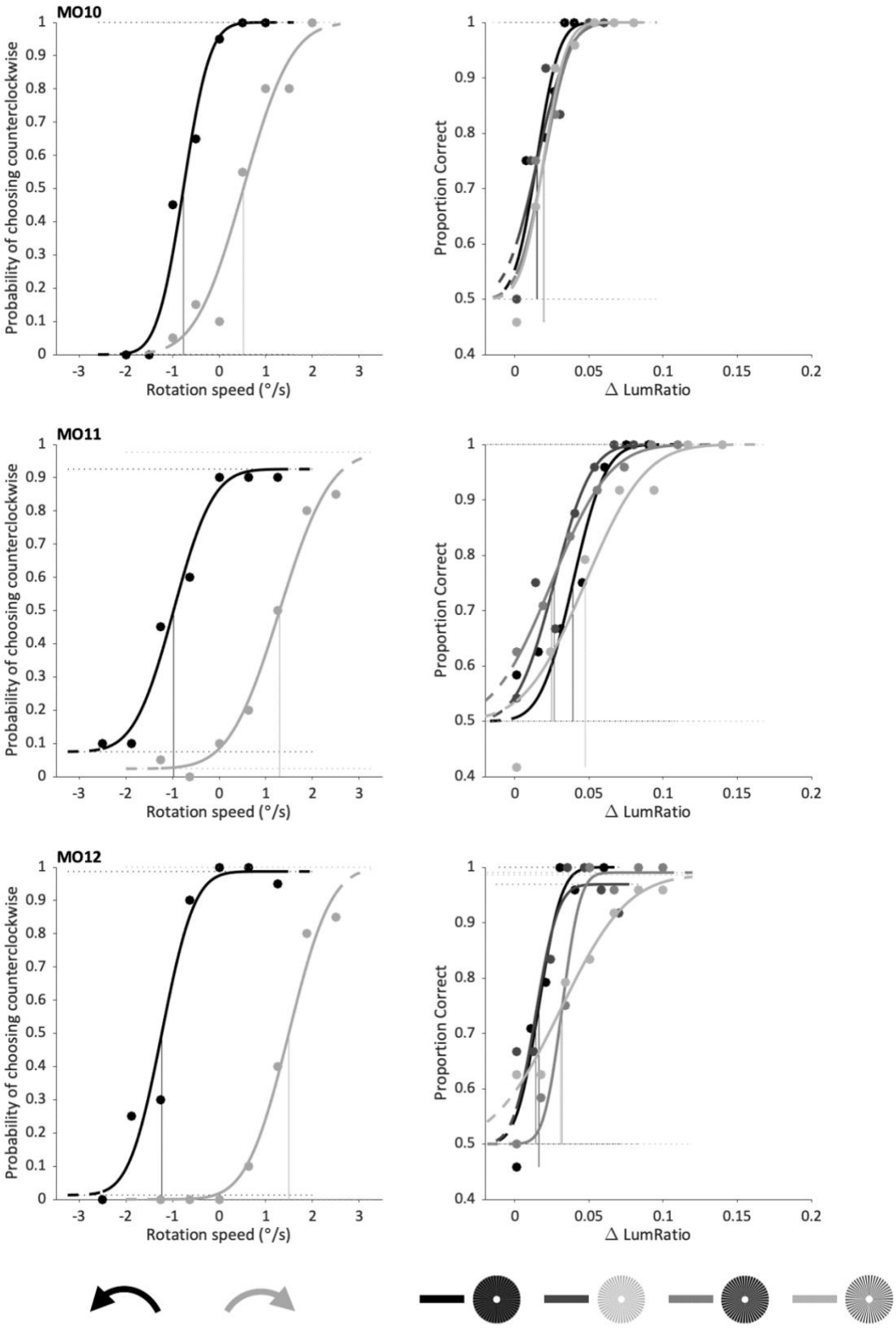

Figure A. 4-11 Data of MO participants 10-12.

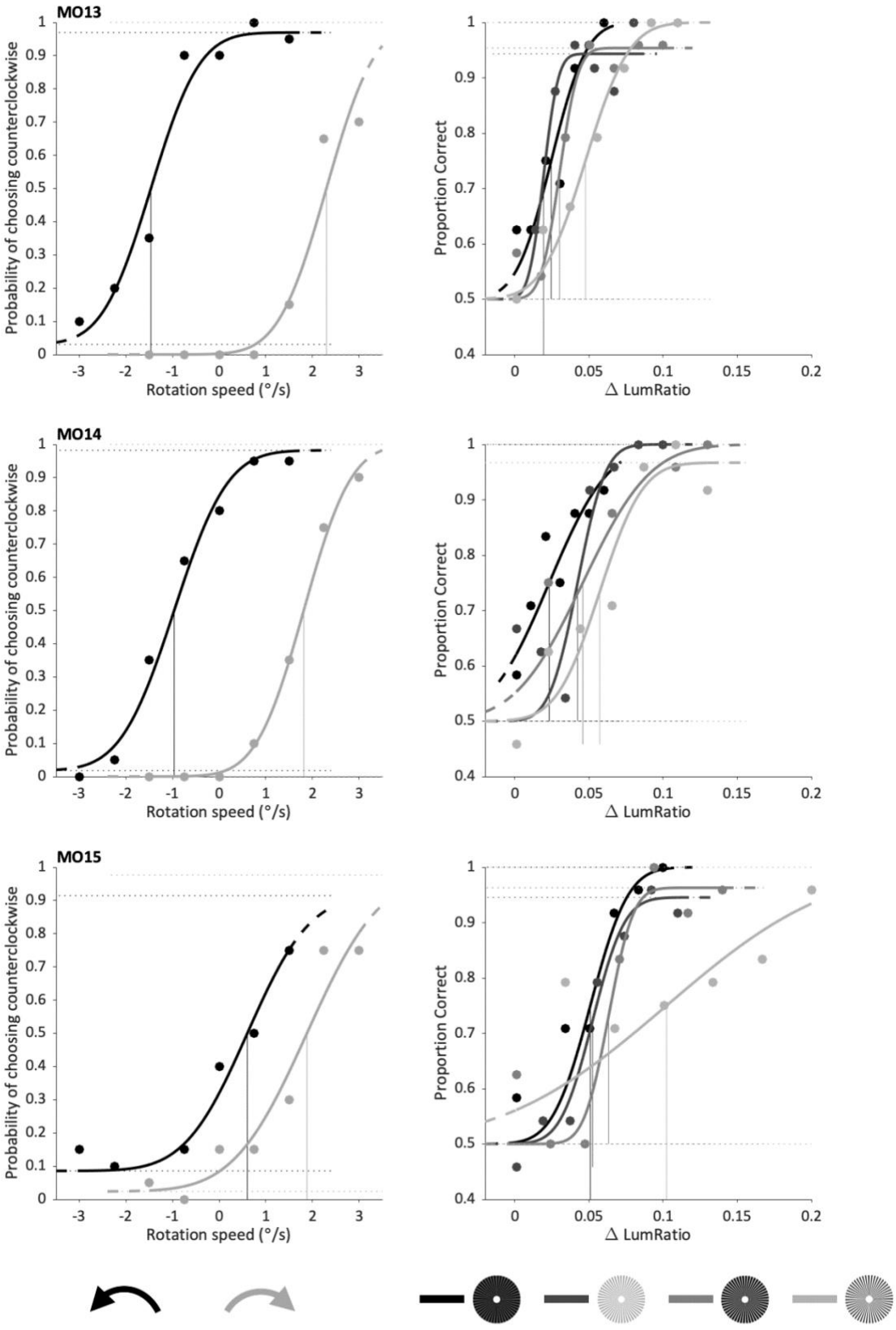

Figure A. 4-12 Data of MO participants 13-15.

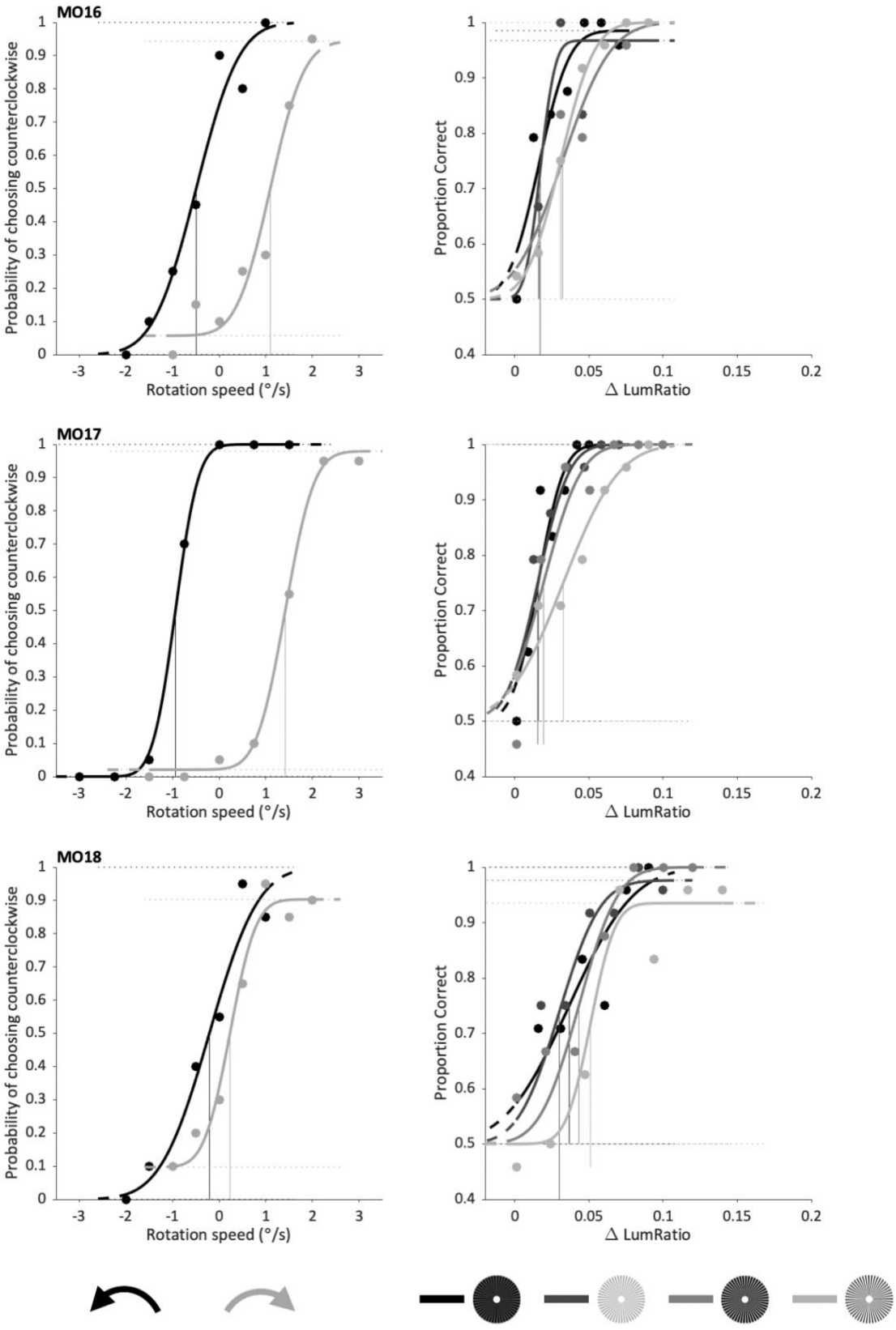

Figure A. 4-13 Data of MO participants 16-18.

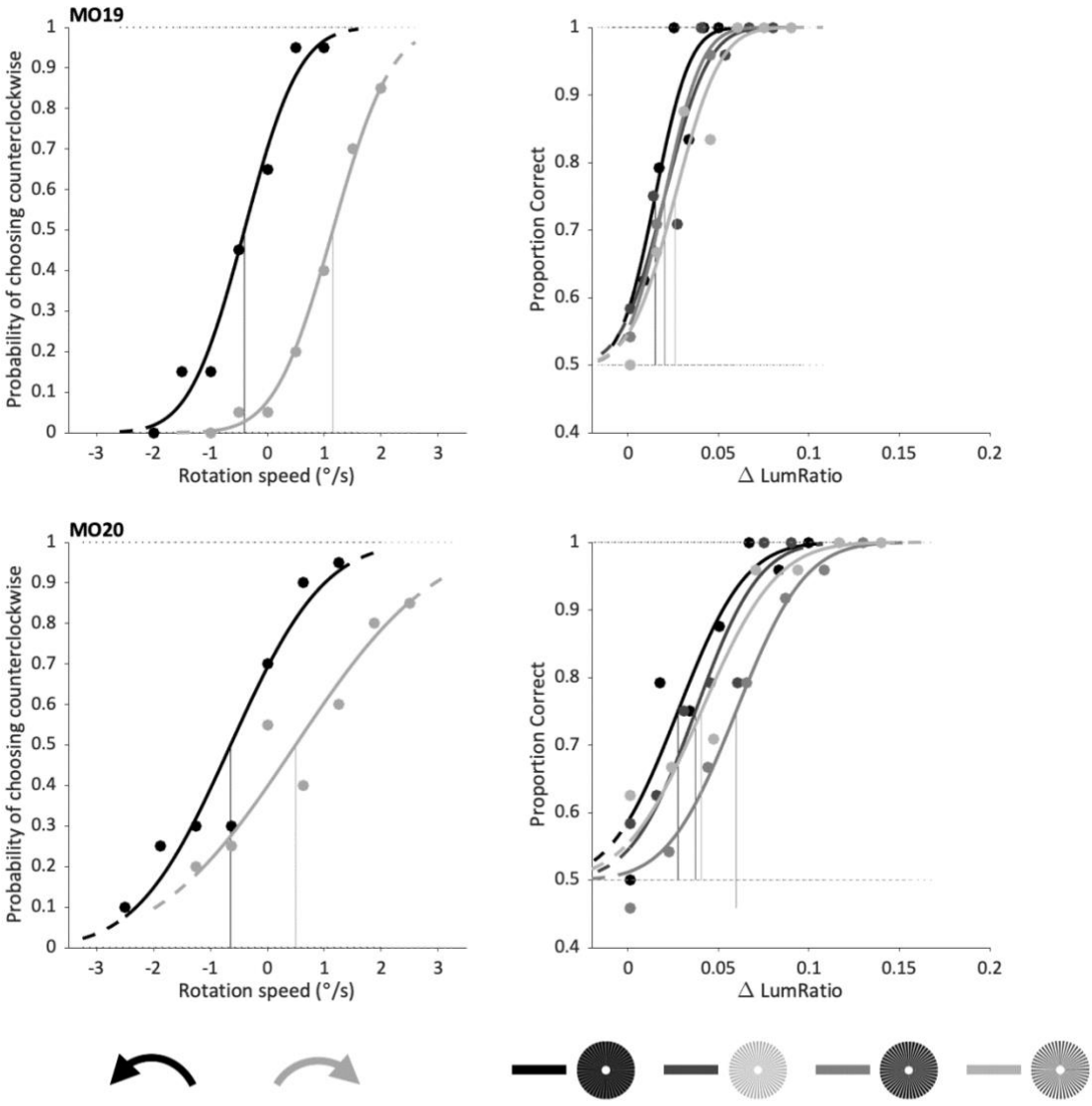

Figure A. 4-14 Data of MO participants 19-20.

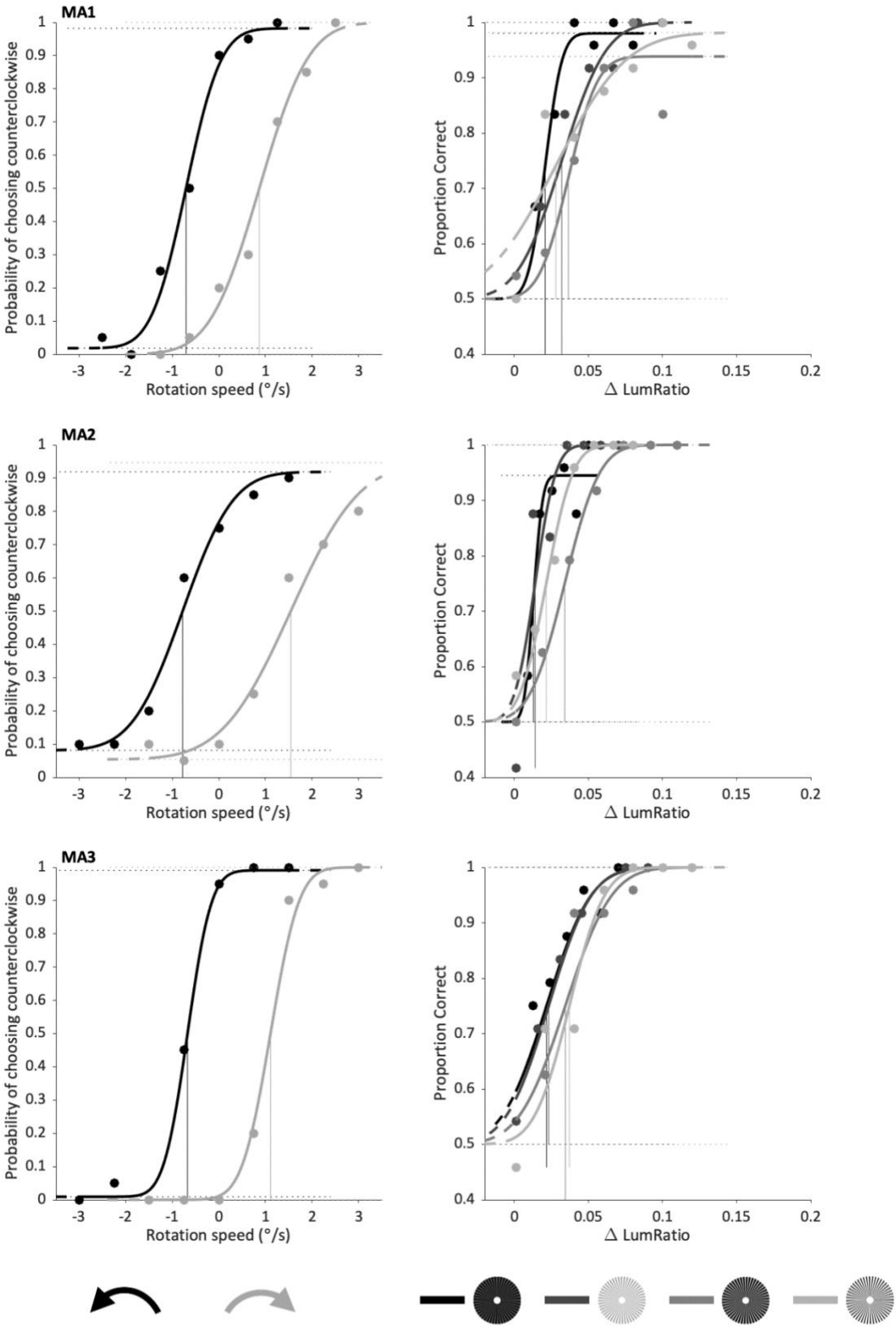

Figure A. 4-15 Data of MA participants 1-3.

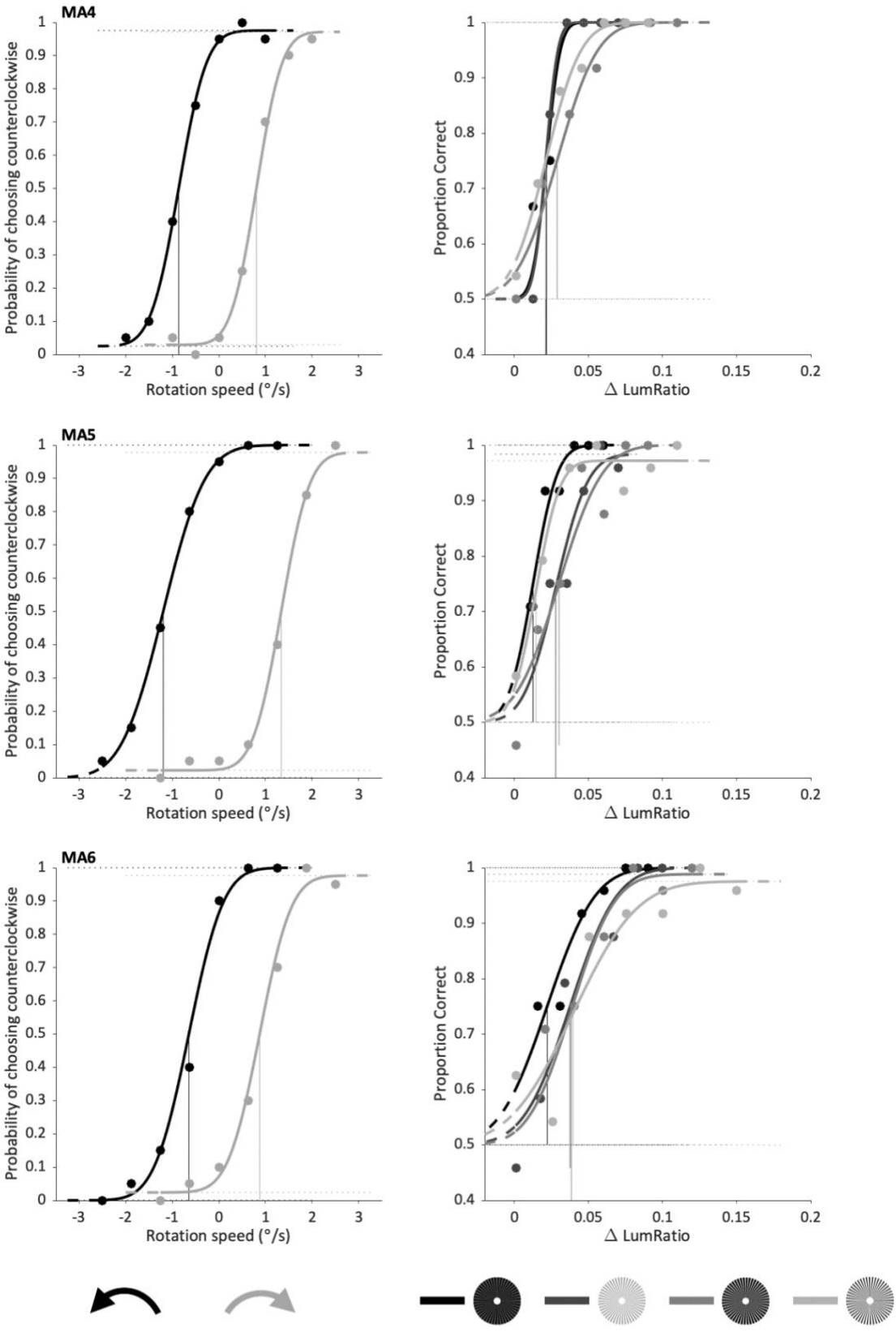

Figure A. 4-16 Data of MA participants 4-6.

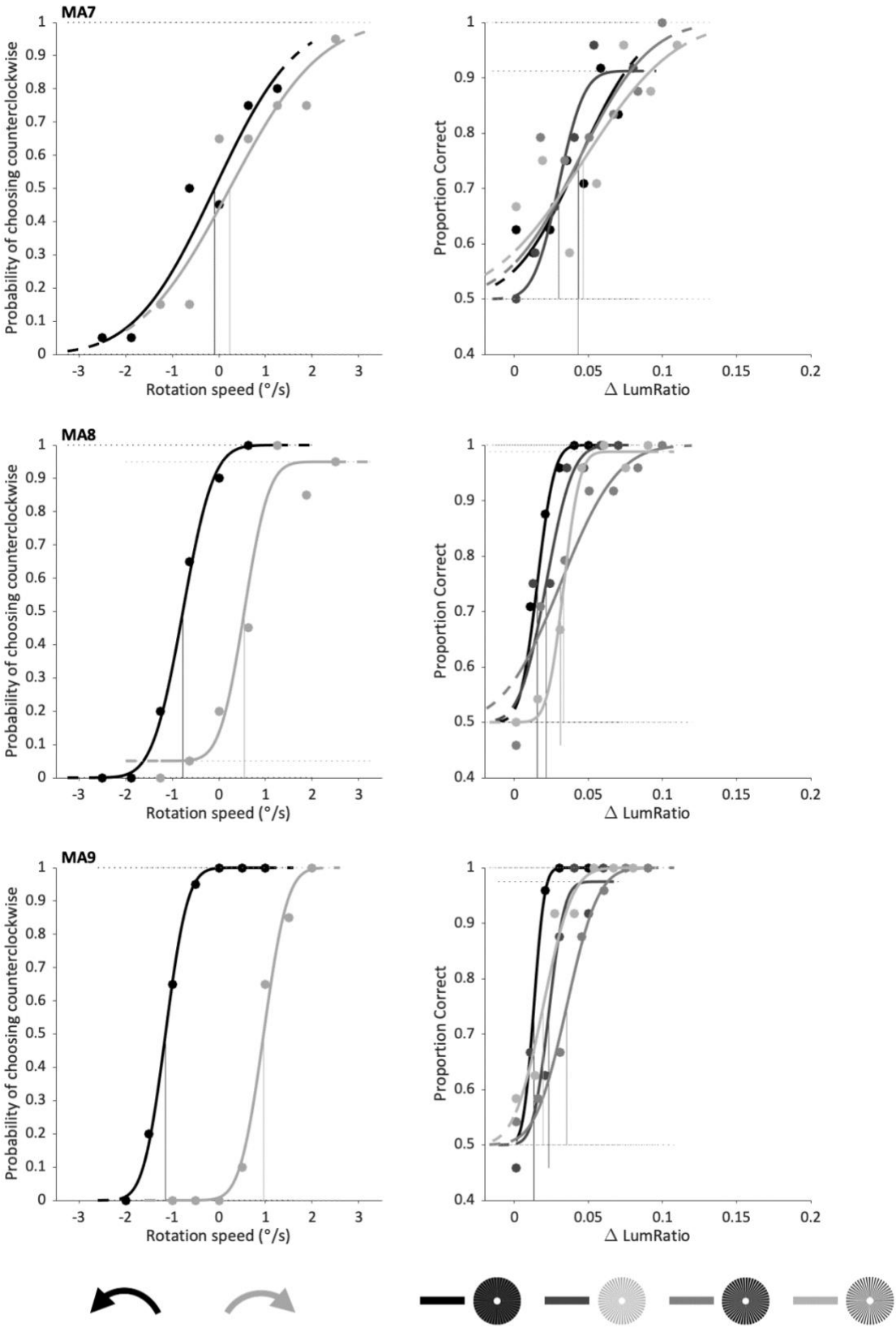

Figure A. 4-17 Data of MA participants 7-9.

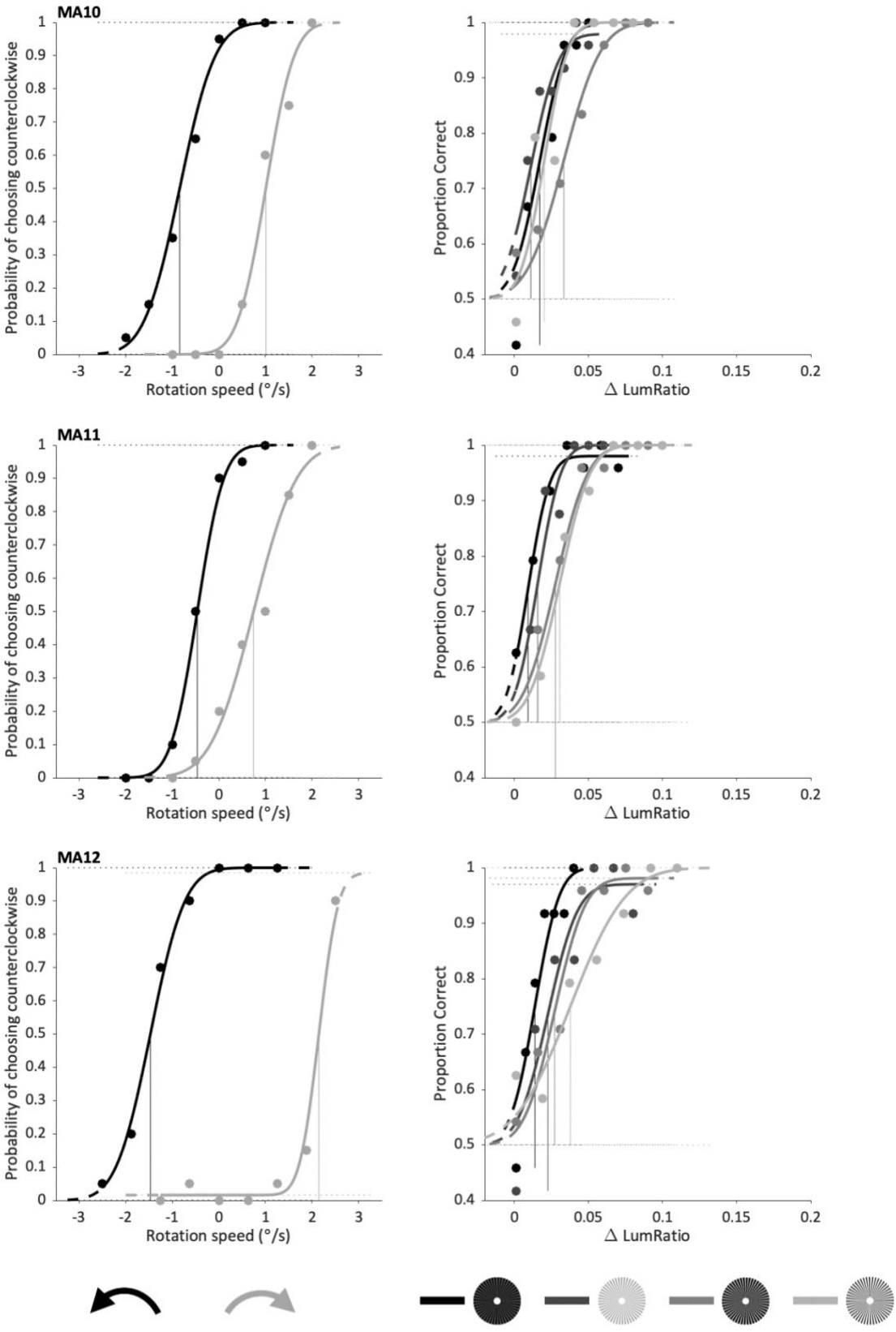

Figure A. 4-18 Data of MA participants 10-12.

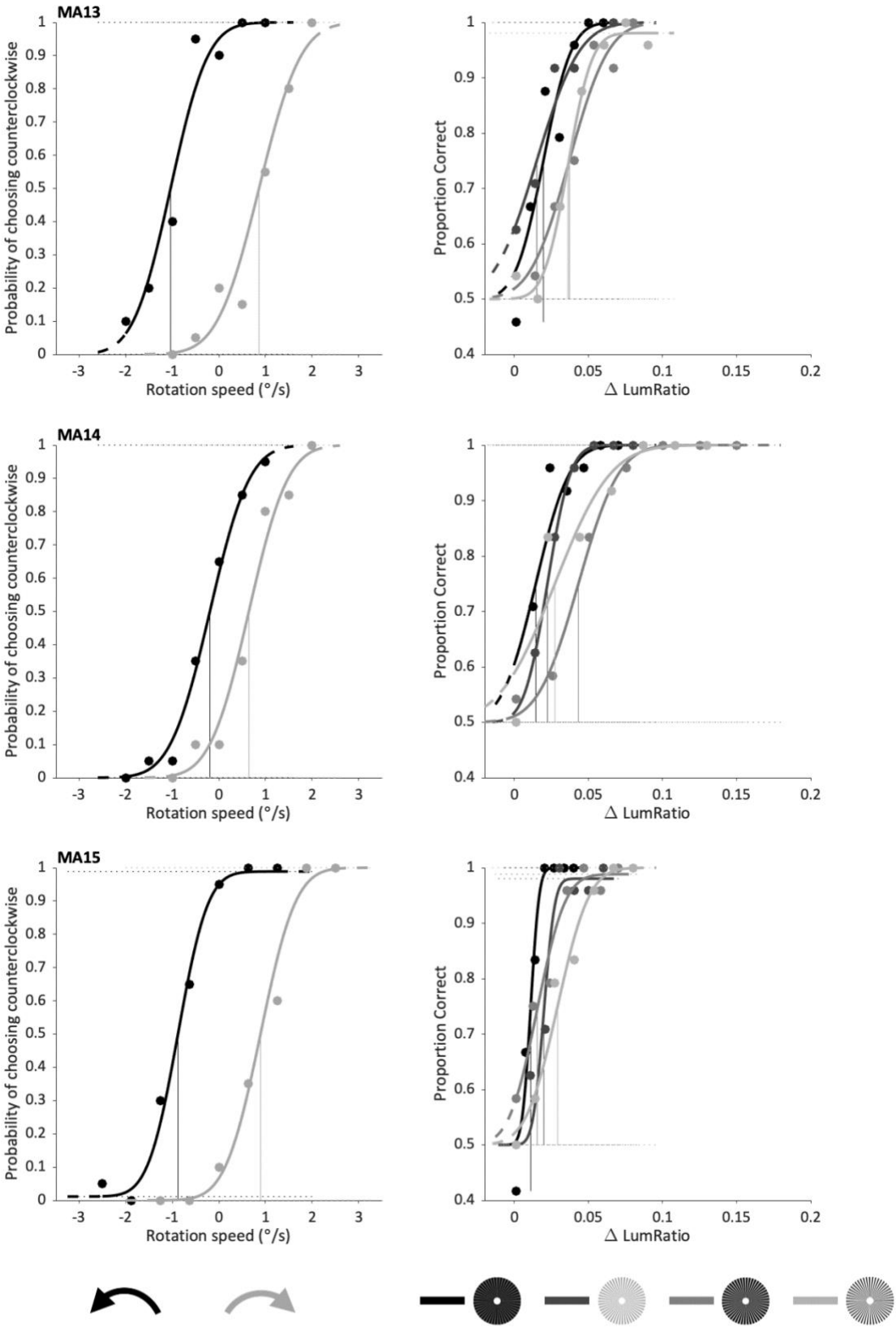

Figure A. 4-19 Data of MA participants 13-15.

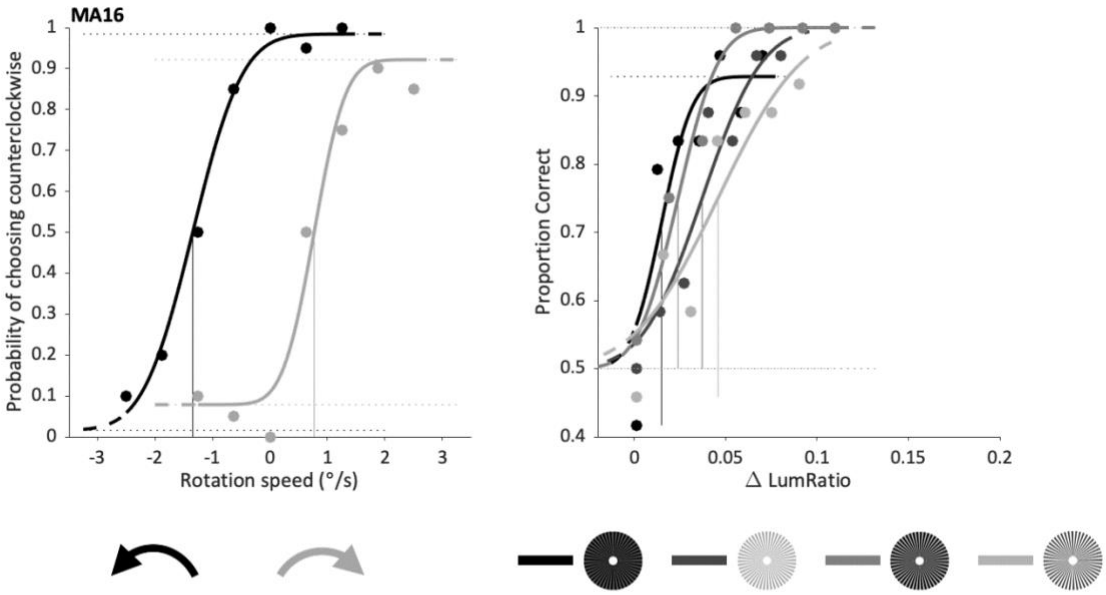

Figure A. 4-20 Data of MA participant 16.

Appendix 5 Correlations between score of individual item of the visual discomfort questionnaire and cancellation speed for Chapter 4

Table A. 5-1 Statistical results of Spearman correlation between cancellation speed and score of each item of the questionnaire on discomfort, headache trigger, and migraine trigger.

Spearman correlation		Discomfort (n=56)	Headache trigger (n=36)	Migraine trigger (n=36)
direct sunlight	Correlation Coefficient	0.103	-0.067	-0.145
	Sig. (2-tailed)	0.450	0.699	0.400
car headlights at night	Correlation Coefficient	0.068	0.035	-0.059
	Sig. (2-tailed)	0.618	0.838	0.732
shafts of light coming through trees or venetian blinds	Correlation Coefficient	0.082	0.209	0.081
	Sig. (2-tailed)	0.546	0.221	0.637
sunlight on water, snow or modern buildings	Correlation Coefficient	0.044	-0.033	-0.249
	Sig. (2-tailed)	0.750	0.848	0.142
contrasting patterns on materials, wallpapers, or pictures	Correlation Coefficient	0.071	0.404*	0.307
	Sig. (2-tailed)	0.603	0.015	0.069
fluorescent lights	Correlation Coefficient	0.069	0.063	0.100
	Sig. (2-tailed)	0.612	0.714	0.563
glare from computer, TV or phone screens	Correlation Coefficient	0.147	0.242	-0.030
	Sig. (2-tailed)	0.279	0.154	0.861
particular colours	Correlation Coefficient	0.176	0.015	0.009
	Sig. (2-tailed)	0.194	0.933	0.961
other visual stimuli	Correlation Coefficient	0.175	0.170	0.161
	Sig. (2-tailed)	0.197	0.320	0.347

*$p < 0.05$

Appendix 6 Correlations between migraine characteristics and experimental measurements for Chapters 4 and 5

Table A. 6-1 Statistical results of Spearman correlation between migraine characteristics and cancellation speed (Chapter 4), questionnaire score (Chapter 4), contrast discrimination thresholds (Chapter 5) and motion sensitivity (Chapter 5).

Spearman correlation (n=36)		**Days since last migraine**	**MIDAS score**	**Life migraine events**
cancellation speed	Correlation Coefficient	0.018	0.083	-0.058
	Sig. (2-tailed)	0.915	0.628	0.737
questionnaire migraine score	Correlation Coefficient	-0.424**	0.276	0.425**
	Sig. (2-tailed)	0.010	0.103	0.010
questionnaire headache score	Correlation Coefficient	-0.320	0.514**	0.316
	Sig. (2-tailed)	0.057	0.001	0.061
questionnaire discomfort score	Correlation Coefficient	-0.184	0.510**	0.156
	Sig. (2-tailed)	0.282	0.002	0.363
Mean contrast discrimination threshold rank	Correlation Coefficient	-0.233	0.160	0.215
	Sig. (2-tailed)	0.171	0.353	0.207
motion sensitivity	Correlation Coefficient	-0.064	-0.004	-0.092
	Sig. (2-tailed)	0.710	0.980	0.594

*p < 0.05

** p < 0.01

In experiment 2 (Chapter 4), 12 Spearman tests were conducted to test the relationship between 3 migraine characteristics and 4 experimental measurements (cancellation speed + 3 questionnaire scores). Holm-Bonferroni is calculated using the following equations:

$$alpha\ for\ smallest\ p\ value\ (0.001): \frac{0.05}{12-1+1} = 0.0042$$

$$alpha\ for\ second\ ranked\ p\ value\ (0.002): \frac{0.05}{12-2+1} = 0.0045$$

Thus, the correlation between MIDAS score and questionnaire headache and discomfort scores are significant.

Appendix 7 Approximate conversion from ΔLumRatio to Michelson contrast for Chapter 5

Conversion from ΔLumRatio to ΔC was calculated based on the assumption that any contrast change between the maximum and minimum luminance of the monitor is linear, given that the monitor was gamma corrected. Implemented formula are listed below:

$$\Delta C = C_{reference} - C_{test}$$

$$C_{reference} = \frac{L_{high} - L_{low}}{L_{high} + L_{low}}$$

$$C_{test} = \frac{(L_{\text{high}} - \Delta L) - (L_{low} + \Delta L)}{(L_{\text{high}} - \Delta L) + (L_{low} + \Delta L)}$$

$$\Delta L = (L_{max} - L_{min}) \times \Delta LumRatio + L_{min}$$

The contrast discrimination threshold (ΔC) in Michelson contrast (Michelson 1927) is the minimum difference between the contrast of reference pattern ($C_{reference}$) and that of the test pattern (C_{test}). A reduction in contrast of the test pattern was achieved by deduction and addition of the same amount of luminance (ΔL) to the brighter (L_{high}) and darker (L_{low}) sections of the reference pattern. ΔL was converted from the arbitrary contrast discrimination threshold ΔLumRatio. The average maximum (L_{max}) and minimum (L_{min}) luminance of the monitor was 140 cd/m^2 and 0.01 cd/m^2 respectively. Assuming that the luminance was 140 cd/m^2 for white (L_w), 93.34 cd/m^2 for light grey (L_{lg}), 46.67 cd/m^2 for dark grey (L_{dg}), and 0.01 cd/m^2 for black (L_b), application of the above described formula in each type of pattern resulted in the conversion formula below:

$$\Delta C_1 = \frac{L_{dg} - L_b}{L_{dg} + L_b} - \frac{(L_{dg} - \Delta L) - (L_b + \Delta L)}{(L_{dg} - \Delta L) + (L_b + \Delta L)} \approx 6\Delta LumRatio$$

$$\Delta C_2 = \frac{L_w - L_{lg}}{L_w + L_{lg}} - \frac{(L_w - \Delta L) - (L_{lg} + \Delta L)}{(L_w - \Delta L) + (L_{lg} + \Delta L)} \approx 1.2\Delta LumRatio$$

$$\Delta C_3 = \frac{L_{lg} - L_b}{L_{lg} + L_b} - \frac{(L_{lg} - \Delta L) - (L_b + \Delta L)}{(L_{lg} - \Delta L) + (L_b + \Delta L)} \approx 3\Delta LumRatio$$

$$\Delta C_4 = \frac{L_w - L_{dg}}{L_w + L_{dg}} - \frac{(L_w - \Delta L) - (L_{dg} + \Delta L)}{(L_w - \Delta L) + (L_{dg} + \Delta L)} \approx 1.5\Delta LumRatio$$

Appendix 8 Correlations between subjective questionnaire scores and contrast discrimination and motion sensitivity for Chapter 5

Table A. 8-1 Statistical results of Spearman correlation between mean contrast discrimination threshold rank, motion sensitivity and score of each item of the questionnaire on discomfort, headache trigger, and migraine trigger

Spearman correlation		**Discomfort (n=56)**	**Headache trigger (n=36)**	**Migraine trigger (n=36)**
Mean contrast discrimination threshold rank	Correlation Coefficient	0.022	0.125	0.327
	Sig. (2-tailed)	0.873	0.469	0.052
Motion sensitivity	Correlation Coefficient	-0.184	-0.247	-0.082
	Sig. (2-tailed)	0.174	0.146	0.634

Appendix 9 Supplementary data of effects of spatial frequency for Chapter 6

The data were collected from 3 participants using the method as described in Chapter 3. In the main experiments, stimuli were in 24 cycles. This experiment was initially conducted to explore the finding that type 2a generated a stronger illusion in Chapter 3. The 36 and 18 cycles pattern of type 3 matched segment widths of thinner (black and white) and thicker (dark grey and light grey) area of type 2a in 24 cycles respectively. Individual psychometric functions are shown in Figure A. 9-1. The results are presented here to demonstrate that the 24 cycles used in the current study tends to be the optimal spatial frequency for the Fraser-Wilcox illusion. A pair sampled t-test showed that the cancellation speed of type 3 stimulus for the 24-cycle condition is significantly faster than the 36-cycle condition ($t(2) = 6.49$, $p = 0.02$).

As the stimulus is wheel pattern and was presented eccentrically (12°), the estimated spatial frequencies (1.1cpd for 24 cycle, 1.6cpd for 36 cycle) are based on the outside radius, where the spatial frequency is the smallest within the pattern (see Figure A. 9-2).

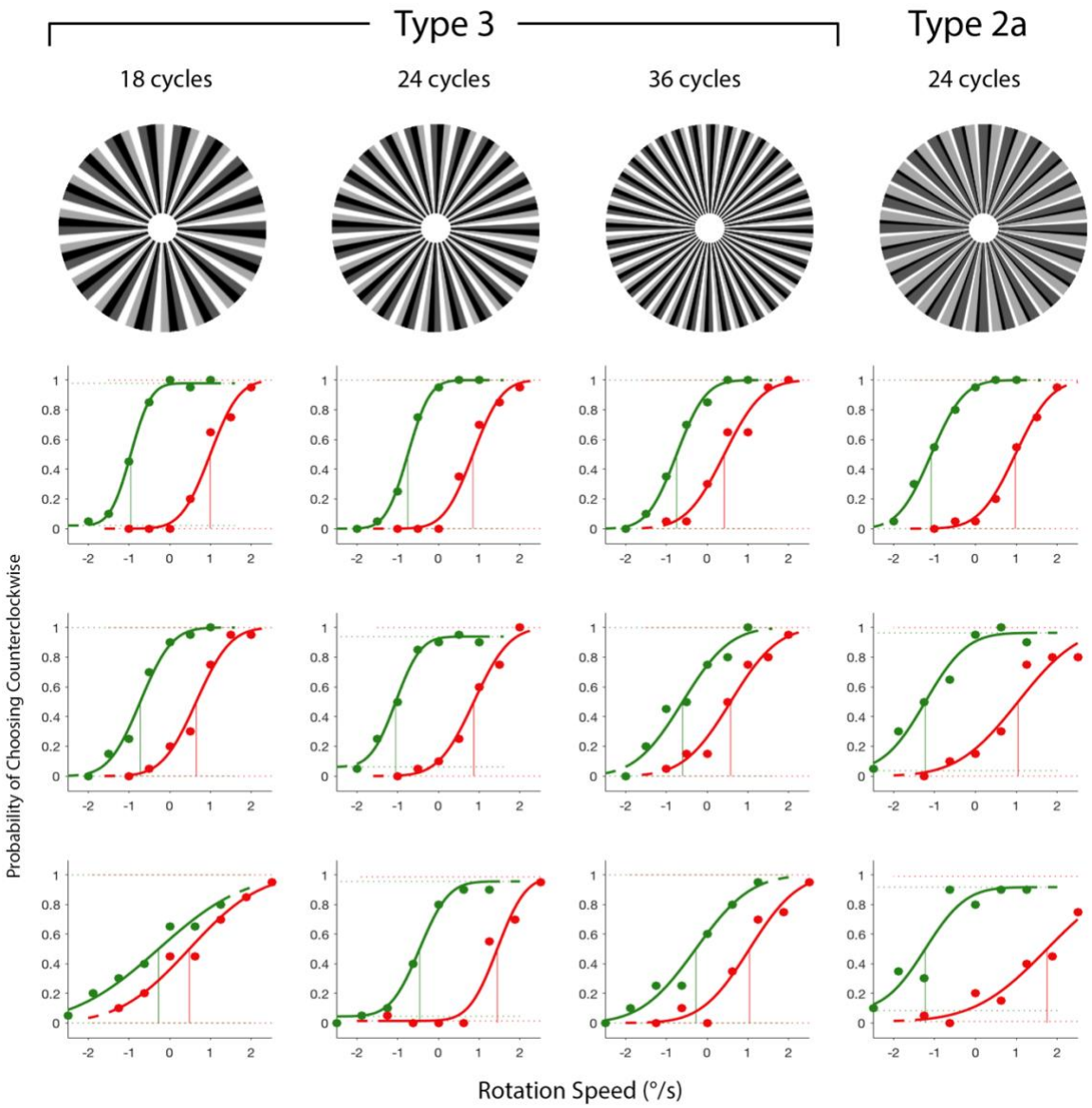

Figure A. 9-1 Individual results (symbols) for the 4 types of luminance profiles (as indicated in the top row) fitted with psychometric functions (solid lines). Each row represents one participant. Red = clockwise pattern, Green = counterclockwise pattern. Positive rotation speed corresponds to counterclockwise.

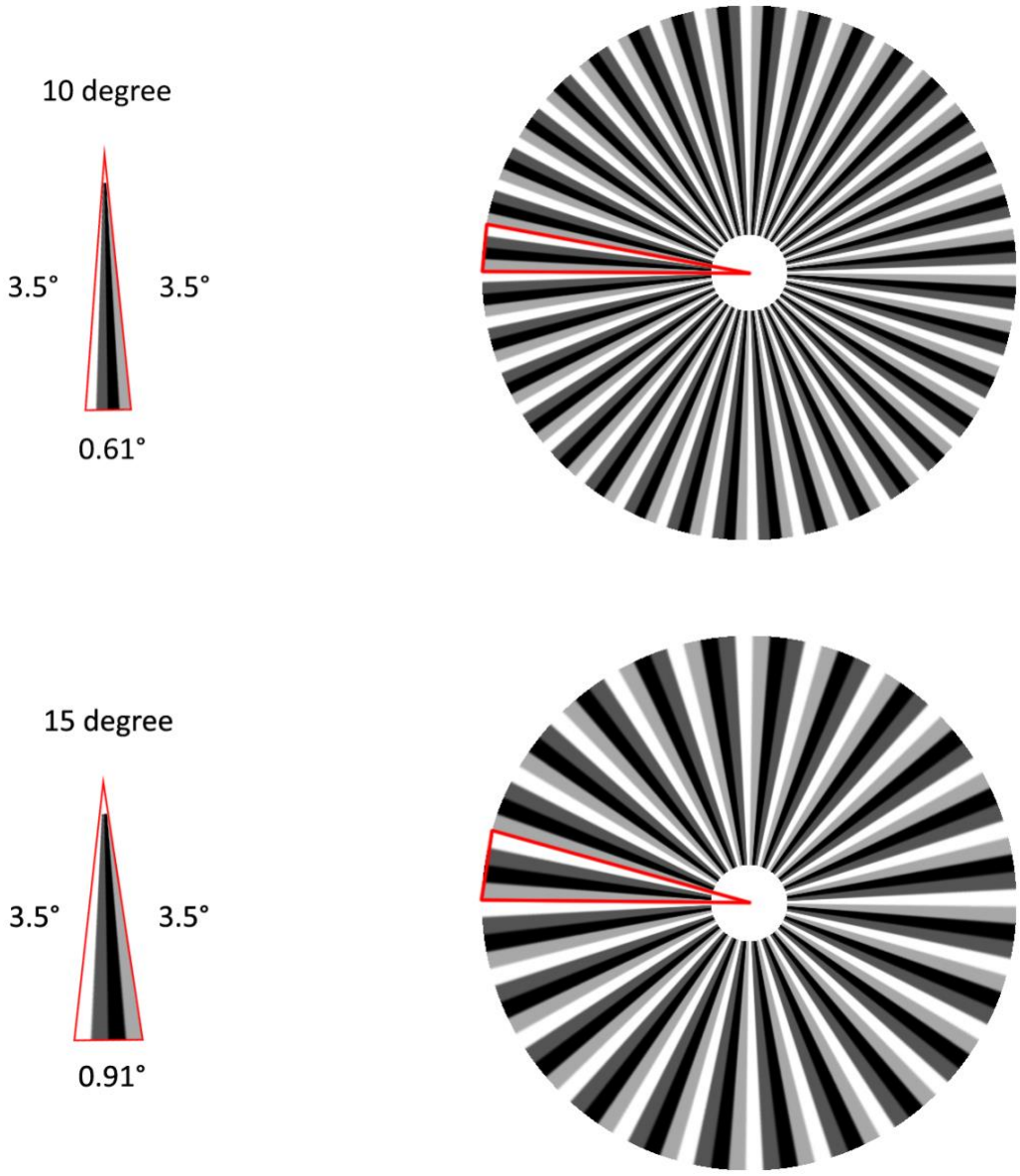

Figure A. 9-2 Illustration of estimating spatial frequency of the 36-cycle and 24-cycle type 3 stimulus. The triangle on the left is obtained from one cycle of the wheel patterns shown on the right. Degree denotes angle in the triangles. °denotes visual angle.

Appendix 10 Response to reviewers

Table A. 10-1 Response to examiner 1.

Examiners comment	Student's response	Change made to thesis (if any)
1. The introduction should motivate your choice of measures more clearly, you allude to this but do not explicitly give the reason for why you chose to use your own measure of visual discomfort rather than existing ones (e.g. Conlon et al., 1999 Visual Discomfort Scale).	The reason why a customised, and not existing, questionnaire about visual discomfort was chosen for this study is because most items in the Visual Discomfort Scale by Conlon et al (1999) asked about reading difficulties. Reading difficulty was not the focus of this study, and the locus of reading impairments has been suggested, by Conlon et al. (2012), to be at processing levels higher than the locus of impairment for visual discomfort. Given that the aim of this study was to investigate visual discomfort in people with and without migraine, we created a questionnaire to specifically enquire about visual stimuli.	p.14 "The reading impairments in migraine and its association with visual discomfort might be an area worth investigating. However, given the complexity of visual discomfort in itself, we created a questionnaire aiming to assess visual discomfort more directly."

2. The methods section should clarify the criteria for "interictal" – this is mentioned later, but it should be here, so that the reader is clear on this from the beginning.	As recommended by the examiner, the criteria that people with migraine need to be tested at least 3 days after the last migraine attack has been added.	p.38 "Migraine participants were contacted the day before the appointment to check recency of migraine events, which allowed individuals who had experienced a migraine attack within 3 days of the proposed test session to be rescheduled."
3. There is an issue with the number of repetitions per data point, this is lower than would normally be the case for the method of constant stimuli. For example, see Chapter 4, "A Practical Introduction to Psychophysics", by Kingdom and Prins (2009). As the number of repetitions is low, estimates for the fitted parameters may be less accurate. For future work, a staircase procedure may have been better for use with clinical groups where the number of trials needs to be limited. As it is, the choice of low number of trials must be justified, and addressed statistically, perhaps using	In the original thesis, it might be ambiguous how many repetitions were collected per data point. To clarify, there were 5 repetitions of each speed included in each run, and participants performed 4 runs in total. Thus, there were 20 trials per data point for the motion illusion task, and 24 trials for the contrast discrimination task. These numbers of repetitions are standard for the method of constant stimuli and psychometric function curve fitting in the applied vision literature.	p.101 "There were 20 trials per data point for the motion illusion task, and 24 trials per data point for the contrast discrimination task."

estimates of the fits. I believe "psignifit 4" will include estimates of the deviance, which would be a measure of the fit. Looking at the individual data in the appendix, the fits for C2 and C3 for the motion task, MO15, MO18, MA1, MA7, MA16 contrast task, for example.	The total number of trials of each task has been added.	
4. Make it clear the first experiment (measuring strength of different types of illusion) was conducted as a short pilot with 4 observers, this will help orient the reader better. You could signpost this to the reader in the introduction, and also in the Method section.	The introduction and methods have been amended for clarity.	p.35 "The first experiment, which is a short pilot with 4 observers, aimed to choose the stimulus to be used in experiment 2 among five types of 'optimised' Fraser-Wilcox illusion." p.46 "This pilot experiment aimed to……"
5. Results would benefit from reporting estimates of effect sizes where relevant, e.g. Friedman's tests, ANOVA, Kruskal-Wallis tests.	As recommended by the examiner, effect sizes have been added throughout the thesis where relevant.	p.v "Thank you Cameron Patrick from Melbourne Statistical Consulting Platform for the statistical advice." p.43 "Partial omega squared (ω_p^2) was used as a measure of effect size for

		ANOVA ……” till the end of the Chapter p.51 “W = 0.9” “, median of difference = 0.84°/s” “, median of difference = 0.90°/s” p.57 “η_H^2 = 0.23” “η_H^2 = 0.43” “, difference of median = 4” “, difference of median = 4” “, difference of median = 3” p.69 “ω_p^2 = 0.747” “, mean difference on log threshold = 0.08, 95CI [0.03, 0.12], d_{av} = 0.417” “, mean difference on log threshold = 0.13, 95CI [0.09, 0.18], d_{av} = 0.764” “mean difference on log threshold = 0.15, 95CI [0.11, 0.19], d_{av} = 0.882”

6. Discussion should consider the effect of eccentricity on the shape of the contrast sensitivity function, as the direct comparison between 1cpd peripherally viewed and 3cpd (or other frequencies) viewed centrally may not be valid.	The primary aim of this thesis was to quantitatively measure a visual motion illusion and its relationship to subjective visual discomfort. The Fraser-Wilcox illusion and contrast discrimination task used in this thesis involved suprathreshold contrast processing, rather than contrast sensitivity. Therefore, we consider it outside the scope of this thesis to discuss the effect of eccentricity on the shape of the contrast sensitivity function, as it is not clear how contrast sensitivity (rather than suprathreshold contrast processing) relates to illusion strength. Nevertheless, I have rephrased the first sentence of the paragraph discussing spatial frequency difference between the current and previous stimuli to indicate that our spatial frequencies and	p.76 “Along with the increased eccentricity, the spatial frequencies of our stimulus were also different from that of the high contrast striped patterns.”

	eccentricities were both different.	
7. “Furthermore, treatments that only act on controlling neurogenetic inflammation but without the effect of vasoconstriction (triptans)…”, rephrase this section, to make it clear that triptans cause vasoconstriction, and these are effective in migraine, whereas treatments controlling only the inflammation, but not causing vasoconstriction, are not effective in migraine. At the moment it is not clear whether or not triptans cause vasoconstriction or not.	As recommended by the examiner, the Introduction has been amended to clarify the effect of triptans.	p.5 “Furthermore, certain triptans, which exhibit both anti-inflammatory and vasoconstrictive effects, are effective acute migraine treatments. Attempted triptan treatments which only act on controlling neurogenic inflammation but without the effect of vasoconstriction do not alleviate or prevent migraine headaches (for review see Goadsby et al. (2017)).”
8. You might briefly describe familial hemiplegic migraine.	As recommended by the examiner, the definition of familial hemiplegic migraine has been added to the Introduction.	p.7 “People with familial hemiplegic migraine experience motor weakness in addition to typical aura symptoms, and have at least one first- or second- degree relative experiencing the

		same migraine condition (International Headache Society, 2018).”
9. Typo – retinal’, there is an extra ‘ symbol	The original sentence was “In humans, aura can manifest as a disruption in ‘visual, sensory, speech and/or language, motor, brainstem, retinal’ functions (International Headache Society, 2018).” Therefore, the ’ after retinal was not a typo but a quotation mark.	No changes were made
10. “Daily administration of migraine prophylaxis” – was this a drug, if so, which?	To describe the study referred to in the Introduction in more detail, the specific migraine prophylactic drugs used by the rats in the study have been added.	p.8 “(topiramate, valproate, amitriptyline, DL-propranolol, and D-propranolol)”
11. Briefly describe clinically silent CSD for clarity.	The definition of clinically silent CSD by the study has been clarified in the Introduction.	p.8 “Woods et al. (1994) proposed that CSD might also occur in migraine without aura attacks, despite the absence of obvious typical migraine aura symptoms.”
12.	As recommended by the examiner, the definition of	p.9

"Another term, lack of habitation…", explain whether this is prolonged (longer lasting response) or simply larger responses (increased amplitude response), some of the VEP literature on migraine cites a cumulative effect of the many repetitions resulting in an overly large response, rather than a response that lasts longer. Rephrase this section slightly to be clear.	habituation has been clarified.	"Another term, lack of habituation, has been used to describe cortical responses that fail to adapt to constant or repetitive visual stimuli in people with migraine (for review see Brighina et al. (2009)). Typically, the magnitude of the cortical response dampens over time with exposure to a visual stimulus. However, several visual evoked potential studies demonstrate that the visually evoked cortical response in people with migraine does not become smaller over time, resulting in an overly large response relative to non-migraine control responses."
13. "The findings of abnormal visual processing have been proposed to be either primarily caused by enhanced excitatory synapses or secondarily caused by weaker	The relevant reference has now been cited in the Introduction.	p.10 "These findings of abnormal visual processing have been proposed to be either primarily caused by enhanced excitatory

inhibitory synapses" – reference who proposed this.		synapses (Welch et al. 1990) or secondarily caused by weakened inhibitory synapses (Palmer et al. 2000)."
14. "light stimulation" is a little vague – viewing a striped pattern is also light stimulation. You want to clarify this here, I believe the paper you are citing is specifically using flicker, but there is also work by this group on the wavelength of the light stimulation. Clarify this section.	A "uniform" has been added in front of the "light stimulation" to indicate that non-patterned uniform light stimulation is the focus of this section.	p.11 "Assuming that interictal visual discomfort induced by uniform light stimulation might have shared mechanisms to ictal photophobia…"
15. Boulloche et al., (2010) reference you describe their findings "In interical migraine participants, such light stimulation could activate the visual cortex even if no pain was applied" But then it is not clear why the next sentence should be concluded: "Hence Boulloche et al., (2010) interpreted their result as lack of habituation". This is also true, they did conclude habituation differences, but it is not clear from the paragraph *why* the authors reached the conclusion of habituation. In the paper they cite	As recommended by the examiner, a sentence has been added between the two disconnected sentences to clarify that the authors' conclusion of lack of habituation in migraine participants was based on both their abnormal cortical responses to low intensity uniform light stimulation and subjective report of cumulative visual discomfort during the test.	p.11 "In addition, people with migraine also reported cumulative increase of visual discomfort throughout the study."

long stimulus duration and the cumulative increase of self-reported discomfort throughout the study, you should make this clear to the reader.		
16. "other clinical populations" – who are they specifically?	As recommended by the examiner, "other clinical populations" have been specified.	p.12 "(e.g. epilepsy and dyslexia)"
17. Haigh et al., (2012) there was no interaction between motion type and migraine group in this study. This would imply that contrast, rather than the motion/lack of motion of the pattern, is important in this group of individuals with migraine. Would this not suggest no difference between the groups in terms of temporal properties? I would revise this last section of the paragraph to indicate findings are more mixed.	The purpose of this paragraph in the Literature Review was to discuss previous attempts to quantify visual discomfort by increasing the spatial and/or temporal contrast of a visual stimulus and directly asking participants when the stimulus was no longer 'bearable'. In the next paragraph, as a summary of this whole section, it has been pointed out that a common disadvantage of all the current measurements of visual discomfort is that they all depend on subjective self-report. To remind the readers of the purpose of this section, I	p. 13 "Overall, it appears that people with migraine show less tolerance to increasing contrast across a range of different stimuli. However, using this method, participants are explicitly asked to stop the stimulation if it becomes too uncomfortable, which can prime a person to react in a certain way if they already know that they find visual stimuli aversive."

	have added a conclusion sentence to this paragraph instead of adding the discussion of the findings of one specific paper as suggested by the examiner.	
18. The relevance of this section 1.5.3 is not immediately apparent, as your study is primarily about illusory motion perception and so I would rephrase this section to make the relevance clearer.	The section subtitle and the first sentence has been changed to make relevance of this section clearer.	p.14 "1.5.3 An indirect path to pattern induced visual discomfort" "Other than attempts to understand pattern induced visual discomfort by inquiring about perception for the high contrast grating stimuli, more contextualised questions might be easier for participants to answer."
19. You make the point that the Conlon et al., (1999) scale mostly refers to reading. Is this a reason for not using this questionnaire in your experiments? If this is the case the rephrase this section to make this clearer.	The reason for not using Conlon's visual discomfort scale was added in response to comment No.1.	

20. You might also consider including the reason why you do not use the Pattern Glare Test directly as well.	Our human research ethics approval restricted the test session duration to 2 hours per visit. We prioritised other tasks that were directed at testing the specific hypotheses.	No changes were made
21. Huang et al., (2011) might be a useful reference to include in the section on BOLD responses. Although this paper uses tinted filters in those with migraine, they also measured cortical activation without filters as a control, and so this evidence may be relevant in this section. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3132147/	As recommended by the examiner, a paragraph describing the suggested study has been added.	p.18 "Huang et al. (2011) studied the impact of tinted lenses for migraine……"
22. Gamma band activity has been associated with eye movement artefacts (e.g. Yuval-Greenberg et al., 2008), and may be a possible confound. This discussion should be included briefly as it is highly relevant to the interpretation of these papers. https://www.cell.com/fulltext/S0896-6273(08)00301-2	In the paper that was suggested by the examiner, eye movement has been identified to generate gamma band activity in scalp-measured EEG. Yuval-Greenberg et al. (2008) suggested that intracranial measured gamma activity might not be contaminated by muscular signals resulting from eye	p.19 *"1.6.1.2 Gamma oscillation measured in magnetoencephalography and visual discomfort"*

	movement given their different features to scalp-measured activities exhibited in previous studies (Lachaux et al. 2000, Tallon-Baudry et al. 2004, Lachaux et al. 2005, Trautner et al. 2006). However, in the paragraph, the only study I have mentioned used MEG gamma band activity, which is unlikely to be associated with the eye movement artefact. I decided to not include the reference suggested by the examiner as I think it might distract the readers and create potential confounds. To guide the readers that the section only describes gamma band activity measured in MEG activity, the subtitle has been amended.	
23. Expand the section on periodically reversed stimuli in EEG, I would use the term SSVEP specifically, to make this clear to the reader. The	As recommended by the examiner, the distinction between SSVEP and ERP has been clarified.	p.19 “For transient event-related potential, a …” “The SSVEP is a periodic VEP elicited by periodic

SSVEP technique is quite different from the traditional, transient ERP method and so this should be clear.		stimuli (Norcia et al. 2015). For periodically reversed stimuli, where the stimulus luminance contrast in consecutive phases are inverted, instead of switching between stimulus onset and offset, the scalp-measured potentials for the two interleaving phases are identical. Thus, the…" "SSVEP" "P100" "SSVEP" "P100"
24. "effect size is small" – quote a few examples, or include a table, as this would be illustrative to your reader.	The table summarising the findings of studies mentioned in the relevant paragraph has been added.	p.21 "(the above-mentioned studies are summarised in Table 1-2)" Table 1-2
25. "the distortion of contrast processing" – I would rephrase this, the contrast sensitivity function is a normal characteristic of the visual system, distortion sounds like this is a fault. Do you mean that the contrast sensitivity function itself is distorted, or that	I referred to neither contrast sensitivity function nor the difference between migraine and control groups. The sentence has been rephrased to clarify that by "distortion" I mean the effect of superimposing	p.23 "The authors suggested that increased difficulties with letter identification might be associated with the visual illusions induced by the striped patterns."

the contrast sensitivity of migraine is distorted compared to controls?	striped patterns on the letter identification task.	
26. When quoting the mean ages, give standard deviations as well. Why age specifically? There are several other possible factors, you might mention these also, e.g. duration of the disorder, attack frequency, cycle length, etc.	I chose to mention the differences in age and duration of migraine between the two studies as I thought they were obvious enough to justify their participants' differences. As recommended by the examiner, migraine frequency and standard deviations are now added.	p.24 "(mean±SD: age 40±13 years; migraine duration 21±12 years; migraine frequency 14±18 per year)" "(age 24.6±8.7 years for MA, 24.6±5.9 years for MO; migraine duration 12.1±8.3 years for MA, 10.4±4.4 years for MO; migraine frequency of 12±7 per year for MA, 8±9 for MO)"
27. "A possible alternative to measuring visual discomfort is to investigate illusory perception" – this statement appears to contradict your earlier statement on page 14: "However, it must also be noted that people who saw illusions from the striped pattern did not always find it unpleasant (Shepherd 2000). You will want to rephrase something here, as it reads as though you are claiming visual discomfort can be measured via the motion illusion.	As recommend by the examiner, the section has been rephrased to clarify that we did not know if visual discomfort can be measured by motion illusion.	p.29 "The increase in reported number of illusions induced by high contrast striped pattern in people with migraine, relative to control participants, has been used as an index of visual discomfort (Shepherd 2000, Huang et al. 2003, Harle et al. 2006, Shepherd 2006, Shepherd et al. 2013). However, the link between visual

		discomfort and illusion is still unclear. Thus, illusory vision perception in people with migraine is investigated in this thesis."
28. Rephrase the statement about a "robust motion illusion". The illusion may well be robust, but the parameters influencing the illusory effect may not be robust, for example, the eccentricity effect was only seen for 2/4 observers, according to the previous paragraph, and so this in itself is not robust. The illusion might well be robust, but is debatable that the parameters have a robust effect on illusion strength.	The examiner is right, 'robust' is not the precise word to be used here since not every observer experiences the same illusion strength from the stimuli. To describe the general effect of stimulus condition on increasing the motion illusion strength, which may not be applicable to each observer, 'robust' has been substituted with 'relatively strong'.	p.33 "…the stimulus parameters to be used in this thesis have been chosen to give a relatively strong motion illusion…"
29. Hypothesis 1 is not well explained from the introduction, you will need to make it clearer that there are different subtypes and you do not know a priori which will elicit the strongest illusion, so you intend to pilot this. Add a short statement to the introduction to make this obvious.	As recommended by the examiner, a sentence indicating we did not know a priori which will elicit the strongest illusion has been added.	p.35 "A priori knowledge of which type would elicit the strongest illusion is not available."

30. Was visual acuity based on self-report, measured by the experimenter, or did participants bring their prescription? If self-report, this may not be accurate, depending on the date of the last eye test. It should be mentioned if this was self-report.	It was not self-reported. Change has been made to clarify that an optometrist vision screening was conducted during the test visit to ensure they meet the inclusion criteria and to provide refractive error correction if needed.	p.37 "(measured during the vision screening as part of their tests visits)"
31. Grammar – experience fewer than, rather than "less than 4 headaches per year"	Grammar has been corrected.	p.38 "…fewer than 4 headaches per year…"
32. You have already included the International Headache Society criteria in the introduction, and so this is repetitive. Remove the version from the introduction and refer readers to the table here.	The repetitive table has been removed.	p.3 "…is shown in Table 2-1 (Chapter 2, page 39)…"
33. How was the diagnosis done, as your headache questionnaire does not map on to the IHS diagnostic criteria? Did you interview participants to establish whether they met the criteria, and ask them to complete the headache questionnaire in addition? More detail needed here for clarity.	As recommended by the examiner, diagnosing details have been added.	p.38 "Headache and migraine conditions were assessed through phone interviews before the test visit."

34. The time to the last migraine attack was recorded, but how was "interictal" defined? I see later (page 50) that this is 3 days after the migraine attack, but you should mention this much earlier.	Change has been made in response to comment No.2.	p.38 "Migraine participants were contacted the day before the appointment to check recency of migraine events, which allowed individuals who had experienced a migraine attack within 3 days of the proposed test session to be rescheduled."
35. The left eye was covered, what was the rationale for monocular viewing? This is not mentioned in the introduction.	The study which determined 12° to be the optimal eccentricity was monocular. The relevant reference has been added.	p.42 "as per Hisakata and Murakami (2008)"
36. Cite the papers by Faul et al., (2007; 2009) when referencing G*Power.	The relevant reference has now been cited.	p.42 "(Faul et al. 2007, Faul et al. 2009)"
37. "No studies to date have measured motion illusion strength between groups" – check this statement. Imaizumi et al (2015) compared illusion strength between migraine and control groups for the rotating snake illusion, please see figure 5: https://www.frontiersin.org/articles/10.3389/fpsyg.2015.00542	Imaizumi et al. (2015) did not quantify motion illusion strength using methods similar to my experiment. They asked for a subjective rating of illusion strength, and did not quantitatively determine. Therefore, there is little relevance in calculating a post-hoc	No changes were made.

/full#h3. You could recalculate your power using this analysis.	power calculation based on dissimilar methodology.	
38. Your sample size seems small, given that you expect individual differences in the motion illusion strength. However, as this appears to be pilot study to establish which of the types elicits the strongest motion illusion, and as the results (page 48) seem to show a similar pattern for all four observers, this does not seem to be so much of an issue. I would highlight that this is a pilot to establish the optimum illusion to use in the main study.	Change has been made in response to comment No. 4.	p.35 "The first experiment, which is a short pilot with 4 observers, aimed to choose the stimulus to be used in experiment 2 among five types of 'optimised' Fraser-Wilcox illusion." p.45 "This pilot experiment aimed to……"
39. The psychometric function toolbox "psignifit 4" does not use Markov chain Monte Carlo methods, this is one of the advantages the authors state in the Schütt et al., (2016) paper.	The examiner is right, I have removed the Markov chain Monte Carlo methods from the sentence.	p.49 "pain-free Bayesian inference (Kuss et al. 2005) were conducted through the 'psignifit 4' MATLAB toolbox developed by Schütt et al. (2016)."
40. Figure 3-6, can you include the error bars for the fits, for example confidence intervals, this should be possible using the "psignifit 4" toolbox, as this will give readers an	The comment about my "little" repetitions per data point has been replied in response to comment No. 3.	p.101 "There were 20 trials per data point for the motion illusion task, and 24 trials per data point for the

idea of the impact of the few repetitions per data point in the function. Here, and throughout the results, you could include estimates of effect sizes.		contrast discrimination task."
41. 5 repetitions of each stimulus, is this sufficient for a psychometric function? The paper by Hisakata and Murakami (2008) report 24 trials for each speed. I can understand when using a clinical population that shorter experiments would be beneficial, however, is five trials sufficient for a good fit? Estimates of the goodness of fit would be helpful to justify the relatively small number of trials from which to estimate your probabilities.	The comment about my "little" repetitions per data point has been replied in response to comment No. 3.	p.101 "There were 20 trials per data point for the motion illusion task, and 24 trials per data point for the contrast discrimination task."
42. Why did you chose these 4 luminance profiles for this section? It appears to me that the contrast range will be different for the first two compared to the second two stimuli. Additionally the overall luminance will be higher for stimulus 2 compared to stimulus 1 for example. Expand the rationale	The contrast range and mean luminance was indeed different between the four luminance profiles which is why there were four, rather than one, conditions. Each luminance profile for the contrast discrimination task consists of two shades,	p.61 "Conway et al. (2005) further demonstrated that each pair of the adjacent elements in the illusory motion stimulus alone can elicit directional selective responses consistent with the overall illusory

for this particular choice of stimulus.	which came from the four shades used in the stimulus of the motion illusion task. As described in the Introduction, the proposed mechanism of the Fraser-Wilcox illusion is that the contrast dependent neural latency differences between adjacent segments created motion signals in a way similar to apparent motion. Thus, contrast processing on each pair of adjacent segments is interested. This rationale for choice of stimulus has been added to the introduction of Chapter 5.	motion direction in both human psychophysical and macaque electrophysiological experiments. Thus, the degree to which responses to the two contrasts levels in each pair of adjacent segments in the illusory motion stimulus are different might affect the illusion strength."
43. There is good use of the visual aid to ensure the understanding of the task.	Thank you	No changes were made
44. Tell your reader the threshold level that has been set (75%).	In section 5.2.1.3 (p.66), it was written: "*Contrast discrimination threshold was the ΔLumRatio at which ψ = 0.75.*" which I think has the same meaning with that the	No changes were made

	threshold level has been set at 75%.	
45. Typo in the figure caption "parrerns".	The "parrerns" has been replaced with "patterns".	p.68 "Motion sensitivity was defined by the mean of the width of psychometic functions of the clockwise (Wcw) and the counterclockwise (Wccw) patterns."
46. Rephrase the first line "Figure 5-9 plots illusion cancellation speed as a function of motion sensitivity, estimated by the width of the psychometric function"	The sentence has been rephrased as suggested by the examiner.	p.72 "Figure 5-9 plots illusion cancellation speed as a function of motion sensitivity, estimated by the width of the psychometric function."
47. "Experiment 2 (Chapter 4) investigated 3 main measures…." Rephrase this as it sounds as though you measured Frazer-Wilcox illusion strength in people with migraine, when in fact this was a short pilot study on a subset of individuals who do not experience migraine.	Experiment 2 indeed measured the Frazer-Wilcox illusion strength in 36 people with migraine and 20 control participants.	No changes were made
48. "people with migraine showed greater postural sway" – this is a bit of an oversimplification of the	The purpose of this paragraph was to briefly remind the readers that my hypothesis, which predicted	p. 74 "…people with migraine showed abnormal postural sway, measured

Imaizumi et al., (2015) paper, rephrase this to clarify this was the case during direct viewing of the rotating snakes illusion, not the case with the 30-second delay.	motion illusion strength to be different between migraine and control groups, was not supported by our findings, before discussing possible explanations. I mentioned the Imaizumi et al. (2015) paper to remind the reader of some background for the hypothesis. The details of Imaizumi et al. (2015) have been described in section 1.7.4. therefore, I think to describe the experimental details here would be redundant and distract the reader. I have edited the sentence to indicate that there are specific conditions apply to the postural sway findings, and pointed to the Introduction where I have described the study in more detail.	in certain conditions (detailed in Chapter 1, page 33), associated with viewing the rotating snake illusion…"
49. The paragraph discussing spatial frequency content – you compare centrally and peripherally viewed spatial frequencies. The peak of the contrast sensitivity function shifts	Replied to comment No.6.	p.76 "Along with the increased eccentricity, the spatial frequencies of our stimulus were also different from that of the

to a higher spatial frequency when viewed peripherally. Revise this section as you are directly comparing 1cpd viewed peripherally to 3cpd (and others) viewed centrally. https://www.researchgate.net/profile/Alan_Johnston2/publication/19537271_Spatial_scaling_of_central_and_peripheral_contrastsensitivity_functions/links/53f498730cf2888a74910d53.pdf		high contrast striped patterns."
50. "In all variations of the pattern sensitivity test" – do you mean specifically the Pattern Glare Test (Wilkins and Evans, 2001), or are you talking about various ways of measuring pattern sensitivity in general? Please clarify this section.	I mean measuring pattern sensitivity in general. Shepherd calls it "pattern sensitivity" and Wilkins calls it "pattern glare" but I think they are essentially the same measurement. Both depend on self-reported illusion numbers by viewing high contrast gratings. Throughout the thesis, "pattern sensitivity test" has always been referred to the test that asks participants to report perceived illusions when viewing high contrast	p.78 "In all variations of the pattern sensitivity test (as introduced in Chapter 1, page 12), which might be calculated based on the number of illusions being reported, rating of illusion intensity, probability of reporting each type of illusion from multiple presentations, or within-subject differences in scores between patterns with different spatial frequencies, the scores were obtained purely

	gratings, which has been defined in Chapter 1.	depending on subjective self-report (Shepherd 2000, Harle et al. 2006, Tibber and Shepherd 2006, Shepherd et al. 2013)."
51. There is work suggesting that visual discomfort can have multiple components contributing to it (e.g. Sheedy et al., 2003). It would help if you could justify why you devised your own measure of visual discomfort, rather than using the validated measures in existence, e.g. the Conlon et al., (1999) scale for example. This relates to the earlier point (introduction) about the rationale not being quite clear.	Change has been made in response to comment No.1.	p.14 "The reading impairments in migraine and its association with visual discomfort might be an area worth investigating. However, given the complexity of visual discomfort in itself, we created a questionnaire aiming to assess visual discomfort more directly."
52. "pattern sensitivity score" – do you mean the Pattern Glare Test? In which case, please cite it here.	"Pattern sensitivity score" has now been replaced by "susceptibility to high contrast striped pattern induced illusions" to reduce ambiguity.	p.80 "Our hypothesis (H3a) that a stronger motion illusion would be correlated with greater discomfort scores assumed that susceptibility to high contrast striped pattern induced illusions would be positively associated with visual discomfort…"

53. "pattern sensitivity test" – do you mean your one from this experiment, or the Pattern Glare Test? If the latter, then the assumption would be that the illusory motion is from a similar origin, but you would need to comment that the Pattern Glare Test is an aggregate score of many different experiences (not just illusory motion), and so people could score highly whilst not experiencing very much illusory motion, potentially.	I agree that "the Pattern Glare Test is an aggregate score of many different experiences (not just illusory motion), and so people could score highly whilst not experiencing very much illusory motion, potentially." However, I have already narrowed it down to assessing the link between subjective intensity rating of 'motion' and illusion strength in the Fraser-Wilcox illusion. Therefore, commenting on how the overall pattern sensitivity score is measured is not necessary at this point.	No changes were made
54. The relevance of the first paragraph of section 6.3.1 is not immediately clear to me. You are quoting masking studies here, which is different from your task. You state this in the second paragraph. And so what is the relevance of these studies? Please either clarify how they relate to your study or remove them.	These masking studies were proposed to measure contrast gain control in V1, which I think is also involved in processing superathreshold contrast discrimination. In my experiment, as there were 4 different reference contrast levels, and there was a significant main	p.83 "Masking effects have also been proposed to assess contrast gain control in people with migraine. Thus, our results might be considered consistent with McColl and Wilkinson (2000)……"

	effect of stimulus type on contrast discrimination threshold, the slope of contrast discrimination threshold as a function of reference contrast level could be used as a measure of contrast gain control. The result of no interaction between group and reference contrast level was interpreted as no group difference in contrast gain control. The masking task in previous studies aimed to separate the transient response and the effect of inhibitory control by manipulating the relative timing of adaptation/masking stimuli. These studies found no group difference in masking effect across varies experimental conditions, which also suggested that contrast gain control was not altered in migraine.	
55. "such as extraction and integration of signal from noise" – you could	As recommended by the examiner, the study (Tibber et al. 2014) that proposed	p.84 "It has been suggested that task performances

mention the Tibber et al., (2014) paper here, this would be very relevant to the point you are making. https://www.ncbi.nlm.nih.gov/pubmed/24677099	that the ability to extract signal from noise was different people with migraine and control subjects has been mentioned. I have also added O'Hare and Hibbard (2016) as this review paper also supported the argument.	might only consistently impaired in the migraine cohorts when the tasks required extraction and integration of signals elements from stimuli that were incorporated with noises (Tibber et al. 2014, O'Hare and Hibbard 2016)"
56. "be different depending on the relative timing of migraine attacks" – by this to you mean cycle effects?	I have rephrased the sentence, if "cycle effects" is more commonly used.	p.86 "Performance on some tasks can be affected by migraine cycle effects"
57. "It was suggested by the authors that the visual information which generated discomfort and that which drove performance on the contrast perception tasks might arise from different visual pathways" – you should include some comment on whether or not you agree with this, based on the evidence.	Based on the evidence, the suggestion by the authors is reasonable. However, there are other possible explanations. The comments that expressed my partial agreement and disagreement has been added.	p.87 "Their speculation is reasonable based on the available evidence. However, to what extent the processing of contrast detection and visual discomfort are exclusively dependent on particular low level visual pathways is still yet to be solved. It is also possible that their distinction occurred at higher level processing stages. For example, the strength of discomfort might not be

		significantly affected by lower level visual input even if its early pathways are partly overlapped with that used for performing the contrast detection task."
58. "…individual differences in strength of the motion illusion suggest that fixational eye movements are critical in generating the motion illusion" – the sentence that follows this one refers to sensitivity to motion leading to more accurate perception of the motion velocity, but I am not sure how this links to the rest of the paragraph. Please clarify this section.	The examiner questioned about the casual link between the last two sentences of the paragraph which I suppose was because of the "therefore" in between them. The mention of fixational eye movement intends to add evidence of precortical origin of the illusory motion signal, which is parallel to its preceding sentences. In other words, all 'illusory' process happened precortically, while at cortical level the motion is not treated differently from 'real' motion. The sentence that followed was a conclusion of the whole paragraph. The concluding sentence has been rephrased to serve its	p.92 "Above all, if motion processing involved in the Fraser-Wilcox illusion is the same as real motion stimuli, it might be reasonable that sensitivity to motion would not make the motion appear faster, but rather, improve how accurately the motion velocity is perceived, just as 'real' motion."

	function for paragraph more clearly.	
59. Section 6.4.3., first paragraph, please comment on why you think the mean cancellation speed might be different in your study compared to previous research.	The original paragraph misled the examiner to think that there requires a comment on the different findings between the current and previous studies. However, that paragraph compared our data and the values predicted by models proposed by previous study. A sentence elucidating the purpose of the paragraph has been added to remind the readers that the values from previous studies were predicted by models rather than collected experimental data.	p.92 "The discrepancy between our data and the values predicted by previous models indicates that the proposed model for motion illusion strength requires refinements with the current empirical findings considered."
60. Appendix 5, table A, check the format of correlation between contrasting patterns and headache trigger, make this consistent across the table. There is a significant correlation between contrasting patterns and headache triggers, you might comment on how this	The significant results mentioned by the examiner were significant before Bonferroni correction for multiple comparisons. Results were only reported in the main text if still significant after Bonferroni correction.	No changes were made

relates to your theory in in the main text (briefly). From the theory in the introduction, you seem to make the case for two separate systems in discomfort, discomfort from patterns in the general population, and a slightly different, trigeminal system association for discomfort from light in the migraine population. This is worth commenting on, in my view.		
61. Appendix 6, table A – there is a correlation between the days since last migraine attack and migraine questionnaire score. I do not see this mentioned in the main text. It would possibly be worth briefly commenting on this in the main report.	It was not mentioned because the significance ceased after Bonferroni correction. As written in Appendix 6: "12 Spearman tests were conducted to test the relationship between 3 migraine characteristics and 4 experimental measurements (cancellation speed + 3 questionnaire scores)" The calculation process for the two correlations that remain significant after Holm-Bonferroni correction was also provided in Appendix 6.	No changes were made

62. References Please include the reference for the International Classification of Headache Disorders. https://www.ichd-3.org/wp-content/uploads/2018/01/The-International-Classification-of-Headache-Disorders-3rd-Edition-2018.pdf	The reference for the International Classification of Headache Disorders has been added.	

Table A. 10-1 Response to examiner 2.

Examiners comment	Student's response	Change made to thesis (if any)
63. Experiment 3, was conducted to determine if either contrast or motion discrimination thresholds were associated with the strength of the motion illusion generated. This was based on previous research on migraine, showing higher contrast discrimination thresholds on those migraineurs reporting greater visual discomfort. While there were no group differences found, there were a small number of extreme scores (see Figure 5.7). Did the candidate investigate possible	To address the examiner's comment, I conducted Spearman's correlation between motion sensitivity and all available measurements in the study (including cancellation speed, individual rank of contrast discrimination, questionnaire migraine trigger score, questionnaire headache trigger score, questionnaire discomfort score, age, days since last migraine, age of first migraine, migraine attacks in the past year, MIDAS score, estimation of life migraine events). Only individual rank of contrast discrimination was	No changes were made

individual differences between participants?	significantly correlated motion sensitivity, which has already been mentioned in Chapter 6 (p.105).	
64. While this is NOT required for the current thesis, it could be well worth examining to raw data for individual participants to determine if there is evidence of individual participants showing evidence of a stronger motion illusion. There individual characteristics could then be investigated to determine if there is any individual evidence of an association between migraine, visual discomfort, contrast discrimination or the motion illusion.	This is an interesting comment, but as noted by the examiner, falls outside the scope of the current thesis.	No changes were made

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