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RECENT UNDERSTANDING OF BINOCULAR VISION IN THE NATURAL ENVIRONMENT WITH CLINICAL IMPLICATIONS

T. Rowan Candy[1,*], **Lawrence K. Cormack**[2]

[1]School of Optometry, Programs in Vision Science, Neuroscience and Cognitive Science, Indiana University, 800 East Atwater Avenue, Bloomington, Indiana 47405, USA.

[2]Department of Psychology, Institute for Neuroscience, and Center for Perceptual Systems, The University of Texas at Austin, Austin, TX, 78712, USA.

Abstract

Technological advances in recent decades have allowed us to measure both the information available to the visual system in the natural environment and the rich array of behaviors that the visual system supports. This review highlights the tasks undertaken by the binocular visual system in particular and how, for much of human activity, these tasks differ from those considered when an observer fixates a static target on the midline. The everyday motor and perceptual challenges involved in generating a stable, useful binocular percept of the environment are discussed, together with how these challenges are but minimally addressed by much of current clinical interpretation of binocular function. The implications for new technology, such as virtual reality, are also highlighted in terms of clinical and basic research application.

Keywords

Binocular Vision; Stereopsis; Natural image statistics; Strabismus; Eye movements

1. Introduction and rationale

Binocular vision is a fundamental component of a typical human's visual function. It consists of the ability to align the eyes in the motor sense and to integrate their images in order to perceive and interact with the dynamic three-dimensional world. Its primary advantage is to help provide a sense of distance and relative depth as we move around in our environment. The importance of this function is potentially demonstrated in its early development in the first months after birth, as infants start to reach and become mobile.

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[*]Corresponding author: T. Rowan Candy, School of Optometry, 800 East Atwater Avenue, Bloomington, Indiana 47405, USA. Phone: (812) 855-9340, rcandy@indiana.edu.

T. Rowan Candy: Conceptualization, Writing- Original Draft, Writing-Review & Editing, Visualization
Lawrence K. Cormack: Conceptualization, Writing-Original Draft, Writing- Review & Editing, Visualization

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While human neonates are almost entirely dependent on caregivers, binocular vision and depth perception facilitate their developing interaction with the three-dimensional structure of the world around them. Yet, at least 3% (MPEDS 2008, Friedman, Repka et al. 2009) of the population are still able to function with limited or no binocular vision as a result of clinical disorders.

Classically, binocular vision is illustrated as pointing the two *foveae* – the central regions of the retinae specialized for high acuity vision – to the same location in a static scene (Figure 1A), which leads to a unified percept of the world after the neural representations of the two eyes' images are combined in visual cortex. These images may include offsets in content between the eyes that form interocular *retinal disparities*, providing a cue for both eye alignment and *stereopsis*. This example of binocular function has typically been studied with the participant's head stationary and with the stimuli presented on a pair of two-dimensional screens, one to each eye. The main goal of this review is to contrast this classical example with a more contemporary approach to understanding binocular function in the dynamic, natural three-dimensional world from the perspective of both typical and atypical binocular vision. This contrast is used to illustrate recent understanding of the characteristics and complexity of the natural environment and tasks as stimuli to binocular function.

The combination of the first studies of receptive field properties of neurons in visual cortex, innovation in engineering enabling stimulus control, and the theoretical framework of psychophysics enabled rapid and meaningful progress in understanding binocular vision in the latter half of the 20th century in many research labs. These studies characterized our behavioral sensitivity to retinal disparity, the response properties of binocular neurons in primary visual cortex and, from the motor perspective, the vergence responses required to align the foveae on the target. In parallel, other studies explored the monocular pictorial cues capable of generating a percept of depth, including looming, image size, shading, occlusions, and the dynamic cues of optic flow and motion parallax. This large body of work is reviewed in books such as Schor and Ciuffreda (1983), Howard (2002), and Howard and Rogers (2002).

As has happened in a number of areas of vision science, more recent work has built on these foundations collected in highly controlled laboratory settings to ask how the binocular visual system functions in its more natural environment (e.g. Liu, Bovik et al. 2008, Sprague, Cooper et al. 2015, McCann, Hayhoe et al. 2018). Rather than asking how the visual system responds to tightly defined stimuli, it is now common to ask how the visual system is able to extract meaningful information from its complex, dynamic, natural environment and how this information is combined to form a stable unified percept of the world on which we can make decisions and act. Put simply, we might want to know which visual information in our environment is actually useful to us, how well we are able to extract it, how we guarantee that that information is reliable, how we integrate it with other cues (including prior knowledge or assumptions about the environment), and how we use it to interact with our surroundings. Plus, how an atypical visual system is able to adapt to its challenges.

Although the progression from measuring responses to simple stimuli, such as dots and gratings, to understanding how the visual system extracts meaningful information from the natural environment to subserve useful behaviors may seem like a perfectly natural one, it belies a half century of debate within the vision research community. In 1966, James J. Gibson published a book entitled “The Senses Considered as Perceptual Systems” (Gibson 1966) that was influential among many psychologists (soon to become known as “Gibsonians”). This book emphasized the importance of several topics we now take for granted, including the nature of information present in the natural environment, the use of information gained from prior experience, and the crucial importance of behavior – behavior both as the ultimate goal of perception but also as a key component of perception itself. Consider looking at a gadget you’ve never seen before and trying to work out what it does; you don’t just passively view it, you pick it up and inspect it from various angles, each movement of your hand creating a different visual stimulus. Not coincidentally, infants and young children do this routinely (Smith, Jayaraman et al. 2018).

Gibson’s book was also written – quite intentionally – as a direct challenge to many fundamental assumptions in sensory biology. Among these were the importance of the retinal image in vision, the use of simple well-controlled stimuli in laboratory settings, and even the Doctrine of Specific Nerve Energies (the work of Müller and Helmholtz directly). Gibson went so far as to question whether the study of sensory arrays, such as the retina, could tell us much about perception. Naturally, many in the field did not agree.

In 1982, an extremely influential book by David Marr entitled “Vision” was published posthumously. In it, he formulated vision as an information processing problem, the goal of which was to create a useful representation of the external world (Marr 1982). The book identified three levels at which vision could be considered: the computational level, the algorithm level, and the hardware or implementation level. These correspond to: what is the problem to be solved?; how to solve it; and how to implement the solution either *in vivo* or *in silico*. Marr’s book was seminal in that it provided both a summary and a roadmap for understanding the visual system by making explicit the value of combining the engineering goal of building working artificial visual systems with the scientific quest to unpack biological visual systems. It unified disciplines and erected a clear, useful scaffolding around the question of vision.

Despite Marr’s crediting Gibson with contributing to the computational level of analysis, Gibsonians criticized the book on several grounds. Marr’s approach began with casting vision as an image processing problem, for example, and Gibsonians considered images irrelevant to vision (optically, the majority of the eyes on the planet – compound eyes – do not in fact form images, but if you have an image to start with, why not use the tools of image processing to emulate the computations done by, e.g., the retina?). The criticism that was perceived to be fatal by many, however, was that the supposed end goal of Marr’s approach was an internal representation of the external world. This can be easily misconstrued as the homunculus fallacy. Of course, the visual system does construct internal representations, and it is difficult to fathom how students of vision could fail to consider them (e.g. Wandell 1995). Rather, the challenge is how the dynamic and noisy peripheral representations (e.g. at the photoreceptor level), can be made robust to the enormous amount of variability present, and how, ultimately, such representations can be interpreted to support behavior.

Some lingering details aside, the main points espoused by Gibson and the general approach elucidated by Marr happily coexist (often without awareness that there was ever a debate) and form what we can now consider to be the working description of the primate (binocular) visual system. Light reflecting from surfaces in the world creates an information-rich optic array that is sampled continuously and dynamically by observers (G = Gibson). At any one time, however, this array in the vertebrate eye is sampled and transformed by layered structures (e.g., retinae, LGN) using what can be approximated by image processing or linear systems operations (e.g. convolution) (M = Marr), many of which serve to reduce noise and exploit statistical regularities in the environment (e.g. reviewed by Field 1994, Geisler 2008). These operations then produce a “representation” or encoding layer that gets read out, or decoded, by a subsequent layer or layers, which then serve as another encoding layer, and so on (M). Along the way, the representations based upon stimulus information are combined with prior information learned through evolution or development to produce improved estimates about the state of the world (G, M). Finally, the process culminates in the ultimate decoding layer, behavior, which in turn alters the stimulus and reinforces perception of the environment (G).

Two things that neither of these authors fully anticipated were the need to cope with the large amount of variability present in real-world stimuli and the (binocular) visual system’s ability to exploit the statistical regularities in visual stimulation that arise from the physics of the environment. These statistical properties of the stimulation we receive from birth have shaped the way in which the visual system encodes and decodes information to guide behavior (e.g. Berkes, Orbán et al. 2011, Purves, Wojtach et al. 2011, Smith, Jayaraman et al. 2018). In the context of binocular vision, this has led to studies of the statistics of natural visual experience (e.g. Liu, Bovik et al. 2008, Sprague, Cooper et al. 2015), the response properties of neurons in extrastriate cortex (e.g. Czuba, Huk et al. 2014, Sanada and DeAngelis 2014), the use of more naturalistic stimuli that consider multiple cues (reviewed by Welchman 2016), plus the development of models of cue integration, decision making and motor responses (e.g. Ernst and Banks 2002, Bonnen, Huk et al. 2017).

This review will consider both motor and perceptual aspects of binocular vision in terms of our more recent understanding of typical and atypical function in the natural world, highlighting the importance of challenges that are not an explicit part of the classical static model. The following sections progress through the components of binocular visual function, highlighting understanding that bridges the gap between the classical model shown in Figure 1A and function in the natural world.

2. Motor Function

2.1 Establishing the monocular image

In the classical illustration of binocular vision, shown in Figure 1A, the eye is pointed at an object of interest (e.g., the blue dot), creating a stable representation of that object and the surrounding scene in the visual system. This serves as a monocular input to primary visual cortex. As we shall see, the reality is more subtle and complex. So much so that we can assert that *one of the visual system’s major challenges is to interpret the meaningful statistical structure (i.e. the signal) given the amount of variability (i.e. the noise) present in* *the input*. This monocular input to primary visual cortex is compared with the input from the other eye, resulting in the computation of depth in the scene with a sensitivity down to seconds of arc of visual angle [1].

The variability in the input does not solely consist of spontaneous sensory neural noise (e.g. Field and Sampath 2017). Recordings of the instability of gaze when an observer tries to fixate a stable point have been provided since at least the middle of the twentieth century (Ratliff and Riggs 1950, Krauskopf, Cornsweet et al. 1960). The measured instability, on the order of minutes of arc, leading to legitimate variation in the information arriving at individual photoreceptors, has been described as a combination of a low temporal frequency drift, high temporal frequency tremor plus small microsaccades, and interpreted as an inability to locate the eye precisely. Interestingly, while the microsaccades are typically found to be binocular, studies of the binocular nature of drifts and tremor have reached mixed conclusions (Otero-Millan, Macknik et al. 2014). Recording these small movements is complicated by the effects of measurement error, but it is clear that some portion of the movements are uncorrelated between the eyes. These demonstrations reveal that *our stable visual percepts belie the significant variability present in the stimulus at the level of the photoreceptors*. With advances in eye-tracking technology, more recent work has reframed the interpretation of these movements into an active process controlled purposefully to optimize vision (Ko, Poletti et al. 2010, Poletti, Listorti et al. 2013, Krauzlis, Goffart et al. 2017). In fact, it is argued that we rarely try to stably fixate a single point in the natural world and that the small microsaccades are more typically used intentionally to explore the object being fixated (reviewed by Rucci and Poletti 2015). This movement of the eye, even while attempting to fixate a single point in an image, has been proposed to introduce signal modulation in the retina over time that increases our sensitivity to fine spatial detail (high spatial frequencies) (Kuang, Poletti et al. 2012). Although there are clearly important sources of measurement noise in these sensitive recordings, this literature is reiterating that the eyes are in constant motion even when we consider them to be in stable fixation. In fact, even animals largely lacking a fovea make spontaneous saccades of just the size needed to generate informative uncorrelated temporal input to the visual system given the natural scene statistics of their environment (Samonds, Geisler et al. 2018). In the center of the fovea a microsaccade can create an image shift over tens of photoreceptors in a few milliseconds, with the mosaics of retinal ganglion cells sending locally correlated patterns of action potentials on a path to the visual cortex at rates of up to approximately 100 spikes per second (e.g. Shlens, Field et al. 2006). A number of groups have documented the stable percept of a target during these eye movements, indicating the presence of a compensatory perceptual mechanism that includes the ability to discriminate target motion from eye motion (Murakami and Cavanagh 1998, Poletti, Listorti et al. 2010, Arathorn, Stevenson et al. 2013). The classical model of binocular vision, then, misrepresents the noisy, dynamic nature of the monocular input to cortex. In fact, to the degree that the cortical input or representation is stable, its stability is likely due to processes fundamental to the early visual system compensating for and exploiting the very nature of the input, potentially

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[1] For reviews of the optical performance of the eye and the sampling properties of the retinal mosaic, please see Artal (2015) and Thibos (2020), respectively.

including the correlated nature of the fluctuations both across time and between the eyes (see Intoy et al 2021 for an example of disruption of the correlation between efferent motor and afferent sensory function).

The unstable nature of the photoreceptor outputs just described occurs under tightly controlled laboratory conditions. When we allow the observer to take their head off the chin rest, leave the laboratory, and move freely through their visual environment, they will engage numerous other motor systems that must be coordinated to produce a stable percept of the world around them. For the purposes of the classical model of binocular vision, the motion of the retinal image resulting from self-motion of the observer must be discriminated from motion of objects in the visual scene to experience a stable world that includes objects located in depth (Matthis, Muller et al. 2020). Without this, it would be unclear whether the world or the observer were moving based on visual information. Typical motor responses in the natural environment that themselves induce motion in the retinal image include saccadic, pursuit, and vergence eye movements, plus head and body movements that also introduce an additional set of reference coordinate systems (for example, is an object straight ahead with reference to the eye, or head, or body?). In coordinating these motor movements, the brain must integrate afferent sensory information with different latencies (from vision and proprioception, for example) and compensate for dynamic retinal images, resulting from eye, head and body movements, to interpret the visual environment. Only rarely are all of these systems stable and yet we are able to integrate these forms of motion to produce a stable percept of the world in milliseconds for actions such as reaching accurately to a moving target (Dokka, MacNeilage et al. 2015, Sasaki, Anzai et al. 2020). In the classical tradition of vision science, subjects were put on a bite bar and told to fixate in order to isolate their specific task – but perhaps the movement of the eyes and the head (the active exploration of the scene) actually allows the system to extract the useful statistical regularities in the stimulus (e.g. Rucci and Poletti 2015, Fulvio, Miao et al. 2021)

The motion of the eyes and head may be helpful for many computations, but humans also generate a stable percept in the presence of these eye and head movements. Thus, at some level, compensation for retinal image motion is required. The signals used for such compensation include combinations of i) the short latency vestibulo-ocular reflex (VOR) that initiates a counter-rotation of the eyes in response to acceleration of the head, ii) an early copy of the impending neural signals about to drive a motor response, termed *corollary discharge or efference copy*, iii) a signal representing the level of ongoing muscle activity indicating, for example, the eye's position in space, termed *proprioception,* iv) apparent dynamic shifts in the receptive field location of a neuron in visual space that predict the location of the neuron's typical receptive field after an upcoming saccade, termed *saccadic remapping* v) *Suppression* of visual perception during saccadic eye movements or vi) the extraction of higher order stable signals such as relative retinal disparity (see below) (signals reviewed by Wurtz 2008, Sun and Goldberg 2016, Wurtz 2018). These signals form logical candidates in computation to support real-time interpretation of retinal image motion, and link research performed in the field of vision science with important general questions in motor neuroscience (e.g. Cullen 2014).

The fact that a typical observer is so unaware of the challenges involved in these computations while we walk through the world indicates the elegance and efficiency of their function and reiterates that monocular fixation does not represent an ‘at rest’ absence of motor activity. Rather, stable visual percepts require highly sophisticated coordination of motor activity on short millisecond timescales and then rapid computation performed on unstable retinal image information. Fixational eye movements and the VOR are now routinely described as belonging to a category of ‘stabilization’ eye movements. For a typical observer, these computations can be performed fast enough to sustain a stable percept almost constantly, a feat that can be appreciated by comparison with a video shot on a phone (without image stabilization) while walking or running. [2]

2.2 Establishing binocular motor alignment of the eyes

A second critical feature of the classical model of binocular vision (Figure 1A) is that the two eyes are able to fixate the same target of interest – the eyes are aligned at the target, albeit with fixation instability introducing small dynamic errors in alignment. Although the eyes are observed to be grossly aligned from birth (Slater and Findlay 1975), neonates are noted to exhibit short periods of apparent misalignment over the first weeks (Horwood 2003). It is only at around 3 months of age that they should be expected to maintain fully consistent alignment to targets at different viewing distances. How infants are able to make use of the information from the two eyes to achieve at least approximate alignment at a range of distances within days after birth is still an intriguing question (Aslin and Dumais 1980, Seemiller, Cumming et al. 2018, Eckmann, Klimmasch et al. 2020). They must then continue to recalibrate this process with the gradual postnatal increase in inter-pupillary distance (IPD) (Pryor 1969, MacLachlan and Howland 2002) and in eye size (Larsen 1971, Mutti, Mitchell et al. 2005). Further, the migration of photoreceptors across the central retina over years after birth poses an additional interesting challenge (Yuodelis and Hendrickson 1986, Hendrickson and Drucker 1992); *a given photoreceptor cannot be associated with a stable visual direction during development*. One can even ask whether there is a single photoreceptor that represents a stable ‘straight ahead’ visual direction across the lifespan.

In thinking about the various motor systems responsible for aligning the eyes, the classical model describes the symmetric vergence responses used to align the eyes in depth along the midline between them (the mid-saggital plane). Depending on the task, these movements have a latency of on the order of 100–200ms and are largely complete in the following 400ms, as demonstrated numerous times in the literature going back to early measurements made by Westheimer and Mitchell (1956). These responses are frequently described as consisting of components in the form described by Maddox (1893): a baseline resting ‘tonic’ response, a response to the apparent proximity of the target, a response driven by neural coupling from accommodation, plus an error-correcting fusional vergence response to eliminate remaining retinal disparity and establish accurate binocular fixation. The fusional, disparity-driven (Rashbass and Westheimer 1961), error-corrector is considered closed-loop in natural conditions because it is the component that provides feedback about response

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[2] A 1999 movie, The Blair Witch Project, which was shot from an unstabilized first-person perspective, made many viewers uncomfortable and even ill – https://www.washingtonpost.com/wpsrv/style/movies/features/witchdizzy.htm

accuracy -- there is a defined endpoint when the retinal disparity of the target being fixated has been reduced to zero. The amount of disparity eliminated to align the eyes at a target is termed absolute disparity (for example, the disparity that would be eliminated to fixate on the grey target in Figure 1A), while the difference in disparity between objects in a static scene is termed relative disparity (for example, the differences in disparity between the targets in Figure 1A). Relative disparity between two static objects will always be constant, irrespective of where vergence aligns the eyes, while the amount of absolute disparity for any given object will depend on the distance at which the eyes are currently aligned. For typical observers, pure vergence has been shown to be a reflex when eliminating absolute disparities around the point of fixation, with the reflex response being less reliable beyond a stimulus of approximately two degrees (Hung, Ciuffreda et al. 1994, Busettini, Miles et al. 1996, Meier, Lundell et al. 2021). Shifts in eye alignment to eliminate much larger absolute disparities are routinely associated with a voluntary largely proximity-driven, rather than reflex, shift in gaze from one object in the scene to another.

The combination of response components, in the theoretical framework described by Maddox, interacting to generate the final vergence motor response forms an apparently redundant system in that it is theoretically capable of generating a larger response than required by the stimulus. The final accurate pure vergence response is a complex combination of these response components that has been modeled by a number of groups (e.g. Hung and Semmlow 1980, Schor 1992, Eadie and Carlin 1995, Semmlow, Yaramothu et al. 2019, Eckmann, Klimmasch et al. 2020). The parallel function of the coupled accommodation system, also described using related response components (Fincham and Walton 1957), establishes the associated focused retinal images to provide, in combination, typical clear and single vision. The summary models of the combined vergence-accommodation system all include weighted contributions of the two sets of response components, with their interactions, in an effort to replicate aspects of the behavior of the biological system. In the context of clinical disorders, these models have also been used to examine the atypical behavior of patients (e.g. Schor and Horner 1989, Sreenivasan and Bobier 2014, Erkelens and Bobier 2020).

The number of studies of the neural circuitry controlling these coupled vergence and accommodation responses has been somewhat limited when compared with studies of the neural circuitry underlying retinal disparity processing in primary visual cortex, for example. This is largely due to the difficulty of accessing the relevant small motor nuclei deep in the brainstem (May, Warren et al. 2018) and the complexity of the different potential cortical computations involved in forming a response goal. These computations can be reflexive or voluntary, and based on form and/or motion cues, for example. The muscles actually enacting the motor responses are the extraocular muscles for vergence and the ciliary muscle surrounding the lens for accommodation. These muscles are innervated by the third (medial, superior and inferior recti, plus the inferior oblique and ciliary muscle), fourth (superior oblique) and sixth (lateral rectus) cranial nerves, whose function and pathways are relatively well understood (although recent studies of the local muscle characteristics and their innervation are suggesting new subtleties; (Büttner-Ennever, Horn et al. 2001, Demer and Clark 2018, Horn, Horng et al. 2018)). The neural circuitry responsible for innervating the cranial nerves, defining the final unitary motor response, is complex as stated above and less well understood. Neurons innervating the cranial nerve nuclei to drive coupled vergence and accommodation responses were first found in the 1980's (Mays 1984, Judge and Cumming 1986) near the third cranial nerve nucleus (the oculomotor nucleus). They were labelled near response cells and are found in an area termed the Supraoculomotor Area (SOA) (May, Warren et al. 2018). By looking at the correlation between the firing rate of these neurons and the motor behavior of an animal model, individual neurons have been shown to fire during only accommodation and not vergence, only vergence and not accommodation or both accommodation and vergence motor responses. This range of responses suggests that the SOA is central in implementing the complex combination of response components. Interestingly, while the computational models of the combined vergence and accommodation system (discussed above) and clinical assessment both routinely characterize the coupling between accommodation and vergence with a single gain value (the amount of vergence driven by a diopter of accommodation, or the amount of accommodation driven by a prism diopter of vergence), a multiple regression analysis predicting the firing rate of individual near response neurons from the final accommodation and vergence motor responses performed by Zhang, Mays & Gamlin (1992) has suggested that the measured gain of the coupling in the behavioral response may in fact represent the combined impact of a population of SOA neurons with different vergence:accommodation gains, as opposed to a population of neurons all with the same gain. This is consistent with the range of gains found across individual neurons previously by Mays (1984) and Judge and Cumming (1986). It is appealing to think of this range as a mechanism that could adapt rapidly to maintain the behavioral gain during changing response mechanics or demands during an observer's life in the natural world, with growth in IPD and early presbyopia for example. There is also evidence of input into these SOA responses from the cerebellum, which is involved in numerous aspects of ocular motor performance and adaptation (Noda, Sugita et al. 1990, May, Porter et al. 1992, Zhang and Gamlin 1998, Takagi, Trillenberg et al. 2001). How this combined system establishes stable *inappropriate* behavioral coupling gains between accommodation and vergence responses in clinical disorders such as accommodative strabismus is yet to be determined.

In the classical simple case of Figure 1A, vergence responses are assumed to occur to a stimulus on the mid-saggital plane – straight ahead on the midline between the eyes requiring the eyes to move an equal amount in opposite directions (moving between the blue and grey dots). We spend almost all of our day fixated at locations off the literal midline, however, on the red or green targets in Figure 1A for example. While we tend to align our head with the direction in which our eyes are pointing when fixating an object (Volle and Guitton 1993), we routinely fixate points in our central visual field without moving our heads (e.g. Figure 3 of Sprague, Cooper et al. 2015). In shifting fixation from a distant target to the right of the mid-saggital plane (e.g. green in Figure 1B) to a near target slightly to the left of mid-saggital plane (e.g. red in Figure 1B), for example, we must perform an apparently asymmetric vergence movement – both eyes will be required to move to the left but the right eye will be required to perform a larger rotation than the left eye in this movement. Theories of the control of these eye movements have been controversial. Assuming equal innervation to the two eyes (Hering's Law), these asymmetric movements have been considered to be a combination of conjugate (saccadic) and symmetric disconjugate (vergence) responses (combining a saccade to the left with a convergence movement in the example given above in Figure 1B) (e.g. Westheimer and Mitchell 1956, Busettini, Miles et al. 1996). The evidence is not fully consistent with this view, however. For example, the responses to these asymmetric stimuli have been shown to be faster than typical symmetric ‘slow’ vergence (Zee, Fitzgibbon et al. 1992), implying that the slow vergence mechanism is not responsible for the depth component of the typical asymmetric behavior. Physiologically, recordings from neurons in the SOA have also not demonstrated the symmetric vergence response characteristics required to be consistent with the behavior (Pallus, Walton et al. 2018), and neurons in the saccadic circuitry have been shown to carry signals indicative of unequal fast monocular saccades (Cullen and Van Horn 2011), as originally proposed by Helmholtz. Data now suggest that the full asymmetric behavioral responses are a result of innervation, coded in position and/or velocity, in a number of both monocular and binocular pathways (e.g. Coubard 2013, Van Horn, Waitzman et al. 2013, Quinet, Schultz et al. 2020). There is much to understand about the sets of neural circuitry underlying the combination of vergence and accommodation in the tracking and jump motor responses that permit us to rapidly fixate and focus on targets in our three-dimensional natural visual environment. Even more so when considering how typical function can be disrupted in atypical clinical cases ranging from manifest misalignment (strabismus) to stress on alignment (e.g. Traumatic Brain Injury (TBI), Convergence Insufficiency (CI)) as discussed below. Put simply, the case of symmetric vergence on the midline emphasized by the classical model represents a relatively small proportion of our typical visual behavior in complex natural environments (e.g. Figure 3 in Sprague, Cooper et al. 2015). As these types of asymmetric eye movements are not yet fully understood, our understanding of the bulk of ocular motor behavior in the healthy and clinical patient is incomplete.

In addition, our rapid symmetric and asymmetric movements used to maintain stable, unified percepts need to function in a dynamic world. As described above, our retinal images are routinely in motion either as a result of self-motion of the observer or motion in the environment. Much of this motion involves a depth component requiring a rapid functional vergence movement. For example, when walking down a trail one might want to track an approaching object, fixate the location of the next foot placement or search for visual objects of interest. The motion of a point in the retinal image of one eye can be summarized using a vector, and the array of vectors representing the current velocities of many points in the retinal image is termed an optic flow field (Gibson 1950). With recent advances in portable eye-tracking technology and computational power, it has become possible to capture and study these natural flow fields (e.g. Matthis, Muller et al. 2020). The difference in the flow fields between the two eyes carries information about differences in both motion (velocity disparity) and position (retinal disparity) over time, that correspond to trajectories in three-dimensional space in the world. A series of studies has asked whether we are capable of using either or both of these cues (difference in motion and/or position between the eyes over time) to indicate a three-dimensional path. This topic will be discussed in more detail below in the context of perception but is clearly also central to generating appropriate motor responses. Studies of the role of these two cues in ocular motor responses to dynamic stimuli have now begun and are suggestive of a role for pure velocity disparity in addition to more classical differences in position in the two eyes (Sheliga, Quaia et al. 2016).

Typically, the classical discussion of aligning the eyes on a target only includes consideration of horizontal vergence responses. As a result of their separation, the two eyes must rotate horizontally relative to each other in order to fixate the same target. In fact, we also routinely experience differences in vertical image position, *vertical disparities* (e.g. Figures 4 & 5 of Sprague et al. 2015), which must be overcome to fixate on corresponding information in the two eyes, a response termed vertical vergence. The distribution of vertical vergence responses is significantly smaller overall than for horizontal vergence, on the order of only 1–2 degrees maximum as opposed to approximately 50 degrees for horizontal vergence movements (Hara, Steffen et al. 1998). Figure 2 illustrates the example of holding a finger close to the left eye (at the approximate location of the red object in Figure 1), where the image of the finger is larger vertically in that eye than the right eye. This creates vertical interocular retinal disparity for the top and bottom of the finger when the eyes are fixating the finger’s center, as illustrated in the color-coded combination image. The eyes must change their vertical vergence alignment if they are to binocularly fixate the top or bottom of the finger. It has been possible to dissociate vertical and horizontal vergence responses in the laboratory using various stimulus characteristics, indicating that these responses are driven at least in part by separate mechanisms (Howard, Fang et al. 2000, Mulligan, Stevenson et al. 2013).

Summary—As we discussed in this section, the eyes never really fixate a target stably, even under well controlled laboratory conditions when the observer’s head is fixed. In fact, both microsaccades and regular saccades, which intuitively might seem incredibly disruptive, are actually necessary for optimal coding of the environment given the statistics of natural scenes (Kuang, Poletti et al. 2012, Samonds, Geisler et al. 2018). When the observer moves freely, the resulting head movements bring additional instability into play, even with the stabilizing VOR. Despite all of this motion, a binocular system must have both eyes working in a coordinated fashion such that they are generally pointing at the same location in the 3D environment. To do this, the eyes make conjugate versional movements involving nearly identical excursions, and disconjugate vergence movements, in which the two eyes move relative to each other. These coordinated movements give us a stable and generally unified percept of the external world despite the fact that the retinal images are in constant motion, and that this motion is not perfectly correlated across the eyes. Classically, vergence responses were considered to be driven by proximity (a catch-all term for a depth estimate from whatever monocular depth cues are available), accommodation, and horizontal absolute disparity. We now know that velocity disparities can also drive both horizontal and vertical vergence, and that alignment responses to locations in eccentric gaze involve innervation in both monocular and binocular neural circuitry. The dissection of “proximity” into sub-components is also ongoing, with many factors known to drive vergence (e.g. looming (McLin, Schor et al. 1988) or motion parallax (Frey and Ringach 2011)). In summary, aligning two eyes in the three-dimensional environment is a difficult task. This task requires a single stable representation of the environment despite noisy input containing multiple cues to depth. Despite this, a single solution – a particular binocular posture –

is required at each point in time, and this posture generally needs to provide useful and predictive information about the visual environment for behavior. In the following section, we will consider what happens when the mechanisms for binocular alignment fail to follow the typical developmental trajectory.

2.3 Binocular motor alignment in the clinic.

There are a number of interrelated clinical disorders that interfere with an individual's ability to achieve binocular motor alignment. Given the complexity of the motor system described above, it can be seen that there are numerous factors that could contribute to clinical abnormality while the visual system either develops to maturity or functions in adulthood with pathology. Research into binocular vision has included the goal of understanding and alleviating these clinical disorders. This next section will discuss the challenges in achieving motor alignment facing patients with a range of visual disorders. These patients will be discussed again later in the context of how their perceptual systems are able to compensate and permit them to function in their environment.

Beginning again with the topic of fixation stability, one of the more significant and long-studied disorders of the visual system is *nystagmus*. This is an inability to stabilize gaze characterized by combinations of large drifts and rapid re-fixation responses. There are numerous forms of nystagmus, with origins ranging from congenital malformation of neural circuitry to forms of pathology in the visual and/or vestibular systems (Abadi 2002, Straube, Bronstein et al. 2012). Intriguingly, the potential for stable percepts remains in early onset cases. These patients are capable of perceptual adaptation despite dramatic retinal image motion resulting from eye movements that are quite visible to another observer (Goldstein, Gottlob et al. 1992, Bedell 2000). This perceptual stability is attributed to the subtraction of eye movement signals from the incoming visual information, the corollary discharge or efference copy discussed above. A typical observer can experience similar retinal image motion without the subtraction of the eye movement signal by pressing repeatedly at the corner of their eye (on the eyelids at the inner or outer canthus).

More subtle challenges to the maintenance of stable fixation include loss of visual sensitivity resulting from the different forms of amblyopia (Maurer and McKee 2018), or loss of vision in the central visual field, a *scotoma*, resulting from age-related macular degeneration (AMD), for example. A number of studies have documented the unstable fixation of patients with amblyopia (Schor and Westall 1984, Carpineto, Ciancaglini et al. 2007, González, Wong et al. 2012, Subramanian, Jost et al. 2013, Kelly, Cheng-Patel et al. 2019, Scaramuzzi, Murray et al. 2019, Scaramuzzi, Murray et al. 2020). In many cases amblyopia is associated with strabismus and, in fact, patients with a strabismic misalignment and no amblyopia have been shown to have less stable fixation than typical observers and, thus, binocular function itself appears important for the development and maintenance of stable fixation (Economides, Adams et al. 2016, Koylu, Ozge et al. 2017, Ghasia, Otero-Millan et al. 2018, Kelly, Cheng-Patel et al. 2019). The subtleties of the developmental interaction between anisometropia, strabismus and amblyopia in patients are still relatively poorly understood (Barrett, Bradley et al. 2013).

Patients with a scotoma in their central visual field, often resulting from pathology in the retina, experience a significant challenge to their binocular function (as illustrated in Figure 3). When viewing monocularly with the affected eye, they can adopt a new point in their visual field that they use for fixation, their *preferred retinal locus* (PRL). Healthy typical observers do not, in fact, fixate with their point of highest cone density and so the process by which the visual system arrives at its preferred locus is of general interest beyond pathology (Putnam et al. 2005). In the example shown in Figure 3, where the patient would place their central region of vision loss to one side and view the shirt on the table with a point in their peripheral visual field. The location of this PRL will depend on the extent and severity of the individual patient's area of loss, most commonly developing below or to the left of the affected region (Fletcher and Schuchard 1997, Kisilevsky, Tarita-Nistor et al. 2016) sometimes even several degrees from the fovea. Given that vision loss can differ in extent and severity between the two eyes of an individual patient, the patient must learn to function using the information available to them from their two disrupted and/or distorted retinal representations, potentially with different PRLs. The advent of high-resolution retinal imaging and perimetry has enabled the careful study of sensitivity across the retina for these patients and re-emphasized the challenges they face in compiling a binocular percept of the world while moving their eyes effectively to explore their full three-dimensional environment (Verghese, Tyson et al. 2016, Verghese and Ghahghaei 2020). Challenges and resulting deficits have been demonstrated in the context of trying to use the peripheral retina for stable fixation and to guide eye movements (e.g. White and Bedell 1990, Crossland, Culham et al. 2004, González, Mandelcorn et al. 2019, Agaoglu and Chung 2020, Maniglia, Visscher et al. 2020), in addition to the problem of integrating information across the two eyes. We now have the technology to develop deeper insights into these challenges that will hopefully drive further innovation in assistive devices and rehabilitation (e.g. Tarita-Nistor, González et al. 2009, González, Mandelcorn et al. 2019, Verghese and Ghahghaei 2020).

Forms of clinical binocular misalignment—A discussion of clinical alignment of the eyes requires an additional set of vocabulary. There are multiple ways in which the eyes can be described as misaligned. The three core forms – fixation disparity, heterophoria, and strabismus – are discussed in the following sections:

Fixation Disparity: The first, and least often recognized, form of misalignment is the small misalignment or vergence error measured when a typical observer fixates a target binocularly and reports that they have single binocular vision. This *fixation disparity* is typically on the scale of minutes of arc and occurs in the presence of apparent gross motor and perceptual binocular fusion. While for most observers its existence is of no apparent practical consequence, this intriguing misalignment raises a question about how precisely and consistently calibrated our perception of 'straight ahead' actually is in relation to the retinal photoreceptor array. The fact that a single binocular percept can exist in the presence of a variable motor misalignment indicates that there is an *area* over which fusion can be achieved, rather than a highly precise correspondence between single points in the two eyes' retinal images (London and Crelier 2006, Jaschinski 2018). In the context of clinical care, a fixation disparity of significant magnitude can be viewed as an indication of fragile binocular function particularly in the presence of symptoms such as headache and intermittently blurred or double vision, termed asthenopia (e.g. Yammouni and Evans 2020, for the topic of eye strain when using digital devices). With the recent advances in eye-tracking technology, we still have much to learn about the interaction between perceptual and motor function in the presence of these small misalignments, whose objective estimation is highly susceptible to measurement error.

Dissociated Heterophoria: When a typical observer fixates a point, such as the blue dot in Figure 1A, and then has one eye covered, the uncovered eye will obviously remain pointing directly at the target, but what happens to the covered eye? If the binocular motor system were stable, the covered eye would remain pointing at the now-unseen target. This condition is referred to as *orthophoria* and is actually rare. More typically, the covered eye will deviate somewhat with a magnitude that changes with viewing distance (Tait 1951). This deviation is referred to as a *dissociated heterophoria* [3] and demonstrates the importance of disparity-driven fusional vergence in maintaining alignment of our eyes in binocular viewing conditions. A dissociated heterophoria, by definition, is observed only when the disparity cue for motor fusion is removed (by covering an eye, for example) and the eyes are said to be *dissociated*. This misalignment only becomes problematic if it is too large, forcing the binocular motor system to strain to achieve alignment at typical viewing distances in binocular conditions. This strain can be associated with asthenopia and development of a fixation disparity. The magnitude at which it becomes too large varies between individuals, depending on their combination of motor response components described above in the section on binocular alignment (Scheiman and Wick 2008).

Interestingly, this dissociated misalignment is capable of motor adaptation. In other words, the magnitude of deviation at a particular viewing distance can decrease after sustained activity at that distance, presumably to reduce the ongoing demand on the disparity-driven fusional vergence system in full binocular viewing conditions (Henson and North 1980, Kim, Vicci et al. 2011, Erkelens, Thompson et al. 2016, Wu, Sreenivasan et al. 2016, and see Averbuch-Heller, Lewis et al. 1999 for a related study of stimulus-driven adaptation of disconjugate saccades). This topic is particularly interesting in the context of patients with disorders of binocular vision, in that they do not appear to have been able to make consistent habitual use of this adaptation to ease their symptoms, yet a change in vergence adaptation ability can be associated with successful treatment (e.g. Schor and Horner 1989, North and Henson 1992, Brautaset and Jennings 2005, Sreenivasan and Bobier 2015). What are the functional limits of the range of motor adaptation in maintaining eye alignment and how can treatment exploit this natural ability to adapt?

An excessive dissociated heterophoria (*exophoria* when the error is divergent and *esophoria* when it is convergent) at one or more viewing distances is associated with discomfort and symptoms of headache and blurred or double vision (Scheiman and Wick 2008). One clinical disorder related to heterophoria, convergence insufficiency, is of particular current interest (Alvarez, Scheiman et al. 2020, Erkelens and Bobier 2020, Scheiman, Kulp et al. 2020). In this condition, the eyes are aligned relatively well for distant viewing, even when dissociated, but have an exophoria when viewing a near target, as though the patient has a

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[3] This dissociated heterophoria is commonly referred to as a patient’s ‘phoria’ in the clinic.

reduced ability to converge to a near target. Two particularly interesting current questions related to this condition are i) why is the magnitude of the exophoria at near viewing distances not highly predictive of the severity of a patient's symptoms (e.g. Horwood, Toor et al. 2014), and ii) if the dissociated heterophoric alignment is typically capable of adaptation towards alignment, why isn't a patient with convergence insufficiency able to reduce their misalignment to be more comfortable (Brautaset and Jennings 2005, Brautaset and Jennings 2005, Sreenivasan and Bobier 2014)? Studies of these patients indicate that we have a lot to learn about the differences between individuals in terms of their complex combination of vergence and accommodation response components described above and how they impact visual comfort in habitual natural settings (Takagi, Trillenberg et al. 2001, Lewis, Clendaniel et al. 2003, Brautaset and Jennings 2005, Brautaset and Jennings 2006, Nilsson and Brautaset 2011). More generally, if the vergence circuitry is capable of adaptation to a sustained new demand (Schor, Maxwell et al. 2002), one might wonder why most people have a heterophoric misalignment at all (Sethi 1986, Dowley 1990). In the context of the visual system being adapted to its natural environment, one might ask whether a heterophoric misalignment is in some fashion optimal for visual function and how that optimal position varies with viewing distance. These are difficult questions to address given the subtlety of the clinical condition and individual differences between patients. As described above, the neural circuitry is also difficult to access in animal models. Further, it is unclear whether these animal models even experience this type of binocular disorder. Mechanistic questions about human neural circuitry are starting to be addressed with functional neuroimaging and video-based tracking of eye position (e.g. Alvarez, Scheiman et al. 2020). Further work in this area holds the potential for clinical therapies grounded in an understanding of the underlying cause of the symptoms and disorder rather than the symptoms alone and efforts in this area have been made by a number of groups (e.g. Schor and Horner 1989, North and Henson 1992, Alvarez, Scheiman et al. 2020, Erkelens and Bobier 2020, Scheiman, Kulp et al. 2020). In the clinic this disorder is typically described as an error in symmetric vergence, but a functional understanding of patients with symptoms associated with an atypical heterophoria will likely also require consideration of the role of the neural circuitry driving the different types of eye movements described above. The patient's habitual visual function, associated with their symptoms in the natural three-dimensional world, largely consists of eye movements other than symmetric vergence on the midline between the eyes.

Interestingly, these same asthenopic symptoms of headache and blurred or intermittently double vision with heterophoria can be associated with other clinical conditions. For example, while some patients with symptoms have no apparent associated conditions beyond heterophoria, others can have experienced head trauma – concussion and mild traumatic brain injury (mTBI) – (e.g. Reynolds, Barker et al. 2019, Santo, Race et al. 2020). The underlying pathology, assessment, rehabilitation and long-term impact of head trauma are receiving significant attention currently, including in the public press. The similarity between the visual symptoms of these patients, others with toxic effects (e.g. from alcohol), and those with non-traumatic binocular vision disorders such as isolated convergence insufficiency invites further exploration. Do these similar symptoms related to daily visual function reflect disruption of the same neural circuitry due to different causes, and is this circuitry therefore a sensitive clinical biomarker in the same way that dizziness is a sensitive clinical biomarker for the vestibular system?

Strabismus: The third and final form of misalignment is strabismus, a condition in which the two eyes are misaligned in full binocular viewing conditions (e.g. in the left column in Figure 4). There are numerous forms of this disorder associated with many causes ranging from genetic mutations to vascular events to tumors to trauma. As such, it is a useful external sign associated with a variety of underlying disorders. The patient is unable to overcome their misalignment using their fusional vergence or vergence adaptation, which would otherwise eliminate any absolute disparity at the point of fixation. If their misalignment is of the same magnitude in all directions of gaze, termed *comitant* strabismus, the underlying cause is proposed to be in the early central (*premotor*) pre-cranial nerve innervation. If the amount of misalignment varies with gaze position, termed *incomitant or non-comitant* strabismus, the cause is typically isolated to the individual cranial nerve innervation or extraocular muscles, or to mechanical disruption resulting from pathology or trauma within the ocular orbit.

Comitant strabismus—If comitant strabismus develops during infancy or early childhood numerous adaptations, largely perceptual, can occur. With this type of strabismus, *suppression* of the neural activity from regions of one eye’s image often occurs, presumably preventing the patient from having diplopia (double vision, Figure 4), such as occurs when typical observers voluntarily cross their eyes. This adaptation will be discussed further below in the section on perception. When one eye is deviated more frequently than the other during the first years after birth, the vision of that eye generally becomes *amblyopic*, meaning that the brain is less responsive to information from that eye even when the other eye is covered. Moreover, the integration of information from the two eyes is permanently disrupted. Although these adaptations may help in avoiding double vision, they are not viewed as entirely beneficial, particularly when vision in the fellow eye can be lost for some reason later in life. Amblyopia develops in visual cortex during the plastic period of experience-dependent synaptic refinement over the first years after birth in humans. It is currently believed to be the result of both attenuated input from the deviated eye and suppressive influence of neural activity from the fellow dominant eye (Sireteanu and Fronius 1981, Sengpiel and Blakemore 1996, Barrett, Panesar et al. 2013, Birch 2013, Ding, Klein et al. 2013, Ooi, Su et al. 2013, Jia, Zhou et al. 2015, Shooner, Hallum et al. 2017, Zhou, Reynaud et al. 2018)

In contrast, the onset of comitant strabismus during adulthood as a result of stroke or mechanical trauma, for example, results in less successful perceptual adaptations. Adults who develop strabismus routinely experience diplopia rather than suppression, and the management of adult patients with binocular vision disorders is more difficult.

Intermittent exotropia—Patients with one form of comitant deviation, intermittent exotropia, form a particularly interesting example of the interaction between motor and perceptual systems. These individuals are only misaligned intermittently, for just seconds at a time, but exhibit the same deviation in all positions of gaze. They can be aligned for much of the day with good acuity with each eye and good stereopsis, and yet, when they are tired or they look at particular viewing distances, their eyes dissociate to a temporary divergent deviation where they typically do not experience double vision. While they are often described as suppressing the vision of one eye to avoid diplopia when they are deviated, there are numerous reports of these patients experiencing a form of ‘panoramic vision’ that implies some form of more nuanced suppression than that of an entire image (Figure 4). In terms of the classical model of binocular vision in Figure 1A, these images during the deviation will not represent matching information in the world and, therefore, binocular processes should not be able to interpret and integrate them (Figure 4). Recent research related to this topic will be discussed in the section on perception below but here, in a discussion of motor alignment, one may ask how eye movements are coordinated to provide single vision through periods of both alignment and misalignment. As discussed above, it is appealing to think of signals such as corollary discharge or proprioception as a motor trigger to switch between perceptual states when alignment or misalignment occurs. One might also ask, for a patient with this form of strabismus, what are the triggers for the intermittent deviation to occur? Are there particular tasks or ocular motor behaviors in the natural world that cause the eyes to dissociate temporarily? Unlike convergent forms of strabismus, exotropia regularly takes the eyes to an alignment that typical observers do not achieve. A typical observer does not diverge their eyes much beyond parallel alignment for distance binocular viewing and so exophoria and exotropia for distance viewing represent a somewhat unnatural state. How does the innervation for this alignment arise?

Intermittent exotropia typically appears around one year of age, after which it may resolve, be intermittent for the patient’s entire life or may deteriorate into a constant deviation over months or years. One challenging question for clinicians is when to intervene, particularly given that these children typically have no amblyopia and have good stereoacuity during periods when they are aligned. Should a young child with a relatively infrequent deviation merely be monitored, or should they receive proactive treatment during a period of limited cooperation to prevent a more frequent deviation? This set of questions is key to the management of these patients and is being looked at currently (e.g. Cotter, Mohney et al. 2014, Joyce, Beyer et al. 2015, Mohney, Cotter et al. 2019).

Refractive esotropia—A different form of comitant strabismus with interesting management questions, *refractive esotropia*, is related to the neural coupling between the accommodative and vergence motor systems. Children with higher amounts of *hyperopia* (far sight) have to accommodate more than typical emmetropes to focus their eyes and are at risk for over-convergence and esotropia when they accommodate to generate a focused retinal image. Those with a higher coupling gain, meaning more convergence per unit of accommodation, are at additional risk. Although infants in general tend to have quite active accommodation and vergence responses by approximately three months of age (Candy 2019), these hyperopes do not tend to develop their refractive esotropia until a peak age of onset of between 1 and 2 years after birth. This later age of onset and the association with refractive error suggest that this might be one of the easier forms of strabismus to prevent, by reducing the accommodative demand and over-convergence through correcting the hyperopia with spectacles prior to the onset of the strabismus. Interestingly only approximately 20% of the children with the amounts of hyperopia that put them at risk for the esotropia go on to develop a deviation. Clinical trials examining spectacle correction of these hyperopes during infancy have demonstrated mixed and only borderline success (Babinsky and Candy 2013, Jones-Jordan, Wang et al. 2020). Consensus is beginning to build that it is the infants who exhibit a reduced accommodative response (a larger accommodative lag) who are at most risk for both retaining their hyperopia and developing the esotropic deviation (e.g. Ingram, Gill et al. 1994, Mutti, Mitchell et al. 2009, Somer, Karabulut et al. 2018). This insight into prediction of strabismus is helpful to clinicians in their management of young patients but does not yet provide clear guidance for the prevention of the deviation.

The development of ocular motor behavior during the first months after birth is particularly interesting in this context. Most infants are, in fact, born hyperopic and then go on to lose this refractive error over the first couple of postnatal years. Their combination of hyperopia with no spectacle correction and a narrower distance between their eyes (interpupillary distance, IPD) implies that they have a greater accommodative demand and reduced vergence demand relative to a typical adult. This would suggest, because of the coupling between accommodation and vergence, that they might be at risk for esotropia or at least esophoria during infancy. It appears, however, that infants with typical amounts of hyperopia have a tendency to an almost adultlike level of exophoria for near viewing at 80cm by 3–5 months of age, with robust fusional vergence responses (Sreenivasan, Babinsky et al. 2016). While we still have plenty to understand about how they are coordinating the different components of their binocular motor behavior, this performance suggests that the developing ocular motor system is capable of adapting to the change in accommodation and vergence demands with growth over the first years after birth and, once again, that this amount of heterophoria is somehow optimal for functioning in the typical natural visual environment. Ocular motor performance is particularly important during this developmental period in that accommodation and vergence responses define focus and alignment of the retinal images during the period when the developing visual cortex is at risk for experience-dependent abnormality in synaptic refinement and clinical amblyopia (Candy, Wang et al. 2009, Candy 2019). Measurement of accommodative and vergence responses in the presence of simulated difference in refractive error between the eyes (anisometropia) and imposed additional conflict between the accommodative and vergence demands have suggested that these responses are relatively robust to the disruption during typical early childhood (Bharadwaj and Candy 2009, Bharadwaj and Candy 2011). In general, young children are able to use visual cues available in the natural environment to coordinate responses to these complex and changing motor demands (Bharadwaj and Candy 2008, Horwood and Riddell 2013). We need to understand how this development can be disrupted in the case of clinical abnormality.

Neural circuitry—When a comitant strabismus does develop, there are two important clinical characteristics. Firstly, whether it is present constantly or only intermittently. And secondly, whether a child always fixates with the same eye (termed unilateral strabismus) as opposed to fixating happily with either eye (termed alternating strabismus). All four combinations of these two factors are possible and tend to be present in different proportions for different forms of comitant strabismus. The origins of these behaviors and the underlying neural circuitry are poorly understood, as is any relevance of age of onset (e.g. infantile esotropes will often have constant and alternating esotropia, while refractive esotropes with later onset are typically intermittent and unilateral at first becoming constant and unilateral over a period of months). These factors have important clinical implications as the more a young child favors one eye, the more likely it is that they will develop amblyopia in the cortical processing evoked when viewing with the other eye (e.g. Birch and Stager 1985). Thus, the varying forms of strabismus do not represent a single clinical condition in that a patient with refractive esotropia and amblyopia can mature to function almost monocularly whereas a patient with intermittent exotropia can have almost typical binocular vision during their periods of alignment. While identifying the neural origin of these differences is still difficult, a number of studies have recently started to examine the neural innervation associated with strabismic motor behavior in animal models (e.g. Das 2016, Walton, Pallus et al. 2017). Although these animal models of strabismus have usually been developed using motor or sensory interventions with no common parallel in typical human strabismus (e.g. alternating monocular occlusion), they can be used to study the impact of disrupted binocular vision on control of motor alignment (rather than to study the cause of the misalignment). These studies suggest that the activity of neurons in the SOA vergence circuitry and in the pontine circuitry guiding saccadic behavior can both be permanently modified by disrupted binocular vision. The responses of the SOA neurons can be associated with the angle of strabismus and disrupted in their velocity coding (Das 2016, Pallus, Walton et al. 2018). In addition, neurons in the saccade circuitry can have responses related to movements in an atypical direction (e.g. a vertical component for a neuron in the PPRF that would typically only fire for horizontal saccades) (Walton, Pallus et al. 2017). These studies are starting to ask how premotor neural circuitry is capable of coordinating a consistent misalignment across activity of the set of extraocular muscles innervated by the three different cranial nerves. Other studies are also starting to consider the genetic associations with comitant strabismus (Shaaban, MacKinnon et al. 2018, Plotnikov, Shah et al. 2019), although they still leave intriguing questions such as why this strabismus appears postnatally, apparently spontaneously.

Incomitant strabismus—Unlike comitant strabismus, with its consistent magnitude of deviation in all positions of gaze, the various forms of incomitant strabismus each have a characteristic pattern of deviation magnitude across gaze position that often indicates the specific locus of disruption in neural circuitry (e.g. Horn and Leigh 2011). For example, a sixth cranial nerve palsy will result in underaction of the lateral rectus muscle and an inability to move the affected eye away from the nose, meaning the eyes will be more misaligned when looking towards objects in the visual field in that direction.

Exciting progress has been made recently in understanding the underlying genetic origins of some of these incomitant disorders (Whitman and Engle 2017). After identifying potential genetic associations in families of patients, these disorders are now being replicated in animal models to gain deeper understanding. For example, Duane’s Retraction Syndrome is one of the most common cranial nerve dysinnervation disorders. With a severity depending on the specific form of the condition, these patients cannot move their eye temporally (away from the nose into abduction) and when they attempt to move it nasally (towards the nose into adduction) the eye moves backwards into the orbit. Their sixth cranial nerve, the abducens nerve, does not fulfill its typical role of innervating the lateral rectus muscle to move the eye temporally and their third cranial nerve, the oculomotor nerve, innervates both the medial and lateral recti rather than just the medial rectus. While this pattern is logical in explaining the absence of abduction in a situation where the abducens nerve would typically be active, plus the retraction of the eye into the orbit when the oculomotor nerve would typically only be adducting the eye, it is only recently that this syndrome has been replicated in mice using genetic modification (Park, Tischfield et al. 2016). These studies have demonstrated that the genetic disorder disrupts axon guidance during developmental growth of the sixth nerve, then resulting in abnormal growth of the third nerve towards both the medial and lateral rectus muscles. Tracking the cause of these forms of strabismus to their genetic origin holds exciting promise for future preventative intervention.

Treatment of strabismus—Most forms of strabismus develop prior to school age, meaning that initial treatment occurs in a pediatric clinic. Unfortunately, current treatment approaches are routinely not fully effective. Despite interventions that straighten the eyes to improve cosmesis, many patients are left with small residual deviations and disrupted binocular function with amblyopia (e.g. Birch and Wang 2009, Wan, Chiu et al. 2018). These interventions range from (i) shifting the retinal image directly while leaving the eyes misaligned (prism) to (ii) manipulating an extraocular muscle and its action to align the eye (surgery or botulinum toxin) to (iii) manipulating the control of eye movements to align the eyes (e.g. strengthening fusional vergence responses, or using lenses to adjust accommodative vergence). Importantly, these approaches are only aimed at treating the consequences of strabismus, rather than its cause.

For example, while patients with comitant strabismus need to fixate a target with one eye during habitual viewing with both eyes, the underlying condition is not actually a disorder of the deviated eye. It is a relative misalignment of the two eyes and the patient is fully capable of fixating a target in any position of gaze when viewing monocularly with either eye. If a child progresses into a unilateral comitant strabismus by fixating consistently with the same eye, the condition then becomes associated with the development of poor vision of the deviated eye, amblyopia, during the sensitive period of neuroplasticity in infancy and early childhood. The less frequently an eye is used to fixate the target during this time, the greater the probability the child will lose binocular neural function and develop amblyopia for the more commonly deviating eye. They may also develop other associated motor conditions such as forms of nystagmus or dissociated vertical deviation (Tychsen, Richards et al. 2010, Das 2016, Walton, Pallus et al. 2017). This leaves the clinician needing to manage the deviation, the amblyopia and any other resultant conditions (consequences rather than cause). When thinking about management of these patients, it is therefore appealing to think of strategies to intervene early in childhood to try to prevent the strabismus and to encourage the patient to view targets with each eye for more balanced periods to prevent amblyopia.

Happily, studies of genetic association are providing insight into the biology actually causing some forms of strabismus and it is hoped that this will lead to management that more directly targets the cause before permanent secondary consequences develop. Other potential treatment approaches currently being considered include manipulation of extraocular muscle function using growth hormone locally administered to the muscle (e.g. Fleuriet, Willoughby et al. 2020). While in the early stages of study, this approach could theoretically permit careful ongoing titration of treatment that could be tailored to the patient's current status, as opposed to a single surgery that requires anticipation of the impact of the subsequent healing process. The relevance of this discussion in the context of binocular vision in the natural world is the fact that strabismus management is clearly more complex than merely needing to realign one eye at a static target in the classical model of binocular vision. Our limited understanding of the complexity of the neural circuitry coordinating eye movements for binocular vision in the full dynamic three-dimensional world has limited current treatment approaches to manipulation of visual input or muscle function (although see Schor 2009). While strabismus surgery is used to weaken or strengthen an entire muscle, recent work undertaken by Demer and his colleagues has suggested more subtle insight into differential function within a muscle (e.g. Peragallo, Pineles et al. 2015) that may also need to be addressed in refining future approaches to strabismus management. The drive to improve these treatments is logical given our currently limited ability in prevention.

At this point we will move into a discussion of the how the brain integrates and interprets the information sent by the two eyes. The discussion above has reiterated that much of the content of the retinal images does not in fact reach perception, though we typically perceive a unified stable representation of the world even in the presence of any of a number of forms of clinical disruption. What have we learned recently about how we build this percept?

3. Perceptual Function

3.1 Interpreting the depth structure in the environment

Once motor alignment has been achieved, perceiving depth structure in the natural environment is not a matter of matching 2D sets of information. In fact, motor alignment facilitates the detection of differences in the two retinal images, both static differences, called *positional disparities* or *retinal disparities*, and differences in the retinal image motion produced by visible objects moving in 3D space, which we will call *velocity disparities*.

There are obvious advantages to having two eyes versus one. Among them are a larger field of view, redundancy (sight is retained if one eye is injured), and probability summation, by which two eyes limited by uncorrelated noise have a statistically better chance of detecting a weak signal than one eye. The chief advantage, however, is *stereopsis*, the ability to acquire information about the third dimension because the eyes are separated in space. In adult humans, the eyes are about 63 mm apart, and the separation is horizontal when the head is level. During development, this value increases by approximately 50% from around 40 mm in newborns (Pryor 1969, MacLachlan and Howland 2002). Because the eyes are so close together, there is a common misconception that stereopsis is only useful at relatively near distances. This is false; stereopsis is useful as far as the eye can see (Liu, Bovik et al. 2008, Sprague, Cooper et al. 2015) because many things in the natural world are very far apart (e.g. the depth difference between a herd of elk at 50m and the backdrop of a mountain at 10km is easily detectable given typical stereopsis).

There are many ways besides stereopsis that organisms get information about the third dimension. Cues such as relative size, occlusion and perspective are present in paintings and photographs. In the real world, however, more cues such as motion parallax or looming permit an organism to compute depth very precisely. Motion parallax occurs when the head moves laterally (easily seen by looking out the side window while riding in a car or train) – stationary objects move in the visual scene at very different speeds in a way that depends precisely on their distance from the observer and the point at which the observer is looking. The resulting velocity signals produced on the retina are used by the brain to compute the three-dimensional (3D) structure of the scene. Interestingly, these cues can all be extracted when viewing with only one eye.

Stereopsis provides essentially the same information as motion parallax but *without the observer having to move*. This is advantageous in terms of both energy expenditure and time (the information for stereopsis is available instantaneously rather than over the course of a movement). But, most importantly, stereopsis can encode the depth of the scene while the observer remains perfectly still and thus less conspicuous. This is helpful for both predators and prey, humans in the wild being both and, in fact, stereopsis is present in both (Nityananda and Read 2017). Because prey have a somewhat competing need for panoramic vision, however, stereopsis in predators is generally better. All known primates from humans to marmosets are thought to have well-developed stereopsis, as do some birds (Pettigrew and Konishi 1976, Fox, Lehmkuhle et al. 1977, van der Willigen 2011) and at least one insect (Nityananda, Tarawneh et al. 2018). Even the mouse, used broadly as an animal model for numerous questions, has been shown to use both positional and velocity disparities despite its relatively poor visual function (La Chioma, Bonhoeffer et al. 2019, Choi and Priebe 2020). Perhaps stereopsis should be assumed to be present in some form in all land vertebrates unless shown otherwise, rather than vice versa.

Positional Disparities—The basic geometry of classic stereopsis is shown in Figure 1A (we say “classic” because we now know stereopsis to be richer and more complex than conveyed in that figure). The figure shows two eyes from above in cross-section looking at the blue object (which makes this object’s location in space the *fixation point*). In typical binocular vision, the retinal images of the blue stimulus are thus assumed to fall on or very near the center of the fovea in each eye due to motor alignment. These image points fall where the line connecting the object of regard to the *nodal point* (optical center) of the eye – the *visual axis* – intersects the retina. These points are considered the origin of the coordinate systems for the retinae in the two eyes. These points, as well as all other pairs of points with identical coordinates in the two eyes are termed *corresponding retinal points*.

The left (red) and right (green) objects are nearer and further from the observer than the fixation point. Consider the green object; By virtue of its depth, the right eye is looking more directly at the gap between the blue and green objects, and the left eye is looking more directly along a line connecting the blue and green objects. As a result, the image of the green object will fall further from the image of the blue point (the origin of our coordinate system) in the right eye than it will in the left eye; the green images will fall on non-corresponding retinal points. Using a Cartesian coordinate system, these points might be, for example, [−2, 0] in the left eye and [−4, 0] in the right. The difference between these two coordinates (left – right by convention) is [2, 0], and is termed a *retinal disparity*. This is traditionally considered to be the sensory stimulus to stereopsis and we will refer to these differences as “positional disparities” to distinguish them from the velocity disparities discussed below. Because these disparities are computed with respect to the fixation point, they are referred to as *absolute dispariti*es as opposed to *relative disparities*, which can be computed between any two points in a scene regardless of fixation. Positive absolute disparities, those that are further from the observer than the point of fixation (e.g. the grey or green objects), are termed “uncrossed” disparities while those nearer and therefore negative (e.g. that of the red object), are termed “crossed” (these odd terms come from the visual appearance of objects on the midline between the eyes – the midsagittal plane – when one alternately closes each eye in turn. Monocular images of a nearer object will appear in the contralateral visual hemifield, while those of a more distant object will appear in the ipsilateral hemifield).

For a given convergence angle (e.g. when fixating the blue object in Figure 1A), Euclidean geometry teaches that the locus of all points in the horizontal plane with zero disparity (stimulating corresponding retinal points in the two eyes), is a circle defined by the fixation point and the nodal points of the eyes. This curve is termed the theoretical *horopter* and is shown by the dashed circle in Figure 1A. Anything inside the horopter has, by definition, a negative positional disparity and will be perceived as nearer than the fixation point by an observer without other cues. Note that this figure depicts an extremely close fixation distance to make the disparities obvious. At more common, realistic fixation distances, the portion of the horoptor roughly straight ahead is much closer to being a frontoparallel plane, and negative and positive disparities thus correspond to things that are nearer or further in an intuitive sense (as opposed being inside or beyond a small circle).

The encoding of absolute positional disparities is relatively well understood in terms of the properties of neurons in the primary visual cortex, V1 (Fleet, Wagner et al. 1996, Ohzawa 1998, Chen and Qian 2004). Ultimately, the disparity map produced by this stage of the visual system can be understood and simulated as a quilt of local spatial cross-correlations of appropriately filtered image patches. In other words, the transformation from a visual scene to a disparity representation of that scene – the *encoding* process for absolute horizontal positional disparities – is, to a first approximation, an answered question. This statement should not be taken to mean that depth perception using binocular vision is a solved problem (or even close) however. One reason is the empirical finding that the perception of depth from absolute disparities is much weaker than that from relative disparities (reviewed by Chopin, Levi et al. 2016), and is in some cases absent. Second, absolute disparity signals, such as represented in primary visual cortex at the scale of a hypercolumn, change drastically with every change in vergence so, practically speaking, with every eye movement. This makes a direct read out of these signals ill-suited as a representation of the environment or as a guide to most behaviors. Thus, while the encoding and decoding of absolute disparity provides sufficient information for changing the binocular fixation from point to point, in order for the binocular visual system to convey useful information about the scene for behavior, a more stable description with a more useful frame of reference is required.

A first step towards a more useful representation would be to compute *relative disparities* between neighboring scene points. Consider a horizontal strip of a visual scene. For a given vergence posture, one could write down a vector of all the absolute disparities in the strip. This is effectively what primary visual cortex, V1, does. Now imagine taking the 1st derivative of the values – this new vector would contain the relative disparities of neighboring scene points and would not change with vergence posture – the differences in disparity between adjacent points would remain constant, and would thus be a useful representation of the world itself irrespective of vergence posture. This encoding of relative disparities seems to occur or at least begin in V2 (Thomas, Cumming et al. 2002). This is particularly interesting because V2 is also the first cortical area that responds preferentially to naturalistic rather than random texture (Ziemba, Freeman et al. 2018); it, in other words, seems to be the first cortical area to incorporate prior expectations about possible scene structure. Whether V2 similarly incorporates natural disparity statistics is not as yet known, although the distribution of disparity sensitivity in V5/MT (DeAngelis and Uka 2003) is well matched to the distribution of naturally occurring relative disparities in the environment (Liu, Bovik et al. 2008, Sprague, Cooper et al. 2015).

The encoding of relative disparity in higher visual areas and, ultimately, the encoding of the 3D environment in a manner than can support behavior other than eye movements is still unclear. For example, it is well established in macaque monkey that area MT has many neurons sensitive to disparity (DeAngelis and Uka 2003), and while some fMRI studies in humans have found evidence for disparity selectivity in the human analog of MT, hMT+ (Neri, Bridge et al. 2004, Rokers, Cormack et al. 2009), at least one other has not (Backus, Fleet et al. 2001). The point here is not that a role for disparity processing in hMT+ is controversial; rather, that it is currently difficult to probe the entire visual cortex at a fine spatial and temporal resolution using realistic 3D stimuli. So, while sensitivity to disparity has been found in almost every visual area (Neri, Bridge et al. 2004), including even inferior temporal cortex (Verhoef, Vogels et al. 2016), the interpretation of this sensitivity is still preliminary.

One interesting recent finding is that area MT in the macaque and area hMT+ in the human are not only sensitive to static disparities, but also encode motion through depth or 3D motion (Rokers, Cormack et al. 2009, Czuba, Huk et al. 2014, Sanada and DeAngelis 2014). These and several other studies from around this time confirmed that, in addition to encoding the positional disparities present in a binocular scene, the visual system also directly compares the motion signals in the two eyes in order to compute motion in the third dimension. In other words, the binocular visual system encodes velocity disparities.

Velocity Disparities—To be truly useful, the visual system not only needs to compute the *positions* of objects in 3D, it also needs to estimate the *three-dimensional motion* of objects, with the depth component of the motion being arguably the most crucial. Until recently, it was thought that the depth component of motion was computed in only the most obvious way, which is to measure the disparity of an object at successive time points and to use differences in position across time to estimate the velocity in depth. Looking back at Figure 1A, consider the green, blue and red ovals to be a single object that moved from the right green position at time *t* to the central blue position at time *t+1* and to the left red position at time *t+2*. To compute the 3D depth motion of this object, the visual system would estimate the lateral motion using the well-understood dorsal processing stream for motion, and also estimate the change in depth by computing the change in disparities over time. It would then combine these to get the "leftward and towards me" motion trajectory through 3D space.

In theory, however, there is a second way to compute 3D motion. When an object moves in 3D, the motion stimuli on the retinae of the two eyes are almost always different. Consider Figure 5a, which shows the view from above of a person looking at an object coming towards them and to the left (just as described above). In this case however, the arrow represents the vector in three-dimensional space that describes the object motion. Figure 5b (lower right) shows the view from behind the right eye, thus showing the motion from the right eye's perspective; the 2D (inverted) version of this view is the retinal stimulus for the right eye. Figure 5c (lower left) shows the same situation from the left eye's perspective. Notice that the projected vectors in the two perspectives (5b vs. 5c) are very different lengths and therefore *the retinal velocities are very different in the two eyes* (an object coming towards the nose will in fact produce motion in opposite directions in the two eyes). Mathematically, a comparison of these velocities can precisely recover the 3D trajectory of the stimulus. However, a huge problem with this theory is that, to compare retinal velocities across the eyes, one would need two pools of neurons sensitive to a range of velocities, one of which was driven by the right eye, and one of which was driven by the left. In the primate visual system, though, motion sensitivity only emerges in primary visual cortex, where virtually all the cells are driven to some extent by both eyes. Thus, the eye-of-origin information required to make a binocular comparison doesn't seem to exist, at least in primates, which would make the use of velocity signals from the two eyes *per se* impossible, even in theory. Indeed, evidence that this cue is used was, at best, equivocal (Harris, Nefs et al. 2008).

Subsequently, however, it was shown that judgements of 3D motion could be dissociated from judgements of 3D position (Rokers, Cormack et al. 2008). As the latter could rely only on positional disparities in the stimuli and the former could not, this was effectively a dissociation between positional disparities and velocity disparities, thus proving that the human visual system could *use velocity disparities per se to judge 3D motion*. Since then, a large body of literature has demonstrated the use of the velocity-based cue (reviewed by Cormack, Czuba et al. 2017). Further, it seems that cortical ocular dominance [4], rather than strictly monocular mechanisms, can allow the visual system to use velocity disparities (Bonnen, Czuba et al. 2020). The difference between the positional and velocity-based cues is in the order of the computations. The same operations are done, derivatives with respect to both time and retinal position, but when computing velocity disparities the change with respect to time is computed first. Despite this striking similarity, the encoding of velocity disparities is not nearly as well understood as of positional disparities, although currently cortical area MT seems to be a very good candidate for the site of this encoding (Czuba, Huk et al. 2014, Sanada and DeAngelis 2014).

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[4] In this context, ocular dominance specifically refers to variation in sensitivity of cortical neurons to input from one eye compared with the other; the tendency of humans to favor one eye over the other - eye dominance - is a different phenomenon.

The depth map and perception—At this point we must make two very important and related points. First, binocular disparities in position and velocity, along with other sources of depth information such as motion parallax, must ultimately be integrated in some way. This is required for the second point, which is that the "output" of an organism, motor behaviors, are unitary. At a given time, the eyes have to point in one direction. Therefore, the *decoding* process to drive motor behavior, including eye movements, must result in a single answer at a given time. Curiously, perception, unlike motor responses, does not have to be unitary; it is, for example, possible to experience double vision and to have one's sense of objects dissociated from one's depth map of the world. This can be easily demonstrated with two pencils (or similar objects) as shown in Figure 6.

To explore this demonstration, take a pencil (or anything else with a visible sharp point) and hold it in front of your eyes, pointing up, at a distance of about half arm's length. Hold a second pencil, pointing downward, immediately above the first, as if trying to touch the points together. Now, while carefully maintaining fixation on the bottom pencil point, move the top pencil directly towards you. It will quickly split into two pencil points yet will also give the strong impression of being in front of the lower point. Thus, the perception of singleness is dissociated from the perception of depth. One simultaneously perceives a single depth impression (a single upper pencil in front of the lower pencil) along with two distinct impressions of direction (one upper pencil to the left, and one to the right). It is tempting to think of this as a dissociation between the ventral ("what") and dorsal ("where") streams of primate visual processing, but it is really a dissociation between two "where" questions – one as to the 2D location that is mapped from the retinal image, and the other as to the 3D location that must be computed from these 2D locations in the two eyes (Lugtigheid, Wilcox et al. 2014, Allison and Wilcox 2021).

Here, it is worth introducing some terminology. *Diplopia* is the perception of a single object in space as two objects in different visual directions – double vision – such as with the upper pencil points in the above example. *Fusion* is the absence of both diplopia and suppression, where the term *suppression* refers to the elimination of information from one eye for the maintenance of single vision. In other words, fusion refers to the alignment and typical binocular integration of information from the two eyes. Confusingly, people also refer to "stereoscopic fusion" to indicate that the visual system has computed a depth estimate from the disparity between two retinal images. Thus, while diplopia and fusion are mutually exclusive, diplopia and "stereoscopic fusion" are not, and we will hence avoid using the latter term any further. The potential confusion does serve to highlight, however, that there are at least two versions of "corresponding" retinal points, one for determining whether the images in each eye lie along the exact same visual direction from an observer, and another for computing a depth map from the disparity information in the two eyes. Put another way "retinal correspondence" does not refer strictly to retinal coordinates, as though one were overlaying two pieces of graph paper; obviously the processes that actually determine "correspondence" are located throughout the brain and are more complicated.

The complicated nature of correspondence manifests itself in clinical tests of fixation disparity, the small remaining motor misalignment when patients report that they are fixating a target binocularly. One such test is the so called "ox oh" test. Figure 7A shows the stimulus for this test seen by each eye: the “O X O” is seen by both eyes just as a physical stimulus would be, and the patient is instructed to fixate the center of the “X” (the “O X O”, rather than a single small point, is presented to give the visual system more information with which to compute a precise binocular correlation and lock motor fusion). The vertical pink lines are presented monocularly; each is seen by only one eye (these are termed “nonius lines”, after Pedro Nunes, who developed the “nonius”, an astronomical instrument that used a precursor to the Vernier scale). When fixation is fully accurate, as in Figure 7B, an observer perceives the pink nonius lines vertically aligned with each other and with the binocular X in the middle. If, however, fixation is slightly too near or too far (panels C and D, respectively), the lines are perceived as shifted laterally in opposite directions. Considering just the pink nonius lines themselves, this is logical; if fixation is too near as in panel C, then the left eye will be pointed to the right of center, and the upper nonius line will thus appear to the left of the center in the left eye’s view (and vice versa for the right eye) – uncrossed retinal disparity. If fixation is too far, then the situation is reversed and the upper line, seen by the left eye, will be shifted to the right, while the lower line, seen by the right eye, will be shifted to the left – crossed disparity. Now for the more subtle part shown in panels C and D, *the nonius lines in each eye have shifted relative to the perceived position of the X, also seen by that eye*. In other words, the nonius line is perceived in a different horizontal direction than the X despite the fact that the nonius line and X are stimulating the exact same horizontal direction on each individual retina (with only a small vertical separation). This simple test of fixation disparity unintentionally demonstrates that *stimuli with essentially the same retinal coordinates in an eye can somehow be perceived in different directions in space*. Most people can be shown to demonstrate this small misalignment of the eyes, fixation disparity, and therefore to experience this dissociation in visual direction in their perception (Goss 1995, Scheiman and Wick 2008).

Taken together, these observations indicate that stimulation of a given retinal point does not produce a unique result nor even correspond to a unique visual direction. They demonstrate that computations underlying perceptual fusion can be performed locally in the image, without aligning to another region of the retinal image. While the underlying correspondence map in typical observers has been shown to be relatively stable (e.g. Hillis and Banks 2001), correspondence in perception appears very much situation dependent. In fact, as described above, an object can be perceived in different visual directions by the two eyes – the sensation of diplopia – while still leading to a percept of depth (Lugtigheid, Wilcox et al. 2014). The definition of correspondence itself is perfectly valid, it is just that perception does not always reflect literal correspondence in the retinal images. Each brain area and each binocular mechanism has, in fact, its own scheme for combining information from the two eyes.

The dynamic complexity of binocular correspondence is rather staggering. Despite this, the primate visual system is capable of deriving a relatively unambiguous and stable dynamic depth map. In order to do so, it must cope with an enormous amount of noise and uses filtered information rather than point-wise luminance values (e.g. disparity energy (Fleet, Wagner et al. 1996) or differences between quasi-local velocities in the two eyes; (Rokers, Cormack et al. 2008)). This was foreseen by Gibson, but also consists of experimentally discoverable computations transforming the information into useful representations (a la

Marr) to generate advantageous behaviors. Crucially, the binocular visual system also uses prior information (e.g. incorporates Bayesian strategies) in producing optimal or near optimal behaviors (Read 2002). Some of these “priors” probably drove the evolution of the binocular visual system from the earliest stages, such as the assumption that there is one physical world and that any differences in the two eyes’ images are due to the spatial offset between the eyes (this assumption is so powerful that if not fully met, the visual system can essentially shut down one image: the condition called *suppression*). Other priors, such as the non-random *1/f* nature of textures in the natural environment, are exploited in receptive field properties (e.g. Ziemba, Freeman et al. 2018). Such priors can be observed in real-time when continuous tracking behavior is measured, a situation in which the visuo-motor system behaves as an optimal Kalman filter type system (Bonnen, Burge et al. 2015, Bonnen, Huk et al. 2017). It is also quite likely that priors for scene statistics are used directly to facilitate the computation of a depth map with stereopsis (Read 2002, Liu, Bovik et al. 2008, Su, Cormack et al. 2013, Su, Cormack et al. 2017).

Good progress has been made recently, both in understanding vision generally and binocular vision specifically, by emphasizing more naturalistic stimuli (e.g. Bonnen, Huk et al. 2017, Downey, Pace et al. 2017, Downey, Pace et al. 2018, Ziemba, Freeman et al. 2018) and tasks over the earlier simpler psychophysical paradigms. The more recent studies are interesting in that they emphasize the understanding of *behavior* rather than *perception*. In this context, as opposed to a purely aesthetic appreciation of the visual environment, perception can almost be viewed as an epiphenomenon in a complex nervous system containing intermediate representations of its environment to support behavior. There is, however, another context in which perception is of central importance. This context is in the clinic, where patients for whom the binocular visual system is not functioning normally must cope with atypical and sometimes disturbing perceptual experiences.

3.2 Interpreting depth structure – Clinical context

There are a number of clinical conditions that challenge the formation of an integrated stable binocular percept of the depth structure in the environment (e.g. Figures 3 & 4). As discussed above, the patient may have unstable fixation or the quality of their images may be degraded by disrupted optics or a pathological scotoma. Image degradation might occur monocularly, meaning that the information gathered by the two eyes is mismatched in quality and any resultant difference in the latency of signals arriving in cortex from the two eyes can also lead to misperceptions of depth, such as the well documented *Pulfrich phenomenon* where an illusion of interocular disparity and depth is produced as a result of signal delay from one eye. Alternatively, misalignment of the eyes for patients with strabismus results in non-corresponding information of equal quality arriving at binocular stages of computation in the brain. In each of these situations, from the patient’s perspective, the key goal is to form a reliable percept of the world on which to act.

In moving to consider the impact of clinical disruption of binocular vision, we cannot assume that a disrupted disparity signal will have the same effect on both motor and perceptual performance. As described above, the motor and perceptual computations are performed at different stages of neural processing (including them being primarily responsive to absolute and relative disparity, respectively). The ultimate impact of a clinical condition on the patient will depend on the information available to the relevant stages of computation and the capability for functional adaptation. The amount of adaptation, in turn, will depend on the age of the patient because age largely determines their potential for neuroplasticity (e.g. Banks, Aslin et al. 1975, Birch and Stager 1985). Some forms of adaptation during early childhood may be beneficial in generating a meaningful percept for action. Others, such as amblyopia or loss of stereopsis, appear to be unfortunate by-products of the need for a meaningful single percept. While some of the adaptations discussed below are typically described in terms of matching the retinal images from the two eyes, recognition that perception, at least in part, is constructed dynamically to reflect the most likely content of the scene appears warranted given studies of these patients and advances in our understanding of typical vision. The shortcomings of the frequent framing of clinical adaptations in terms of a literal comparison of retinal images will be discussed below.

The clinical challenges discussed in the section on motor performance will now be discussed in terms of their impact on perception:

Unstable images—Observers with typical vision do not perceive misleading movement of their visual world when they make fixational, saccadic, vergence or smooth pursuit eye movements, even though the image of the environment is sliding across the retina. The brain is capable of temporarily suspending perception (e.g. during saccadic suppression; (Krock and Moore 2014, Binda and Morrone 2018)), compensating for motion in the sensory information arriving during an eye movement to provide stable perception (e.g. during fixational eye movements; (Poletti, Listorti et al. 2010, Arathorn, Stevenson et al. 2013)), using statistical regularity to make perceptual (e.g. in the Flash-Lag effect; (Hogendoorn 2020)) or motor (e.g. Kowler, Rubinstein et al. 2019) predictions, or attributing retinal image motion to eye, head or body movement rather than movement of objects in the scene. Much of the recent work on these topics is adding to our understanding of how these computations are performed and applied in perception within milliseconds, permitting interaction with the world despite the latency between an event happening physically in the scene and its perception forming in the brain.

Patients with clinical disorders also make use of these strategies in adapting to their visual experience, particularly when the onset of the condition occurs during the first years after birth. One of the most impressive examples is patients with early onset forms of nystagmus. These children can perceive a stable world with no inappropriate motion despite uncontrollable motion of their eyes (e.g. Bedell 2000), even to the point of being unable to perceive their own eyes moving when looking in the mirror. While compensation for movement of the whole retinal image during nystagmus can be achieved using a subtraction of the mean retinal image motion or the signals driving the eye movements (corollary discharge), local compensation for movement of the eyes within a mirror image of the face is a more subtle and complex coordination question, requiring some form of perceptual suppression. For an interesting demonstration of this phenomenon, it is helpful to view one's face in a mirror from a distance of approximately 10cm. After looking directly at the pupil of the right eye, switching fixation to view the pupil of the left eye requires a saccadic eye movement of around 30 degrees, yet we do not perceive this eye movement when viewing in the mirror; an example of saccadic suppression of perception. It is helpful to watch the movement of somebody else’s eyes while they perform this task as a confirmation of the suppression effect.

In general, patients with relatively small amounts of fixation instability and a functioning binocular visual system are capable of experiencing stereopsis and percepts of depth, somewhat like observers with typical amounts of fixational eye movements. These patients tend to have reduced sensitivity to depth however, which can be attributed to a combination of loss of overall spatial sensitivity with smearing of the retinal image, developmental deficits in binocular computation, and any amblyopia that has developed during early childhood (e.g. Scaramuzzi, Murray et al. 2019). Recent studies of visual processing during fixational movements hold exciting promise for mechanistic understanding of the adaptation performed by these patients (Otero-Millan, Macknik et al. 2014, Rucci and Poletti 2015).

Disrupted images—Disruption of the retinal image caused by optical effects can occur in a number of formats. It could be in one eye or both, it could be the result of simple refractive error or a more complex optical distortion such as that resulting from cataract, astigmatism, or keratoconus (Atchison, Schmid et al. 2020, Nilagiri, Metlapally et al. 2020). The core themes defining the impact of optics on binocular perception are i) whether image content is missing entirely (e.g. high spatial frequency content and detail from a blurred image) or shifted spatially in the eye (with prism or magnification, for example), and ii) whether the optical disruption develops early in life during the period of significant developmental neuroplasticity leading to permanent loss of function, or after early childhood when performance will only be limited by disruption of image content (Banks, Aslin et al. 1975, Birch and Stager 1985).

In cases of matched disruption in the two eyes (equal refractive blur, for example), the key question becomes what can be inferred about the world based on prior knowledge and the currently available sensory information. Matched loss of fine detail in the two eyes will limit the potential for fine stereopsis (e.g. Schor and Wood 1983, Schor, Wood et al. 1984, Ding and Levi 2021). Cases of unequal disruption in the two eyes form a more profound challenge to binocular vision (Sherafat, White et al. 2001, Smith, Allison et al. 2019, Marella, Conway et al. 2021). In fact, loss of information from only one eye can result in poorer binocular performance than matched loss of the same information from the two eyes, even though one eye still has a typical retinal image. For example, sensitivity to the smallest disparities is degraded more if contrast is reduced in one eye than if it is reduced by an equal amount in both, implying that thresholds actually get worse if contrast is *increased* in one eye; this phenomenon is referred to as the “stereo contrast paradox” because, in general, visual function tends to increase with increasing contrast (Cormack, Stevenson et al. 1997, Stevenson and Cormack 2000). This phenomenon appears maladaptive for function in the natural world and is hard to reconcile given that a typical image is available from one of the eyes.

Anisometropia: One relatively common example of a difference in optical disruption occurs when the two eyes have different refractive errors, *anisometropia*, typically resulting from matched optical power but different eye sizes. This form of difference in retinal image quality can arise naturally during childhood, if the two eyes grow unequally and the child has no optical correction. Alternatively, it can be intentionally provided by a clinician to an older presbyopic patient who can no longer accommodate and who benefits from having one eye focused optically for distance and one for near. Clinicians create this latter situation, termed monovision, for adult patients using contact lenses or sometimes intra-ocular lenses after cataract removal. It is less likely to be effective in the form of spectacles because lenses of different power also create different magnification when positioned away from the eye, as spectacles are. Many adult patients are able to adapt to monovision while others are unable to tolerate having only one eye in focus and, in fact, there is recent evidence that monovision correction could produce misperceptions of depth (Chapman, Scally et al. 2011, Ito, Shimizu et al. 2014, Burge, Rodriguez-Lopez et al. 2019, Smith, Allison et al. 2019) and loss of motor alignment (e.g. Ito, Shimizu et al. 2014).

Monovision and childhood anisometropia present an interesting challenge to the brain. While the information available at large scale (low spatial frequency) is present and largely matched in the two retinal images, the information at high spatial frequencies will be reduced in whichever eye is more defocused at the relevant viewing distance. The actual focus of the two retinal images will depend on the accommodative behavior of the patient, but any consensual (binocular) innervation to accommodation forces the anisometropia to remain and only one eye can be fully focused at any distance (Almutairi, Altoaimi et al. 2020). The brain must learn to combine one more blurred and one more focused image in order to generate a binocular percept, raising interesting questions about the role of eye dominance in adaptation to this situation (e.g. Han, He et al. 2019). In addition, as accommodation and vergence are coupled, a difference in accommodative demand for the same object in depth will result in different vergence postures for that object even though there can be only one fully appropriate vergence angle (e.g. Bharadwaj and Candy 2011).

Loss of retinal function: Loss of function in localized areas of the retina in conditions such as age-related macular degeneration (Figure 3) or glaucoma constitute a different type of disruption of the retinal image. In these cases, discrete patches of retinal function are lost as a result of destructive pathology and scarring. Interestingly, everybody has a localized area of retina in each eye where there is no light capture: the blind spot in the temporal visual field corresponding to the location where the axons of retinal ganglion cells leave the eye in the optic nerve. These are located about 15 deg laterally from the central fovea and about 2 deg below the horizontal meridian; they are not small, being approximately 5 deg wide by 7 deg high. These positions in the two eyes are associated with different retinal image content because they are located nasally on each retina and are thus in the temporal visual field of each eye. That we see a continuous world with both eyes open is perhaps not surprising; one eye provides the information where the other eye is lacking. Surprisingly, however, the blind spot is also imperceptible when viewing with one eye only. There is no “hole” in the visual field, and we’re only aware of the absence of sensation when a small object is placed into the blind spot and disappears. In primary visual cortex, the blind spots manifest as regions of monocular input in Layer IV roughly four ocular dominance columns wide (Tootell, Hadjikhani et al. 1998, Awater, Kerlin et al. 2005, Adams, Sincich et al. 2007), which begs two questions. First, how does the filling occur under monocular viewing conditions, when several ocular dominance columns cease to be active in one cortical hemisphere? Receptive fields tend to increase in size up the visual cortical hierarchy – later stages of processing effectively integrating over larger and larger swaths of V1 – so the “filling in” may not be an active process at all, but rather an epiphenomenon of increasing spatial integration. On the other hand, there is evidence that other types of filling in are indeed active processes (Anstis 2010), and so this is an open question. Second, how is a depth map formed in these regions of visual space? If the “filling in” of the blind spot simply reflects passive integration by larger receptive fields, the resulting map would likely consist of some form of local continuation through that region (disparity selective MT receptive fields, for example, have a diameter roughly equal to their eccentricity, so those centered on the blind spot would be integrating over a horizontal extent about 3x the width of the blind spot). If the filling in is an active process (Maus and Whitney 2016), however, the characteristics of the resulting depth map would depend upon where in the hierarchy it occurred. Interestingly, the absence of an object in one eye near the fovea can produce a reliable and ecologically valid stereoscopic percept in the case of occlusion (Kaye 1978, Wilcox, Harris et al. 2007).

It is appealing to think that the brain might implement an approach similar to that used for the blind spot when compensating for local pathological loss in the visual field. In these cases, however, there may or may not be loss at corresponding locations in the two eyes — the size of the area of loss (scotoma) may vary dramatically between eyes and patients — and there may be distortion of the retinal image rather than complete loss. Evidence suggests that the functional impact of the pathology is highly dependent on these clinical characteristics and that, in some cases at least, a patient with disease in both eyes may perform better when viewing with one eye alone (e.g. Tzaridis, Herrmann et al. 2019, Silvestri, Sasso et al. 2020, Tarita-Nistor, Mandelcorn et al. 2020). Fortunately, recent advances in consumer technology have provided exciting opportunities for assistive devices to help these patients function (e.g. Deemer, Swenor et al. 2019). Hopefully we will soon start to understand binocular computations in these situations and be able to provide more help to these patients based on an understanding of the construction of their visual percepts. At what point is a local loss too large or too deep to allow a productive filling in process to occur or to benefit the patient? The time is perhaps right, given the current resolution of fMRI and the spatial resolution available with microperimetry, to explore the relationships in visual cortex between the blind spot (Tootell, Hadjikhani et al. 1998, Awater, Kerlin et al. 2005), normal perceptual filling in (Weil and Rees 2011), and pathological scotomas (Plank, Frolo et al. 2017).

Misalignment of images—The most obvious form of disruption of binocular vision occurs in strabismus. In this case, the gross motor alignment of the eyes is inappropriate and any given point in the scene will therefore be imaged onto anatomically non-corresponding retinal locations in the two eyes. Hence, any given hypercolumn in primary visual cortex will receive input from one location in the scene from one eye, and another (laterally offset) location from the other eye (Figure 4). Note that hypercolumns generally do get input from *slightly* different local scene regions, providing binocular disparity, but this input is spatially correlated and forms the basis of stereopsis. When the misalignment of the eyes does not generate a compensatory vergence response, the inputs are consistently from completely different local scene regions and the results of any local disparity computations do not yield valid depth information about the scene. The question then becomes how a computation designed to combine information across the eyes deals with inputs whose combination can provide no meaningful interpretation. Interestingly, a typical observer will experience disparity comparable in magnitude to a strabismic deviation when voluntarily changing fixation from one distance to another, but a patient with strabismus is unable to generate the realignment vergence movement that the typical observer generates.

Patients with strabismus confront what has traditionally been framed as two basic perceptual challenges, diplopia (double vision) and what has been termed *confusion* (Figure 4) (Von Norden and Campos 2002, Chap 13). The first challenge, diplopia, arises because the same point in the scene is imaged on the two retinae at different eccentricities and is thus perceived as being in two different visual directions in space. The second challenge, confusion, is a logical consequence of the first. If a scene point sits at different visual directions from the two eyes, it follows that a matched *visual direction* for the two eyes must encode and represent *different scene points*. Confusion, then, refers to the simultaneous perception of two overlaid scene regions; two objects occupying the same place at the same time (Figure 4).

When typical adults are presented with different objects at the same retinal location (such as when looking into a monocular microscope with both eyes open), they will not generally experience confusion (overlaid percepts). Rather, they will experience *binocular rivalry*, in which perceptual awareness switches between one eye and the other on the timescale of seconds [5] (e.g. Alais and Blake 2005). In the laboratory, this is easily demonstrated by presenting a vertical grating, for example, to one eye and a horizontal grating to the other, while observers continuously report via button press which orientation they currently perceive. Binocular rivalry provides a useful tool to isolate perception from the sensory information arriving from the two eyes in visual cortex. It is not, however, a phenomenon that has much relevance to our typical goals in the natural world. Some aspects of this experience are especially interesting in the context of strabismus, however. For example, a body of work has demonstrated that typical rivalry does not consist of crisp switches in perception from one eye to the other. In fact, percepts can be a patchwork mix of regions from one eye with regions from the other eye (e.g. Alais and Melcher 2007) indicating local computation in the percepts. Other evidence even suggests that, when the two stimuli are switched rapidly between the eyes, an observer will experience a slower rivalry between percepts of the objects in the retinal images rather than between eyes (Logothetis, Leopold et al. 1996, Christiansen, D'Antona et al. 2017) and that this object-based rivalry can be either synchronous or asynchronous for different objects across the visual field (Slezak, Coia et al. 2019). Are these demonstrations of local resolution of perceptual ambiguity, and basis in objects, an attempt by the typical brain to infer the most likely local structure in the scene despite incompatible retinal images, and is this a behavior that can be leveraged by patients

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[5] Some readers may be able to experience this percept if they adjust the vergence position of their eyes to free fuse the two panels in Figure 3. Aligning the images at corresponding points in the two eyes can result in perceptual fusion of the matching peripheral information with an alternation over time between experience of the simulated scotoma and table.

with strabismus? The analysis below of the evidence from strabismic patients suggests that this might be the case in at least some situations.

Patients who develop strabismus during infancy or early childhood tend to develop permanent perceptual adaptations in response to the challenges of diplopia and confusion (adults with later age of onset are not able to do this – something about this plasticity is lost in mid-childhood). The adaptations have been studied and are commonly characterized, using clinical tests, as taking one of two forms, either *suppression* or *anomalous retinal correspondence* (ARC) (Von Norden and Campos 2002). A common logical description of suppression is that the patient is only consciously aware of input from one eye; they have suppressed the information from the other eye to avoid diplopia and confusion. ARC, on the other hand, is described as an apparent shift in the mapping of one eye's input into binocular representation in visual areas of cortex, so that matching points in the scene are associated with each other rather than the anatomically corresponding points on the retina. For example, the central fovea in one eye would be associated in binocular cortical computations with an eccentric point in the other misaligned eye, ideally with the eccentricity matching the amount of eye misalignment. While this phenomenon is termed anomalous *retinal* correspondence, the remapping is proposed to actually occur in cortical stages of computation where the information from the two eyes meets (Von Norden and Campos 2002, Chapter 13). *The clinical management of adults with these perceptual adaptations must be performed carefully*. If the patient has pure suppression and no ARC, the eyes could in theory be aligned perfectly for cosmetic purposes with no negative consequences, although it would not be advisable to risk losing the suppression if the eyes will not be perfectly aligned. If, however, the patient has developed ARC, then aligning the eyes could potentially disrupt their perceptual adaptation and result in confusion and diplopia at an age when their brain is less effective at adaptation (e.g. Bagolini 1985, Von Norden and Campos 2002).

While suppression of one eye's image and ARC are appealing in their logic, there are numerous observations revealing subtleties that make these descriptions incomplete as generalizations from clinical assessment to function in the natural world. Patients do exhibit stereotypical suppression-like or ARC-like behavior on clinical tests, providing metrics that can be associated with or predictive of clinical outcome after treatment, but observing how the patients are functioning in the natural world with both eyes viewing leaves many unanswered questions (Jennings 1985). It makes one wonder to what degree the format of the tests determines our description of the disorders rather than revealing their true nature. Some of these subtleties are described below:

Incomplete suppression: There are a number of ways in which suppression of the information from one eye has been found to be incomplete in patients with strabismus. Studies have frequently noted information only being suppressed at the fovea of the deviated eye and at the retinal eccentricity in that eye receiving the same image as the fovea of the fixating eye (reviewed by Von Norden and Campos 2002). This behavior, found in some forms of strabismus, appears to address the problems of foveal diplopia and confusion directly but leaves one asking what is happening in the rest of the visual field, where there is much weaker suppression if any. The notion is that these patients suppress the content of the central retinal image from their weaker/deviated eye and function binocularly in their peripheral visual field where typical vision is relatively coarse and we are not as sensitive to spatial position and misalignment (e.g. Sireteanu and Fronius 1989, Cooper, Feldman et al. 1992). Logic based in overlaid retinal image content from the two eyes in visual cortex would suggest that the patient should experience diplopia in the regions of the binocular visual field that are not suppressed. Given that much of a typical observer's visual world lies off the empirical horopter and that a typical observer is able to ignore or tolerate *physiological diplopia and confusion* in the peripheral visual field, does the strabismic patient with central suppression and no diplopia merely tolerate diplopia in the rest of their visual field in much the same way as a typical observer?

Patients with exotropia form a particularly interesting case in considering perceptual suppression. If their perception with both eyes viewing included information from both eyes in any fashion, their divergent deviation would act to expand their functional horizontal visual field (Figure 4). Interestingly, this phenomenon has been reported for these patients and termed 'panoramic' vision (e.g. Cooper and Feldman 1979, Economides, Adams et al. 2012). They do not appear to suppress one eye's image to function fully monocularly and a more recent assessment of their perception suggests that, when presented with a purple stimulus and glasses with one red lens and one blue lens, they report seeing the stimulus with their fixating eye (e.g. red percept) in much of the visual field but also their deviating eye (e.g. blue percept) in parts of the visual field (Economides, Adams et al. 2012). These data did not indicate a form of binocular percept (purple), but also did not indicate total suppression of the deviating eye. Studies of these exotropic patients have often described their suppression as occurring in the nasal visual field of the deviating eye (temporal retina), as this is where the visual fields of their two eyes overlap (Figure 4) (reviewed by Serrano-Pedraza, Clarke et al. 2011). This leads to an interesting challenge in interpreting visual direction. The furthest temporal region of each eye's visual field (nasal retina) encodes information that is not captured by the other eye and therefore information in the cortical representation of this *monocular crescent* must be assigned a direction in the world and integrated into perception without the benefit of binocular computation and registration. In these cases of divergent strabismus, this temporal visual field (nasal retina) would represent a region of the visual scene displaced temporally by the angle of deviation. If the monocular crescent was the only region of the visual scene perceived from the deviated eye, due to suppression in all typically binocular cortex, the nasal edge of the visual field of the fixating eye would be represented in cortex immediately next to a representation of the displaced monocular crescent from the deviated eye and a section of the visual scene would, therefore, not be represented (shown by the grey box in the bottom left panel of Figure 4). This specific prediction results from mapping in visual cortex as opposed to the visual field or retinal image.

Does the unified perception of these patients integrate this information effectively to provide a meaningful estimate of visual direction? Answering this question reveals fundamental characteristics about perceptual adaptation. Studies of the saccadic eye movements of strabismic patients have shown that they are capable of computing and making an eye movement to bring their previously deviated eye to the target and leave their previously fixating eye now deviated – in the clinic this capability is termed *alternating fixation* and these eye movements have been termed *fixation switch saccades* or *crossover saccades*. The ability to perform these eye movements implies that visual direction can be computed accurately for the deviated eye. It suggests a tight and subtle interaction between motor and perceptual computation (Economides, Adams et al. 2014, Das 2016) without which the patient could experience a jump in visual direction when shifting fixation and perception from one eye to the other.

Another complexity in the interpretation of testing with specialized clinical or lab stimuli is the consistent report of suppression not being complete for patients with strabismus. As has been observed during binocular rivalry in typical observers, there are now numerous demonstrations of influence from the suppressed deviated eye in the suppressed region of the visual field during binocular or dichoptic viewing (e.g. Baker, Meese et al. 2008, Ding, Klein et al. 2013, Chima, Formankiewicz et al. 2016).

There are many fundamental questions still to be addressed. These include: How are all of these factors combining to result in a meaningful percept of the world for these patients? Have comfortable patients learned to ignore diplopia and confusion in the way that those with typical vision are unaware of physiological diplopia and confusion? Does the development of suppression in the central parts of the visual field imply that it is not possible to ignore confusion and diplopia in these regions?

Inconsistent ARC: The ability to retain a consistent sense of visual direction while actively viewing with both eyes despite misalignment of the eyes is consistent with the concept of anomalous retinal correspondence described above. ARC is defined as a lateral shift in the correspondence between the eyes' inputs in cortical computations. The subtleties of ARC defined using clinical tests are difficult to interpret, however. In the ideal situation, the anomalous correspondence achieved in binocular viewing would provide perceptual alignment of the image on the fixating fovea with the point in the other eye where the image of the same target is formed – the perceptual shift compensates for the motor misalignment. This situation is termed *harmonious ARC* in the clinic. Some patients, however, are noted to have a shift in correspondence that does not compensate for the motor angle of their misalignment, a situation termed *unharmonious ARC*, or that even shifts in the opposite direction, termed *paradoxical ARC* (Jennings 1985). These definitions are based on the results of specific clinical tests but do not address how these patients are functioning in their habitual natural visual environment. Does their anomalous correspondence compensate for their angle of deviation in habitual viewing conditions and, if not, why do they not experience diplopia?

Other patients have been noted to have retinal correspondence that changes over time, frequently with their motor alignment (Kerr 1968, Kerr 1980, Daum 1982, Cooper and Record 1986). For example, some patients with intermittent exotropia have been noted to have ARC when their eyes are deviated but normal fovea to fovea retinal correspondence when their eyes are aligned, with good stereopsis. This behavior is termed 'co-variation' in the clinic, in that their perceptual state has been noted to co-vary with their motor alignment (Ramachandran, Cobb et al. 1994). While this behavior has a limited clinical description, even less is known about perception in the natural world and the underlying neural circuitry and computations – the implication, at least, is that perceptual adaptations can be modified dynamically in these patients.

Combinations of suppression and ARC: Intriguingly, patients have been shown to have unstable suppression depending on the content of the visual stimulus, and even some of the earliest clinical assessments of ARC include descriptions of how patients' perceptual adaptation can change depending on the task or test they are given (Bagolini 1976, Schor 1977, Deguchi, Yokoyama et al. 1993, Cooper, Feldman et al. 2000). For example, they can switch from anomalous retinal correspondence to suppression depending on the lighting or image size. These dynamic changes in perception, that do not elicit reports of symptoms from patients, do not appear consistent with perception of a literal overlaid combination of their two retinal images. There are also reports of a shift in correspondence, ARC, that is not consistent across the visual field (Sireteanu and Fronius 1989, Harwerth and Fredenburg 2003), and of simultaneous ARC and suppression (Serrano-Pedraza, Clarke et al. 2011).

All of these observations raise the question of exactly how clinical suppression and ARC are permitting patients to avoid confusion and diplopia when functioning in the suprathreshold natural world (Barrett, Panesar et al. 2012). How is perception providing an apparently stable and unified percept of the visual world when it is now routinely possible to demonstrate evidence of the influence of information from a deviated eye in binocular viewing during "suppression"? The literature suggests some dynamic switching between adaptations in different viewing conditions, yet strabismic adults are unable to develop this behavior despite the dynamic characteristics of typical vision described above. What are the relative roles of incoming afferent information (bottom-up) and feedback (top-down) influences in these neural computations? Is there a role for endogenous or exogenous attention (Zhou, Deng et al. 2016)? These questions are not new and have challenged clinicians and vision scientists for decades (Jennings 1985). There have been a number of attempts to deepen our understanding through theories of percepts being generated in head- or world-centric coordinates rather than retinal visual direction (e.g. Schor 2015), or based in an active perceptual inference or construction of the content of the visual scene (Michaels 1986, Purves, Wojtach et al. 2011, Vishwanath 2020). None of these specific theories developed to address inconsistencies in the current evidence have gained wide acceptance, yet the well-documented shortcomings of the bottom-up framework remain. We still have a lot to understand beyond the well-characterized representations in early stages of visual cortical processing. Recent evidence of dynamic adjustment of coordinate systems in neural representations (e.g. Sasaki, Anzai et al. 2020) might provide an exciting framework to help us understand these fascinating clinical phenomena. And these clinical phenomena, in turn, may reveal novel insights about coordinate system transformations through the visual hierarchy.

4. Future directions and applications

As just stated, a number of authors since Gibson and Marr have proposed theories about how the brain might be achieving typical (Michaels 1986, Purves, Wojtach et al. 2011, Vishwanath 2020) or atypical (Kerr 1998, Schor 2015) binocular vision in light of the complexities of function beyond the task described in Figure 1. The goal of the current review is not to support any one of these theories in particular or propose another, but to highlight the fact that converging evidence suggests important roles for extrastriate cortex in natural binocular vision, beyond the simple local binocular comparisons routinely modeled in V1. Recent work reviewed here has highlighted the importance of almost constant motion in the retinal image and the role of top-down recurrent influence on perception. With the new knowledge and tools available to undertake these studies, this is an exciting time to consider longstanding inconsistencies that have challenged current textbook understanding of binocular function.

Recent understanding of the structure of binocular information in the natural world and perceptual processes in typical vision have highlighted the importance of their role for the typical observer. These insights, combined with the advent of new technologies such as augmented and virtual reality (AR and VR), hold promise for more effective clinical care. Figure 1 was used to contrast the limited classical illustration of static binocular vision with the richness of spatial and temporal statistical structure in the environment and the sophistication of the biological system we use to interpret the information – the statistical structure being what allows the visual system to have “priors” (i.e. knowledge about things that are likely to occur). The extent to which we are able to rehabilitate the vision of patients beyond cosmetic realignment of their eyes will depend on our understanding of the brain’s use of information available from the natural world to guide perception, decision making and action. Is the key neural circuitry plastic at the time at which we attempt to treat it? Can it be modified by manipulations of experience we are capable of providing? If the circuitry is not plastic, can we provide meaningful assistive devices that leverage other information to help the patient? All of these questions are currently relevant in the sense that we are moving towards more binocular forms of technology and patients are appropriately asking what their visual systems are capable of. Specific future directions are discussed below.

4.1 Understanding typical binocular processing

4.1.1 Cortical processing

Macaques and Humans: Since the discovery of disparity sensitive neurons in the visual cortex of the cat (Barlow, Blakemore et al. 1967) and macaque (Hubel and Wiesel 1970) much progress has been made in understanding the processing of binocular information in the brain. A few key factors limit progress, however. While a key advantage of macaques is the similarity between their visual systems and behavioral repertoires and those of humans, this very similarity can be disadvantageous. For example, in both humans and macaques, the cortical surface is folded into many sulci and gyri. This not only makes doing single unit electrophysiology difficult, but it also renders some areas (e.g. MT) unavailable for both implanting electrode arrays and doing optical imaging. In macaques (and humans), fMRI provides a technique for looking at large swathes of brain despite the sulci and gyri, but it suffers from low spatial and temporal resolution. Further, the hemodynamic signal is nuanced and cortical gross and functional anatomy is variable (quite variable in humans in fact), so the location and number of functional brain areas determined by fMRI is controversial. Moreover, seemingly similar experiments can disagree on whether a given area encodes a given stimulus property (see above regarding area MT). Finally, given the seeming near-ubiquity of disparity selectivity in both the dorsal and ventral pathways, techniques are needed that can help uncover what disparity signals are doing in a given area, rather than discovering if they are present in a given area.

Mice: In neuroscience and medicine, mice are an effective model system for many reasons. First, they are lissencephalic (lacking sulci and gyri), meaning that virtually the entire cortical surface is easily accessible and the topography is more straightforward. Electrophysiology with arrays, optical imaging (both of intrinsic signals and with voltage sensitive dyes), two-photon imaging, and optogenetics can be used in virtually any cortical area or areas. Moreover, the thinness of the skull means that wide-field imaging can be done without penetrating the skull. Sadly, the mouse visual system differs greatly from the primate visual system in almost every measurable dimension, and some would argue that it is qualitatively different. While they do have binocular vision and stereopsis (Samonds, Choi et al. 2019) both in their forward and upper visual fields, they primarily use whisking to explore their peri-personal space (e.g. Sofroniew and Svoboda 2015).

Marmosets: Fortunately, there is an animal model that is a happy compromise between the macaque and the mouse that could serve as an important complement to the macaque for vision research: the common marmoset (Mitchell and Leopold 2015). Marmosets are primates and are similar to humans in many respects, or at least much more human-like than mice are. Like humans, they rely heavily on vision, are dexterous, very social, and use an extensive vocal repertoire to communicate with conspecifics making it likely that they share common natural visual goals with humans. Their cortical organization is very similar to humans but, structurally, their cortex is lissencephalic like mice, meaning that the entire cortex is available for imaging and recording techniques that are greatly hampered by the presence of sulci and gyri. Not only is it possible to do imaging and recording from marmosets in head-fixed situations, but electrophysiology can be done during free behavior using either tethered or wireless implants (Nummela, Jovanovic et al. 2017). Tokunu et al. (2015) provide an overview of the marmoset model for neuroscience.

4.1.2. Behavioral studies—

There are some maturing and emerging technologies that could be extremely valuable for vision science. These technologies allow participants to engage with more realistic stimuli and behave in a more complex and naturalistic manner.

Virtual Reality: The first and most mature of these technologies is virtual reality (VR). Unlike traditional displays, VR produces an immersive environment in which the user can move around a scene. Moreover, the use of regular VR gaming controllers allows the user to interact with a scene using their hands and arms. More advanced haptic glove controllers allow the natural use of the hand and fingers to interact with objects, complete with haptic feedback.

A huge potential advantage of VR systems is that they readily lend themselves to continuous response paradigms, such as tracking, catching, or striking (e.g. Diaz, Cooper et al. 2013, Backus 2018). They can also be used to study things like memory and attention in environments that are much more likely to reflect how these processes work in the real world. As VR systems are inherently binocular, it is possible to do a wide variety of experiments involving depth perception in general and binocular vision in particular. One disadvantage of VR systems is that the accommodative demand is fixed. The optics of the headset focus the eye at the screen at a hopefully comfortable, but fixed, accommodative demand. This means that the accommodation and vergence demands will only be consistent when the observer fixates at this distance in the virtual environment. For all other fixation distances, there will be a mismatch between the accommodative and vergence demands, possibly leading to discomfort (see below).

Light field and holographic displays: Promising new types of technology that could have enormous implications for both viewer comfort (see 4.5.2) and vision research (both basic and clinical) incorporate displays that reproduce the entire light field, not just an image. This can be done using either light field displays or holography. Despite the names, both techniques aim to simulate the entire light field – the direction and perceived color of light passing through each pixel (or "holgel") of the display – such that all properties of a real 3D scene, including the need for accommodation, are present. This means that the viewer must accommodate as well as verge their eyes when viewing objects in the scene, and there is thus no conflict between vergence and accommodation as there are in other 3D displays. In a holographic display, the display surface is a hologram: an interference pattern between a coherent reference beam and beam illuminating the scene to be viewed. For dynamic displays, the interference pattern would be computed rather than generated physically. The chief advantage of a hologram is that the view of the scene as a function of viewing angle is essentially continuous, but significant technical challenges stand between theory and useful displays. These include fast computation of the interference patterns, the technical aspects of the display elements, and the method of illumination to achieve full color displays. Light field displays are conceptually simpler than holographic displays. In a light field display, each "pixel" is actually a small lens over a small display of sub-pixels, each sub-pixel displaying the correct color and intensity of light needed for a particular viewing angle through the small lens. Each lens – each pixel on the display surface – can thus be thought of as emitting a family of rays through a solid angle, with each ray conveying the correct information for a given viewing angle of the 3D scene. Light fields are computationally intensive, but in the last decade "near-eye" light field displays have been developed by companies such as NVidia, raising the intriguing prospect of light field displays for VR. These displays are potentially extremely realistic and could represent a huge leap forward in rendering stimuli for vision research in general and binocular vision experiments in particular.

Adaptive optics: Adaptive optics systems, originally developed for astronomy, use a deformable mirror or mirror array to correct the optical wavefront for distortions introduced by optical media (such as the atmosphere or the cornea, lens, and aqueous and vitreous humors in the eye). Interestingly, the resolution of the photoreceptor array in the eye is roughly matched to the optics of the eye (because there is no evolutionary advantage to one being better than the other). Hence, the optics of the eye itself prevent imaging of the retinal photoreceptor array with conventional optics. With adaptive optics, however, not only is it possible to image the photoreceptor array, but it is also possible to place very small stimuli at precise retinal locations (Arathorn, Stevenson et al. 2013). This has obvious implications for exploring the nature of retinal correspondence in the binocular visual system and, in fact, a binocular version of an adaptive optics eye tracker has been developed recently (Stevenson, Sheehy et al. 2016).

Scene capture and eye tracking: As we have tried to emphasize in this review, the binocular visual system has evolved to function (near) optimally in the particular terrestrial environments of planet earth. All aspects of the visual stimulation resulting from natural environments – disparity and spatial structure for example – have particular statistical distributions. These distributions characterize the stimuli likely to be encountered by the visual system throughout both evolution and development. Thus, they are not just passive input, but rather sculpt the very nature of the anatomical and physiological mechanisms underlying binocular vision. In short, disparity selective receptive fields in V1, for example, are what they are because they are optimally suited to the statistics of natural scenes (e.g. Burge and Geisler 2014).

In order to determine the statistical distributions of the actual stimuli received by observers, we require knowledge about 1) the distributions of information in scenes encountered by observers and, because the human eye is foveated 2) a characterization of where people look in those scenes. Early attempts to characterize the distributions of the binocular disparities encountered by the visual system were crude, but they did reveal two important characteristics (Liu, Bovik et al. 2008). First, humans encounter a variety of retinal disparities at all viewing distances, so stereopsis does not operate only at near viewing distances as is commonly believed. Second, the distribution of disparities in the natural environment is well matched to the distribution of disparity sensitivity in human visual cortex (DeAngelis and Uka 2003, Liu, Bovik et al. 2008).

More recent studies have used eye trackers and scene cameras to more precisely and thoroughly characterize the environment and stimuli to vision (Sprague, Cooper et al. 2015). As head mounted eye trackers and scene cameras have become smaller and lighter, and SSD devices have allowed for massive amounts of data to be stored in relatively lightweight computers carried in a backpack worn by the user, it has become possible for users to go out in the world to perform a variety of tasks while the data are collected and stored. Once observers have done a task (gone for a hike, say) wearing the apparatus, the eye movement data can be registered to the scene data to yield the observer’s actual visual stimuli encountered during the task. Once this is done, the distributions of spatio-temporal stimulus properties can be computed for each eye and, in turn, the distributions of position and velocity disparities can be determined (Matthis, Muller et al. 2020). These data will provide valuable guidance in determining what the neural mechanisms should be for encoding the available binocular information.

It is also now possible to study free moving marmoset behavior and the corresponding visual stimulation more directly. Recently, a deep neural network-based system called DeepLabCut (Mathis et al. 2018), has been developed to do general markerless pose estimation in freely behaving laboratory animals. This system has now been shown to successfully track freely behaving marmosets (Huk, personal communication). Thus, it will soon be possible to do experiments in the lab in which an animal does a natural dynamic task requiring depth perception (such as hunting an insect), while the behavior, and the scene in its entirety (and therefore the actual binocular visual stimulation) are captured and, simultaneously, electrophysiological data are being recorded. This ability to have access to the input and output of an organism with neural responses during a natural task involving depth perception would be unprecedented in vision science. Moreover, as the recording implants are chronic rather than acute, data can be gathered over epochs of learning and the entire lifespan.

4.1.3 Models and Artificial Visual Systems—Basic vision research and all the fields concerned with building artificial visual systems (e.g. computer science, electrical engineering, and robotics) have had a mutually beneficial relationship for quite some time (as nicely illustrated by Marr’s book). Those building artificial visual systems naturally turned to biological visual systems for inspiration, and vision scientists naturally looked to successful artificial visual systems to see which algorithms worked, and how. One somewhat humorous example of this interaction is a paper by H. K. Nishihara (1984). At the time, the “binocular matching problem”, was thought to be a more difficult problem than it turned out to be, and random dot stereograms, as popularized by Julesz (1971) (though actually invented by a photogrammetrist named Clause Ashenbrenner in 1954, see Shipley 1971), were thought to represent the limiting case of maximum difficulty. Nishihara developed a real-time robotic binocular visual system to do stereoscopic depth perception based on a model of human stereopsis by Marr and Poggio (1979). However, to get the system to work in environments containing large homogenous surfaces such as walls, he mounted a projector between the cameras to project a dense random texture onto the environment in order to give his system actual information to work with – he turned his robot’s world into a random dot stereogram to make it *easier* to recover depth through stereopsis! This, in turn, made those of us studying biological binocular vision rethink how we approached the problem, and we began discarding “matching” based methods for correlation-based ones (e.g. Stevenson, Cormack et al. 1989, Cormack, Stevenson et al. 1991).

More recently, deep neural networks inspired by biological nervous systems have been shown to be able to solve a variety of classification and estimation problems. They have also been used to simulate early visual cortex, and the resulting receptive field structures can indeed resemble those found in early visual cortex, even non-linear (complex) cells in V1 (Ukita, Yoshida et al. 2019). Thus, just as the interplay between robotics, image processing algorithms, and biological vision yielded insights in the past, the same is holding true with deep networks for visual estimation and categorization. The impact of deep neural networks will almost certainly be much greater however; their intentional structural similarity to the nervous system means that electrophysiological-like experiments can be done *in silico*, and compared directly with experiments done *in vivo*. Further, if a network incorporating stereopsis (e.g. Nguyen, Kim et al. 2018) can be shown to behave in a primate like way, it could then be perturbed, by degrading or shifting the input to one “eye”, to potentially gain insights into disorders of binocular vision.

4.2 Individual differences

Scientific studies spanning the spectrum from neuroscience to social psychology have tended to analyze group behavior (means, standard error of the mean, etc) while ignoring individual behavior (except perhaps to remove outliers!). Studies of binocular vision are no different and have tended to look at trends in performance in the population. Happily, however, there is now a considerable literature looking at individual differences in performance. These differences are particularly interesting in the context of binocular vision because an extensive literature has demonstrated the redundant nature of cues to distance available for both motor and perceptual function (e.g. Landy, Maloney et al. 1995, Jacobs 1999, Knill 2005, Seydell, Knill et al. 2010, Ban, Preston et al. 2012, Tidbury, Brooks et al. 2016). If numerous cues can all contribute to the final percept and motor response, how different individuals weight and learn to use the different cues, and how the weighting relates to their daily function become meaningful questions. A number of studies have started to ask these questions (Jacobs and Fine 1999, Haijiang, Saunders et al. 2006, Jain and Backus 2010, Horwood and Riddell 2013, Allen, Haun et al. 2015, Fulvio and Rokers 2017).

In thinking about the development of the visual system and these redundant cues, one can ask whether the weighting of cues that an individual establishes is related to their clinical outcome (Barendregt, Dumoulin et al. 2014, Horwood and Riddell 2014, Maloney, Kaestner et al. 2018). Plus, the extent to which this weighting can adapt to growth, challenges or attempts at preventative treatment. We still need to understand the factors that permit successful adaptation during growth and yet are incapable of overcoming clinical abnormality. This abnormality can be anything from excessive fixation disparity or heterophoria (e.g. convergence insufficiency) to mild traumatic brain injury and concussion, to strabismus. After all, in the clinic, particularly for binocular vision, it can be vitally important to treat the individual patient and not the population average.

4.3 Can strabismus and amblyopia be prevented?

The typically developing human visual system starts to establish its binocular motor and sensory/perceptual functions during the first weeks after birth (Aslin and Dumais 1980, Candy 2019). Binocular function undergoes continued maturation for years after birth (Giaschi, Narasimhan et al. 2013, Freud and Behrmann 2017, Norcia, Gerhard et al. 2017) but the basics are present early, with at least some infants being capable of generating vergence responses to absolute retinal disparity by 5 weeks of age (Seemiller, Cumming et al. 2018) and sensory responses to binocular correlation and relative disparity at approximately 8 weeks (Norcia and Gerhard 2015). A manifest deviation in binocular viewing conditions, strabismus, is rarely present at birth. The more common forms of strabismus – such as infantile esotropia, intermittent exotropia or refractive esotropia – develop months or even years after birth. Unfortunately, the combined strabismus prevalence of only approximately 3% (MPEDS 2008, Friedman, Repka et al. 2009) makes longitudinal studies of large numbers of infants who go on to develop a deviation somewhat impractical (e.g. Babinsky and Candy 2013, Somer, Karabulut et al. 2018, Jones-Jordan, Wang et al. 2020). Particularly given that strabismic misalignment of the eyes can have numerous causes, meaning that there are likely to be quite different sets of predictive factors depending on the underlying cause in question, and that prevention and treatment will both be heavily dependent on the cause of the deviation.

Even so, the fact that we are currently rarely able to fully cure strabismus and the fact that we define the associated amblyopia as a result of disrupted visual experience motivate earlier intervention for these patients to potentially prevent their vision loss. With that goal in mind, it will be important to understand for the different forms of strabismus whether the deviation is a result of a binocular system that never developed or one that started to develop normally and then derailed (Birch and Stager 1985). Would the goal of an early intervention be to prevent the actual deviation or to optimize a child’s visual development by managing a form of strabismus that cannot be prevented – e.g. by preventing amblyopia during the period of maximal neuroplasticity (Banks, Aslin et al. 1975)? In thinking about the development of amblyopia it will also be important to understand how young children with strabismus develop a motor eye dominance. Establishing alternating fixation, the ability to fixate freely with either eye, once a strabismus has developed has been shown to maintain the visual function of both eyes with minimal evidence of acuity loss, although it does not support fully binocular vision in the sense of image integration and stereopsis.

Beyond the motor characteristics of strabismus, there is still much to learn about the perceptual components and how they can be managed optimally. In some cases, adaptations such as suppression permit the patient to interact with the world without experiencing disruptive diplopia. In intermittent forms of strabismus, a patient may be capable of typical binocular visual function with normal retinal correspondence for some of the time with a deviation and abnormal retinal correspondence at other times. What are the perceptual consequences of this apparently bi-stable motor state in the dynamic natural world discussed above? Can we titrate preventative motor interventions to permit these perceptual adaptations to compensate for any remaining deviation if the prevention is not fully successful? This is a complex question that will not be easy to address. We have at least started to understand that the typical motor binocular system is quite robust within weeks after birth (Sreenivasan, Babinsky et al. 2016, Seemiller, Cumming et al. 2018, Candy 2019) and therefore that it may be possible to discriminate atypical development early in infancy. This goal raises the intriguing question of whether an atypical visual environment during early infancy (e.g. a blank wall) is capable of disrupting the natural statistical experience required for typical motor and perceptual development of vision.

4.4 The relationship between anisometropia and disrupted binocular development.

It is well-established from studies of clinical patients that anisometropia and strabismus are commonly associated in early childhood, and that anisometropia alone can be associated with amblyopia and reduced stereopsis (Barrett, Bradley et al. 2013). We still have much to learn about the role of anisometropia in the disruption of typical binocular development. A difference in retinal image quality between the eyes is known to disrupt the binocular vision of adults (e.g. Cormack, Stevenson et al. 1997), but its impact at different stages of infancy still needs to be understood; specifically, the sensitivity of different levels of neural computation to its impact as a function of age. Interestingly, current evidence suggests that anisometropia itself is unstable during early infancy (e.g. Almeder, Peck et al. 1990) and, therefore, being able to predict which infants will not lose their difference in refractive error will be key in predicting the patients who will present with anisometropia, strabismus and amblyopia later in childhood (Barrett, Bradley et al. 2013).

Uncorrected anisometropia during childhood forms naturally occurring monovision during an important period of experience-dependent synaptic plasticity in the brain. The challenge of integrating the different information from the two eyes in this case leads to an abnormal bias towards responses to information from the eye that is presumed to be habitually more focused, and a permanent loss of sensitivity to information from the other eye – amblyopia -- plus poor performance on tests of stereopsis and binocular function. It can occur for patients with as little as one diopter of difference between the refractive error of their two eyes (reviewed by Barrett, Bradley et al. 2013). Current models and recent approaches to the management of amblyopia (Levi 2020) have emphasized the role of binocular visual experience and frame amblyopia as resulting from a combination of attenuated responses to information from the amblyopic eye with abnormal balance of interocular inhibition between the eyes in cortical computation (Sireteanu and Fronius 1981, Sengpiel and Blakemore 1996, Barrett, Bradley et al. 2013, Birch 2013, Ding, Klein et al. 2013, Ooi, Su et al. 2013, Jia, Zhou et al. 2015, Shooner, Hallum et al. 2017, Zhou, Reynaud et al. 2018). Interestingly, the advent of binocular approaches to amblyopia therapy highlights the importance of any impact of atypical motor performance, and raises questions such as how to present the images used in therapy at “corresponding” retinal points in the two eyes while the eyes might be intermittently misaligned or exhibiting unstable fixation.

Beyond the clinic, amblyopia has been noted in research labs to be associated with a broad range of visual deficits in both motor and perceptual performance (Maurer and McKee 2018). One intriguing question is whether we will ever be able to manipulate visual experience during treatment to reverse the developmental impact of abnormal experience and, therefore, whether we will be able to fully treat the complete spectrum of amblyopic vision loss, especially given the loss of neuroplasticity with age. Section 3.1 above emphasized the complexity of visual information in the natural environment, and the range of computations that a typical brain is performing in binocular function. Even if a pervasive alteration of visual experience proved able to reverse the abnormal development in animal models, it seems unlikely that such a treatment would be practical for human children. This further motivates attempts to prevent rather than treat amblyogenic disruptions of visual development in infancy and early childhood. Anisometropic amblyopia is a particularly logical candidate for prevention in that the optical disruption is relatively easy to correct and all neural sequelae are disruptive (amblyopia, loss of stereopsis etc). An important question in this effort is to ask which natural image statistics need to be present in the retinal images, and at what age, to permit typical development (e.g. Vogelsang, Gilad-Gutnick et al. 2018, Eckmann et al. 2020, Klimmasch et al. 2021). In addressing these questions, it will be imperative to consider the impact of any prior treatment on the visual system of patients being studied.

4.5 New technology

Screen distances—One notable recent change in human behavior is the use of electronic devices at different near viewing distances. Rather than only specialized occupations (e.g. watchmakers or microscopists) requiring working distances other than typical book reading, many people now routinely use cellphones, tablets, laptops, and desktop computers. Each of these devices is designed for use at a different range of viewing distances for typical activities in work, school, home and anywhere leisure activities occur. This progression has led to engaging with screens, particularly with phones, while performing other activities and therefore changing viewing distance much more frequently than in the past. This requires a wider range of function from the coupled accommodation and vergence motor systems in youth and during aging. Adaptations to manage the aging of the accommodation mechanism and presbyopia require optical corrections to all of these viewing distances, potentially consisting of a multifocal solution (e.g progressive spectacle lenses, multifocal contact lenses or monovision) or multiple pairs of reading glasses of different powers. The visual system must function in all of these situations to provide meaningful information to the patient, and these days in particular, it must provide the motor coordination to interpret detailed information on a small two-dimensional screen. The role of this coordination and the impact of accommodation on retinal image quality in the development of myopia have been a concern for a number of decades.

Augmented and virtual reality—Beyond needing to interpret 2D images at a range of viewing distances, recent advances in technology supporting augmented and virtual reality have raised the prospect of their use in education, therapy, entertainment, and assistive devices for those with visual impairment, for example. These technologies, more than other screens, can capitalize on the separate presentation of information to the two eyes to create a three-dimensional depth map of the visual scene. Consideration of the neural coupling between accommodation and vergence is important in the design of these devices as the use of a single screen plane with the potential to present disparities representing a wide range of viewing distances puts these two motor responses in potential conflict with each other. The challenge of presenting realistic dynamic three-dimensional content at appropriate accommodation and vergence demands has been significant, a problem that has limited the use of 3D cinema and TV to date (Shibata, Kim et al. 2011, Paulus, Straube et al. 2017, Tychsen and Foeller 2020). Recent advances in technology, some of which were described above, hold promise for achieving this goal and present exciting new opportunities for dynamic three-dimensional stimulus presentation at a wide range of viewing distances.

Binocular function in rehabilitation of visual impairment—The classically discussed clinical disruption of binocular function is misaligned eyes, but there are more subtle clinical challenges to binocular vision and depth perception. For example, as discussed above, pathology causing distortion or scotomas will result in a patient needing to find the correspondence between two imperfect retinal images, with the potential for PRLs and eccentric viewing. Numerous recent innovations in image enhancement technology are now being adopted in devices to assist those with visual impairment (e.g. Hwang and Peli 2014, Kinateder, Gualtieri et al. 2018, Angelopoulos, Ameri et al. 2019) and it is exciting to consider the potential for binocular devices to increase independence for these patients, particularly for the young who rely on these devices to learn about and interact with the world.

5. Overall summary

The classical static model of human binocular function (Figure 1A) is now well understood to represent a very limited binocular task. Full binocular vision encompasses a significantly wider range of dynamic inputs, challenges, computations, and goals. These have been studied for decades and are discussed to some degree in books and reviews. Recent studies, in particular, are providing deeper insight into the tasks and computations involved in binocular function in our habitual natural world, with understanding of the statistical structure of that experience. These new insights are teaching us about the ways our visual systems are adapted, and adapting, to the tasks they undertake with core relevance to the development of novel technology from wristwatches to autonomous vehicles and in the clinical prevention and management of conditions such as amblyopia, strabismus, asthenopia, anisometropia, presbyopia and various forms of visual impairment.

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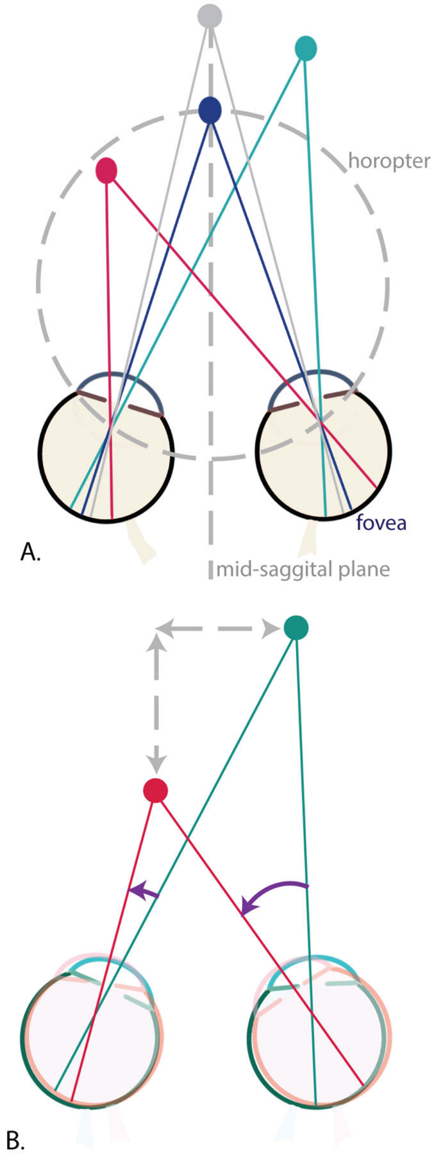

Figure 1: A classical illustration of interocular retinal disparity.

Panel A presents a series of colored objects. The eyes are fixating the dark blue one on the mid-saggital plane and the theoretical horopter for that fixation distance is illustrated by the dashed grey circle. The images of this object sit on the fovea in each eye, with the images of the other objects falling at eccentric locations. The grey object provides a simple example of uncrossed disparity from the horopter. If the eyes were to now align at that object, its absolute uncrossed disparity would reduce to zero, while its relative disparity to the blue object would remain constant irrespective of the fixation and alignment distance of the eyes. The green and red objects illustrate the more typical natural situation of objects located away from the mid-saggital plane, in uncrossed or crossed disparity, respectively, from the horopter. *Panel B* illustrates that changing fixation from the green object to the red object involves an eye movement with both a lateral and depth component, and that the required angular rotations of the eyes are not equal and symmetric (purple arrows).

Figure 2: An illustration of the presence of both horizontal and vertical retinal disparities when an object is located off the mid-saggital plane between the eyes (e.g. at the location of the red object in Figure 1). The left eye's image is colored in the combination image for clarity, and it is assumed that the eyes are fixating the middle knuckle of the robot's forefinger.

Figure 3: An illustration of the impact of vision loss in the central visual field

(e.g. resulting from age-related macular degeneration, AMD). If the patient is attempting to view the shirt on the table, as seen in the left panel, their vision loss results in a scotoma at that point of fixation as shown in the right panel. Interestingly, under- or over-converging your eyes to align and fuse the images in these two panels provides a demonstration of the challenges of combining non-corresponding information with unilateral retinal pathology.

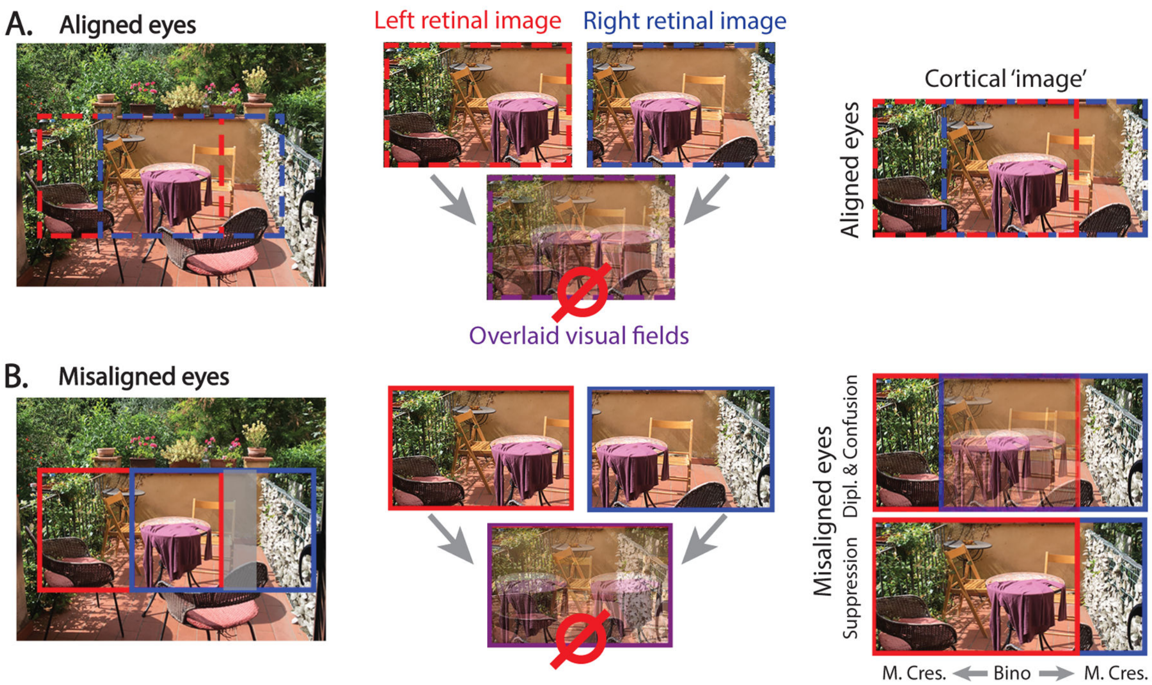

Figure 4: An illustration of the binocular integration of images from eyes that are aligned (row A) or misaligned (row B). The images in the left column illustrate the scene with simulated visual fields for the left (red) and right (blue) eyes. The aligned case illustrates the typical central binocular overlapping field with monocular regions in the temporal extremes. The misaligned simulated exotropia in row B illustrates the reduced binocular overlap and extended monocular regions present with the divergent deviation of the right eye. The middle column provides the relevant visual fields for each eye and a reminder that binocular integration is not merely a question of overlaying these fields/retinal images. The right column follows the basic principle of mapping in primary visual cortex, where the binocular visual field is represented with aligned information and appropriate transition into the monocular crescents for aligned eyes and conflicting information in the misaligned case. The cortical representation for the patient with exotropia might imply diplopia and confusion in the nominally binocular cortex, as shown in the top example in row B, or, if the image from the right eye is suppressed in binocular cortex, shown below, any percept from the right eye's monocular crescent would result in an apparent missing section of the visual scene (as illustrated by the grey region in the left column scene). These potential cortical 'images' illustrate some of the challenges faced by the brains of these strabismic patients in compiling a stable unified percept of the world.

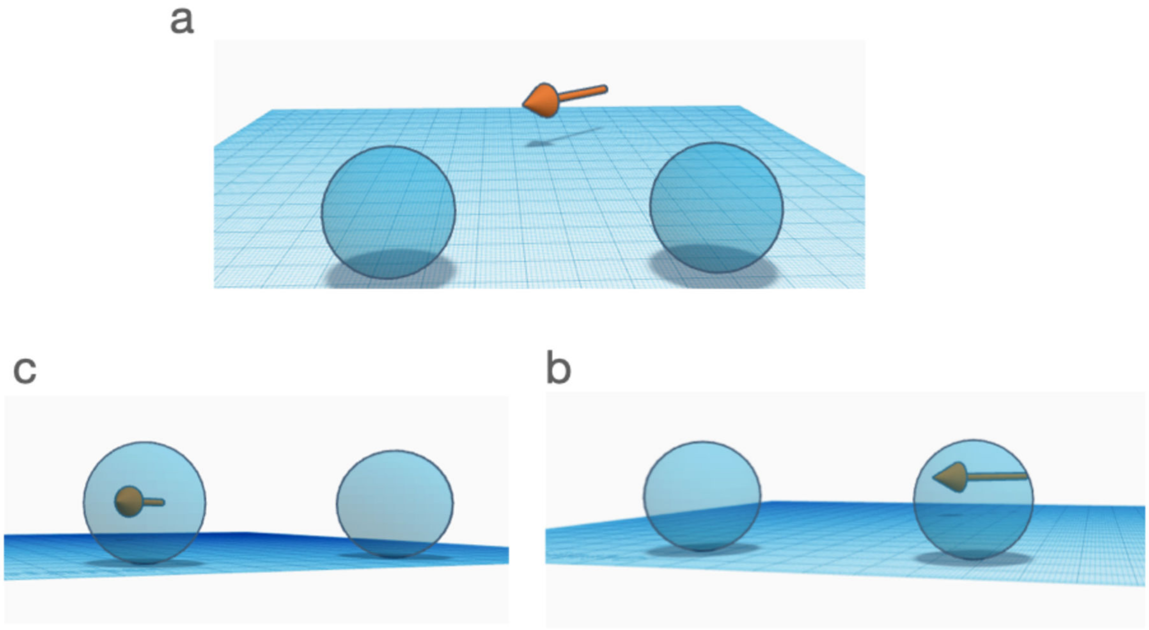

Figure 5: An illustration of the concept of interocular velocity difference.

Panel a represents the two eyes and an object moving along the red arrow in front of them. Panels b & c demonstrate the different retinal information generated by this trajectory in the two eyes, by viewing from behind the right (panel b) and left (panel c) eyes.

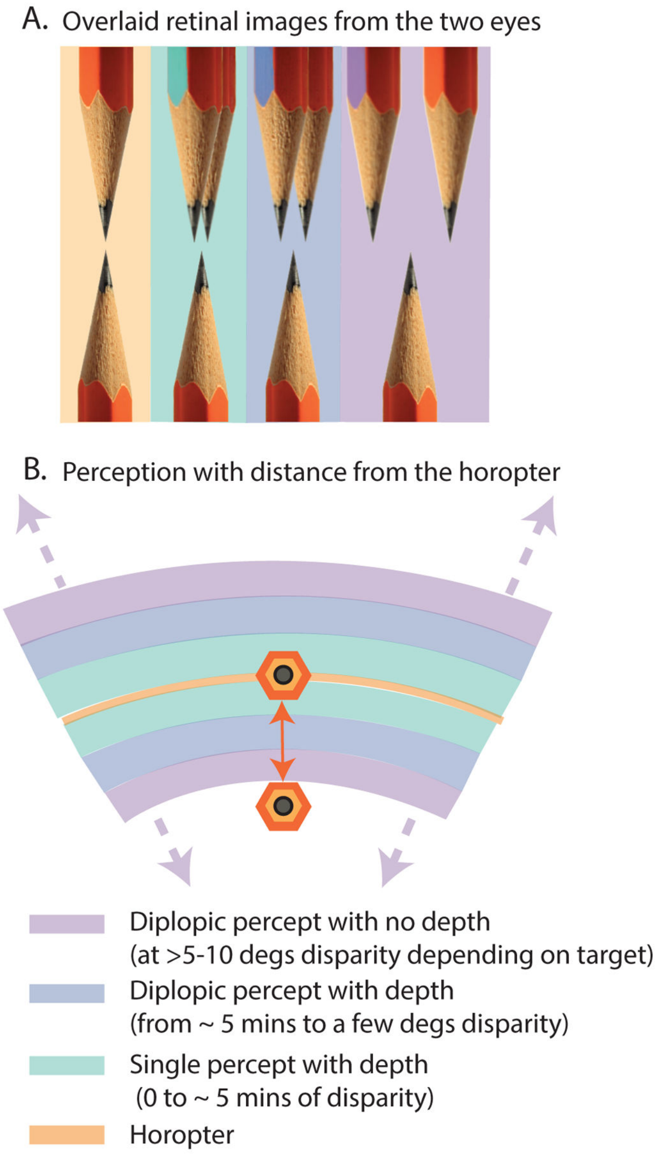

Figure 6: An illustration of the different percepts with distance from the horopter.
The top pencil is moved forward or backward from vertical alignment with the bottom pencil, while binocular fixation remains on the point of the bottom pencil. *Panel A*: An illustration of the overlaid retinal images in each region. *Panel B*: The orange region represents the horopter; the green region is classical stereopsis, where the top pencil generates retinal disparity but the percept is fused and single with a depth difference from the bottom pencil; in the blue region the percept is double but still includes a depth difference from the bottom pencil; in the purple region the percept is double with no sense of depth. The approximate angular extents of these regions are provided, but their exact values will depend on the characteristics of the stimuli.

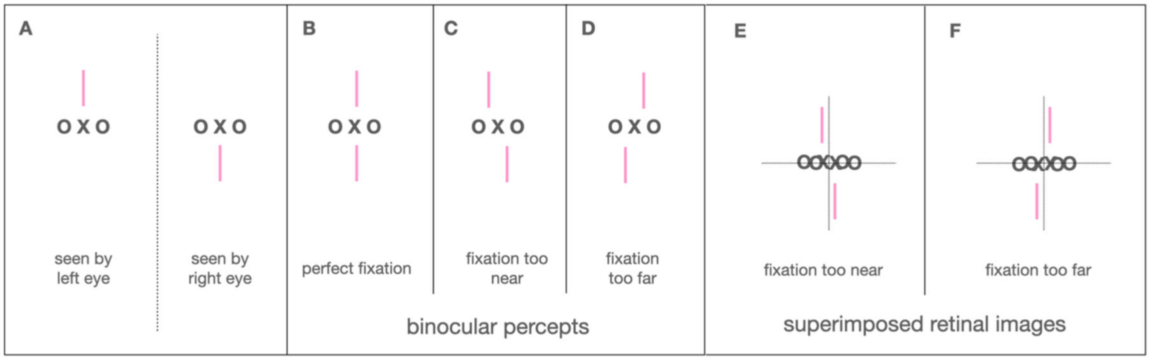

Figure 7: An illustration of a typical clinical fixation disparity test.

The images presented to the left and right eyes are shown in *panel A*. When the eyes are aligned accurately, the combined percept would be as seen in *panel B*. More commonly observers note a perceived offset of the monocularly presented lines, as shown in *panels C & D*, even though the overlaid retinal images for the corresponding small misalignments of the eyes would be as shown in panels E & F.