Orienting of covert attention by neutral and emotional gaze cues appears to be unaffected by mild to moderate amblyopia

Amy Chow

Department of Optometry and Vision Science, University of Waterloo, Waterloo, Canada ✉

Yiwei Quan

Department of Psychology, University of Waterloo, Waterloo, Canada ✉

Celine Chui

Department of Psychology, University of Waterloo, Waterloo, Canada ✉

Roxane J. Itier

Department of Psychology, University of Waterloo, Waterloo, Canada ✉

Benjamin Thompson

Department of Optometry and Vision Science, University of Waterloo, Waterloo, Canada
Centre for Eye and Vision Research, 17W Science Park, Hong Kong
Liggins Institute, University of Auckland, Auckland, New Zealand ✉

Amblyopia is a developmental disorder of vision associated with higher-order visual attention deficits. We explored whether amblyopia affects the orienting of covert spatial attention by measuring the magnitude of the gaze cueing effect from emotional faces. Gaze and emotion cues are key components of social attention. Participants with normal vision (n = 30), anisometropic (n = 7) or strabismic/mixed (n = 5) amblyopia performed a cued peripheral target detection task under monocular and binocular viewing conditions. The cue consisted of a centrally presented face with left or right gaze (50% validity to target location) and a fearful, happy, or neutral expression. The magnitude of spatial cueing was computed as the reaction time difference between congruent and incongruent trials for each expression. Fearful facial expressions oriented spatial attention significantly more than happy or neutral expressions. The magnitude of the gaze cueing effect in our cohort of mild-to-moderate amblyopia was comparable to that in normal vision and was not correlated with the severity of amblyopia. There were no statistical group or amblyopia subtype differences for reaction time in any viewing condition. These results place constraints on the range of attentional mechanisms affected by amblyopia and possibly suggest normal covert processing of emotional face stimuli in mild and moderate amblyopia.

Introduction

Amblyopia is a neurodevelopmental disorder of vision caused by an impediment to binocular vision such as anisometropia, strabismus, or visual deprivation that is present during early childhood development. Clinically, amblyopia presents as a unilateral loss of visual acuity and impaired stereopsis associated with chronic interocular suppression of the amblyopic eye (Birch, 2013; Hamm, Black, Dai, & Thompson, 2014; Kiorpes, 2006; Meier & Giaschi, 2017; Wallace, Repka, Lee, Melia, Christiansen, Morse, Sprunger, & American Academy of Pediatric Ophthalmology/Strabismus Preferred Practice Pattern Pediatric Ophthalmology Panel, 2018). More generally, amblyopia affects a broad range of sensory functions in both the amblyopic (Asper, Crewther, & Crewther, 2000a; Asper, Crewther, & Crewther, 2000b; Baker, Meese, & Hess, 2008; Hess, Thompson, & Baker, 2014; Hess & Howell, 1977; Levi, 2020; Levi & Harwerth, 1977; Mullen, Sankeralli, & Hess, 1996; Pardhan & Gilchrist, 1992) and non-amblyopic fellow eye (Birch, Jost, Wang, Kelly, & Giaschi, 2019; Meier & Giaschi, 2017). These sensory deficits impact visuomotor behaviors such as saccadic eye movements (Ciuffreda, Kenyon, & Stark, 1978a;

Ciuffreda, Kenyon, & Stark, 1978b; Gambacorta, Ding, McKee, & Levi, 2018; Mackensen, 1958; Niechwiej-Szwedo, Goltz, Chandrakumar, Hirji, & Wong, 2010; Niechwiej-Szwedo, Chandrakumar, Goltz, & Wong, 2012; Perdziak, Witkowska, Gryncewicz, Przekoracka-Krawczyk, & Ober, 2014; Perdziak, Witkowska, Gryncewicz, & Ober, 2016; Perdziak, Gryncewicz, Witkowska, Sawosz, & Ober, 2019; von Noorden, 1961) and hand-eye coordination (Grant, Melmoth, Morgan, & Finlay, 2007; Grant & Conway, 2015; Grant & Moseley, 2011; Melmoth, Finlay, Morgan, & Grant, 2009; Niechwiej-Szwedo, Goltz, Colpa, Chandrakumar, & Wong, 2017; Niechwiej-Szwedo, Colpa, & Wong, 2019). In particular, saccadic and manual response times are significantly delayed for stimuli viewed through the amblyopic eye (Gambacorta et al., 2018; Hamasaki & Flynn, 1981; Levi, Harwerth, & Manny, 1979). Even after visibility is accounted for, an irreducible response latency delay remains in strabismic amblyopia (Gambacorta et al., 2018; Levi et al., 1979; Pianta & Kalloniatis, 1998).

Amblyopia is associated with reduced fixation stability and it has been proposed that frequent fixational eye movements cause unintended shifts of spatial attention that may contribute to attention deficits in amblyopia (McKee, Levi, Schor, & Movshon, 2016; Verghese, McKee, & Levi, 2019). In amblyopia, fixation stability is poorer for the amblyopic eye because of increased microsaccades and ocular drifts (Chung, Kumar, Li, & Levi, 2015; Ciuffreda, Kenyon, & Stark, 1979; González, Wong, Niechwiej-Szwedo, Tarita-Nistor, & Steinbach, 2012; Kelly, Cheng-Patel, Jost, Wang, & Birch, 2019; Raveendran, Babu, Hess, & Bobier, 2014; Raveendran, Bobier, & Thompson, 2019a; Raveendran, Bobier, & Thompson, 2019b; Shaikh, Otero-Millan, Kumar, & Ghasia, 2016; Subramanian, Jost, & Birch, 2013). Fixation is less stable in strabismic amblyopia than anisometropic amblyopia (Chung et al., 2015; Schor & Hallmark, 1978), with more frequent microsaccades and overall displacement from the locus of fixation (Chung et al., 2015). The presence of microsaccades creates a motor refractory period ranging from 150 to 200 ms that can delay the initiation of subsequent saccades (Chung et al., 2015; Otero-Millan, Troncoso, X. G., Macknik, S. L., Serrano-Pedraza, I., & Martinez-Conde, 2008; Schor & Hallmark, 1978) and delay target detection (McKee et al., 2016; Verghese et al., 2019). Eye movements and visual attention are intricately linked, because attention is often allocated to the locus of visual fixation and overtly shifted in conjunction with eye movements (Goldberg & Wurtz, 1972; Rizzolatti, Riggio, L., Dascola, I., & Umiltá, 1987). Spatial attention can also be deployed covertly, whereby the locus of attention is shifted without a change in fixation (Beauchamp, Petit, Ellmore, Ingeholm, & Haxby, 2001; Corbetta, Akbudak, Conturo, Snyder,

Ollinger, Drury, Linenweber, Petersen, Raichle, Van Essen, & Shulman, 1998; Moore & Fallah, 2001; Nobre, Gitelman, Dias, & Mesulam, 2000). Nevertheless, even on a covert attention task, observers inadvertently make small microsaccades in the direction of the cued location (Engbert & Kliegl, 2003; Hafed & Clark, 2002; although see Horowitz, Fine, Fencsik, Yurgenson, & Wolfe, 2007; Meyberg, Sinn, Engbert, & Sommer, 2017 and McCrackin, Soomal, Patel, & Itier, 2019 with gaze cueing). Target discrimination appears to be better when microsaccades are directed toward the target location (Yuval-Greenberg, Merriam, & Heeger, 2014). As a result, microsaccades may interfere with the orienting of covert attention in amblyopia.

There remains considerable debate regarding to what extent attentional processing is impaired in amblyopia. Several studies in both humans (Ramesh, Steele, & Kiorpes, 2020; Roberts, Cymerman, Smith, Kiorpes, & Carrasco, 2016) and macaques (Pham, Carrasco, & Kiorpes, 2018) found normal spatial cuing of attention in amblyopia, even demonstrating that valid cueing (congruency between cue and target) alleviated the amblyopic eye contrast sensitivity deficit (Pham et al., 2018). In addition, participants with amblyopia performed normally on a simple visual search task involving a distinctive target feature that readily captured attention (Tsirlin, Colpa, Goltz, & Wong, 2018). Conversely, in a conjunctive visual search task requiring a serial search strategy, participants with amblyopia processed items at a slower rate (with either eye) than controls, suggesting a bottleneck of attentional processing (Tsirlin et al., 2018). Several other psychophysical studies have reported attentional deficits affecting both eyes in amblyopia. For example, when performing a line bisection task with either eye, individuals with amblyopia demonstrated a rightward bias similar to patients with a lesion to the right posterior parietal cortex, an area involved in the orienting of spatial attention (Thiel & Sireteanu, 2009). This effect was more pronounced in participants with strabismic amblyopia than anisometropic amblyopia. In addition, attentional tracking of multiple moving objects performed monocularly revealed an amblyopic eye deficit that extended to the fellow eye under high attentional loads (Ho, Paul, Asirvatham, Cavanagh, Cline, & Giaschi, 2006; Secen, Culham, Ho, & Giaschi, 2011). This tracking deficit could not be attributed to impaired motion perception alone and therefore reflected a visual attention deficit (Ho et al., 2006; Secen et al., 2011). A subsequent study used a dichoptic multiple-object tracking task to assess whether attention was allocated unevenly between the two eyes when both eyes were open. A bias in the allocation of attention toward the fellow eye was observed in strabismic but not anisometropic amblyopia (Chow, Giaschi, & Thompson, 2018). A similar effect has recently been reported for a dichoptic enumeration

task whereby amblyopic eyes contributed less to task performance than fellow eyes, and strabismic amblyopia was associated with a larger interocular imbalance than anisometropic amblyopia (Wong-Kee-You Wei, & Hou, 2020). The recruitment of additional attentional resources under high attentional load also appears to be impaired in amblyopia (Farzin & Norcia, 2011). Overall, psychophysical studies indicate that although spatial cueing appears to be intact, higher-order attentional processes may be impaired in amblyopia.

Many of the attentional deficits documented in amblyopia persist despite prior treatment. Although treatment is generally successful in recovering visual acuity in the amblyopic eye, visual processing in amblyopia remains abnormal (Arden, Barnard, & Mushin, 1974; Birch et al., 2019; Hamm et al., 2014; Meier & Giaschi, 2017; Tao, Wu, Gong, Chen, Mao, Chen, Zhou, & Huang, 2019). In particular, individuals with previous treatment of amblyopia still display attentional deficits that affect both the amblyopic and fellow eyes (Chow et al., 2018; Ho et al., 2006; Hou, Kim, Lai, & Verghese, 2016; Secen et al., 2011; Thiel & Sireteanu, 2009; Wang, Crewther, Liang, Laycock, Yu, Alexander, Crewther, Wang, & Yin, 2017; Wong-Kee-You et al., 2020). An electrophysiological study found that despite past treatment, the modulatory effect of a simple central spatial cue is reduced in primary visual area V1, as well as in higher-order visual areas V4 and MT+ for both the amblyopic and fellow eye in strabismic amblyopia (Hou et al., 2016). Similarly, a generalized reduction of activation across the brain areas comprising the attentional network has been observed in strabismic amblyopia even after surgical treatment to alleviate the amblyogenic factor (Wang et al., 2017). On the other hand, some psychophysical studies in mild and treated populations found no attentional deficit (Ramesh et al., 2020; Roberts et al., 2016). Additionally, a correlation between the depth of attentional deficit and the severity of amblyopia (defined as interocular VA difference) is seldom observed (Chow et al., 2018; Farzin & Norcia, 2011; Ramesh et al., 2020; Roberts et al., 2016; Wong-Kee-You et al., 2020; although see Hou et al., 2016; Popple & Levi, 2008; Tsirlin et al., 2018). This discrepancy merits further investigation.

In this study, we explored cueing of covert spatial attention with cues that involve higher-order processing. We were interested in the possibility that amblyopic eye attentional deficits would emerge within a cueing task if complex visual processing was required to process the cue. Attention can be engaged by social cognition (Hayward & Ristic, 2015; Itier & Batty, 2009; Nummenmaa & Calder, 2009), so we used a dynamic gaze cueing task (Driver, Davis, Ricciardelli, Kidd, Maxwell, & Baron-Cohen, 1999; Friesen & Kingstone, 1998; Frischen, Bayliss, & Tipper, 2007) that oriented

visual attention using gaze directions embedded within emotional faces (McCrackin & Itier, 2018; McCrackin & Itier, 2019). Compared to spatial cueing using arrow cues, the gaze direction of a face is more ecologically valid and reflects social interactions in real-world situations. Following another's gaze is critical for joint attention and inferring the mental states of others (Baron-Cohen, 1995; Stephenson, Edwards, & Bayliss, 2021). This form of social attention, which relies on intact face processing (Burra, Kerzel, & Ramon, 2017), integrates local processing of gaze cues with global processing of a face and its emotional expression and involves a distributed network of thalamic and cortical brain regions (Itier & Batty, 2009; Sabatinelli, Fortune, Li, Siddiqui, Krafft, Oliver, Beck, & Jeffries, 2011). By using a dynamic sequence in which a face morphs from a neutral expression to an affective state, a stronger gaze cueing effect is elicited (for gaze cueing reviews, see Dalmaso, Castelli, & Galfano, 2020; Frischen et al., 2007). Although early studies in amblyopia found poor accuracy for identifying facial expressions during amblyopic eye viewing (Lerner, Pianka, Azmon, Leiba, Stolovitch, Loewenstein, Harel, Hendler, & Malach, 2003), poor performance was also found for inverted faces, suggesting that the deficit lies in featural component processing rather than face configural processing. A follow-up study by the same authors found that reduced activation of extra-striate areas was not face-specific and could be attributed to the reduced visibility of the facial features (Lerner et al., 2006). Individuals with amblyopia also showed no deficits on the Mooney face task, commonly used for assessing face detection and relying on holistic face processing (Cattaneo, Vecchi, Monegato, Pece, Merabet, & Carbon, 2013). These findings indicate that limitations on face perception in anisometropic and strabismic amblyopia may be driven by resolution deficits rather than impaired face processing per se.

In normal vision, processing of gaze cues occurs spontaneously, improving detection of peripheral targets in the direction of gaze (congruent) as compared to targets that appear on the opposite side (incongruent) (Driver et al., 1999; Friesen, Moore, & Kingstone, 2005; Friesen & Kingstone, 1998; Frischen et al., 2007). Although spatial cueing using salient flashes or arrows may be intact in amblyopia (Pham et al., 2018; Ramesh et al., 2020; Roberts et al., 2016), it is unclear whether social cueing based on gaze and emotional cues is affected. Emotional facial expressions modulate the gaze cueing effect in neurotypical observers, especially when the face reacts with an emotional expression after gaze aversion, akin to someone reacting to what they were seeing (Lassalle & Itier, 2015b). Fearful expressions (which signal nearby danger) orient spatial attention more strongly than neutral expressions (Chen, McCrackin, S. D., Morgan, A., & Itier, 2021;

Graham, Kelland Friesen, Fichtenholtz, & LaBar, 2010; Lassalle & Itier, 2013; Lassalle & Itier, 2015a; Lassalle & Itier, 2015b; Mathews, Fox, Yiend, & Calder, 2003; McCrackin & Itier, 2018; McCrackin & Itier, 2019; Neath, Nilsen, Gittsovich, & Itier, 2013; Putman, Hermans, & van Honk, 2006; Tipples, 2006). Happy expressions (which suggest a possible reward) orient attention to a similar degree as neutral faces (Bayless, Glover, M., Taylor, & Itier, 2011; Chen et al., 2021; Graham et al., 2010; Hietanen & Leppänen, 2003; Lassalle & Itier, 2013; Lassalle & Itier, 2015b; Neath et al., 2013; Putman et al., 2006; Tipples, 2006). Recent studies have reported a slightly larger orienting response for happy compared to neutral faces as well, but still of smaller magnitude than the orienting response to fearful faces (McCrackin & Itier, 2018; McCrackin & Itier, 2019).

In this study, we explored whether amblyopia reduces the extent to which emotional face cues orient covert attention. We recruited participants with mild, moderate, or previously treated amblyopia to ensure that the face images were clearly visible to the amblyopic eye and that the local processing of gaze position required for the gaze cueing effect could occur. If the development of social attention to visual cues is affected by amblyopia, we would expect that the gaze cueing effect of a fearful emotional face would be weaker when viewing with an amblyopic eye compared to the fellow eye and to normal control eyes. We also explored whether the magnitude of the gaze cueing effect differed by amblyopia etiology, because attentional deficits may be more pronounced in strabismic amblyopia.

Methods

Participants

Thirty participants with normal vision (mean age ± SD: 20.8 ± 2.4 yrs; 22 female) and 12 participants with amblyopia (mean age ± SD: 27 ± 11.1 years; five female) were recruited at the University of Waterloo. We aimed to recruit 30 participants in both groups, but we were not able to reach this number for the amblyopia group during the recruitment period. All participants provided written informed consent, and the study protocol was approved by the institutional ethics committee, in accordance with the Declaration of Helsinki. Participants either received course credit or were remunerated for their time. Individuals were ineligible for the study if they self-reported a history of psychiatric or neurological disorder (including seizures or epilepsy) or a past loss of consciousness longer than five minutes associated with head trauma. Participants also reported no recent use of antidepressant or

antipsychotic drugs or medications containing cortisone and no regular or recent use of drugs or alcohol.

Clinical assessment included visual acuity (using an electronic ETDRS chart), eye alignment (distance and near cover test) and stereoacuity (Randot Preschool Stereotest; Stereo Optical Co. Inc., Chicago, IL, USA). All participants wore their habitual correction as needed. Participants with normal vision had best-corrected visual acuity better than 20/25, with no greater than a 1 logMAR line difference in visual acuity between the eyes, and no history of binocular vision disorders. Amblyopia was defined as a minimum of a 2 logMAR line interocular difference in visual acuity or a 1 logMAR line difference with a history of amblyopia treatment, caused by anisometropia (>1 diopter interocular difference or >1.5 diopters of cylinder in one eye) or strabismus (including history of strabismus surgery), with normal ocular and general health. Clinical details for individuals with amblyopia are summarized in Table 1.

Apparatus

Participants performed the experiment in a chinrest with head stabilization while wearing an Eyelink II head-mounted eye tracker (250 Hz; SR Research; Mississauga, Canada). Eye tracking data were used only to ensure central fixation. Stimuli were presented using Experiment Builder (SR Research; Mississauga, Canada) on a 27″ ASUS PG278QR LCD monitor (2560 × 1440 resolution, 120-Hz refresh rate; Taipei, Taiwan) from a viewing distance of 50 cm.

Stimuli

Face stimuli previously used in McCrackin and Itier (2018) were used in this experiment. These faces (four male and four female; identities 02, 03, 06, 09, 20, 22, 24, 27) were selected from the widely available NimStim database[1] (Tottenham, Tanaka, Leon, McCarry, Nurse, Hare, Marcus, Westerlund, Casey, & Nelson, 2009) and cropped to remove the hair, ears, and clothing. Each face expressed one of three emotions (fear, neutral and happy) and had averted left or right gaze. Each face was vertically flipped to counterbalance any facial asymmetries. To account for apparent motion of the mouth in happy and fearful expressions, neutral expressions with averted gaze featured tongue protrusion (McCrackin & Itier, 2018). Each face (15.9° wide × 23.1° tall) was presented centrally on a white background with a fixation cross between the nasion and the nose.

ID	Age/gender	Type	Fellow eye VA (logMAR)	Amblyopic eye VA (logMAR)	Stereoacuity	Ocular deviation (near)	Clinical history
A01	28/M	A	0.00	0.40	>800″	NS, ortho	Dx at 22 yo, no patching or surgery
A02	25/F	A	0.00	0.70	>800″	NS, 12△ XP	Unknown history
A03	18/F	A	−0.10	0.20	>200″	NS, 4△ XP	Patched 1h/day, no surgery or VT
A04	19/M	S	0.00	0.20	>800″	4△ LXT	Dx at 4 yo, wore glasses and patched for 4 y, no surgery
A05	19/M	M	0.00	0.10	800″	4△ RX(T)	Patched × 3 y, VT 30 mins/day, 5x/week
A06	46/M	S	0.00	0.40	>800″	8△ RET	Dx at 4 y, surgery for ET, patched 8h/day
A07	46/M	S	0.00	0.20	>800″	35–40△ LET	Dx at 1 y, had 4 surgeries at 1, 2, 3, 10 yo, patched, no diplopia
A08	24/M	A	−0.10	0.20	60″	NS, ortho	Dx at 16 yo, wore glasses, no patching, VT × 2 months
A09	20/F	A	0.00	0.10	100″	NS, 4△ XP	Dx at 4–5 yo, patched, no surgery, OS suppression
A10	42/M	A	−0.10	0.20	100″	NS, 4△ XP	No patching or surgery
A11	18/F	S	0.00	0.10	400″	4△ LXT	Dx at 5 yo, wore glasses since 5–6 yo, patched × 2 y, no VT, OS suppression
A12	19/F	A	−0.10	0.10	200″	NS, ortho	Dx at age 7, patched 4–6 hrs/day, no VT or surgery

Table 1. Clinical details for participants with amblyopia. *Notes:* M = male, F = female, VA = visual acuity, A = anisometropia, S = strabismus, M = mixed (anisometropia and strabismus), NS = non-strabismic, XP = exophoria, X(T) = intermittent exotropia, RET = right esotropia, △ = prism diopters, Dx = diagnosed, y = years, yo = years old, VT = vision therapy (orthoptics or dichoptic binocular amblyopia treatment).

Procedure

For participants with normal vision, the dominant eye was defined as the eye more sensitive to blur in the presence of a +2.00 DS lens placed monocularly over each eye while binocularly observing letters 2 logMAR lines above their best-corrected visual acuity threshold (Pointer, 2012). The dominant eye in participants with amblyopia was defined as the eye with better best-corrected visual acuity.

First, to control for any effect of amblyopia on the perception of emotional faces, all participants rated valence and intensity for 48 faces (across all emotional expressions and gaze directions). Each face was presented to only the non-dominant/amblyopic eye for 400 ms. Participants rated the valence (1 = very negative to 9 = very positive) and intensity (1 = not intense to 9 = very intense) for each face on a visible Likert scale using keyboard presses.

Second, to measure attentional cueing with emotional face cues, we used an established spatial cueing task (McCrackin & Itier, 2018). After a brief period of

fixation (pseudo-random period of 500–800 ms), a neutral face with direct gaze appeared for 300 ms. Gaze was averted to the left or the right for 100 ms and the expression then changed to fearful, neutral (with tongue protrusion) or happy for 400 ms (Figure 1). After face offset, a target asterisk (1.3° × 1.3°) was presented 20° to the left or right of fixation and participants had up to 500 ms to respond to the location of the target using arrow keys while maintaining central fixation. Reaction time and accuracy were measured.

All participants were informed that gaze direction was not predictive of target location but to still attend to the emotional expressions because participants would occasionally be asked to verbally report the most recent emotional expression. Gaze cues were congruent or incongruent with target location and had 50% validity. Each block consisted of 384 trials (64 trials per condition) presented in a randomized order and took 30 minutes to complete.

All participants completed 3 blocks (viewing conditions: dominant eye, non-dominant eye, both eyes) within one session (1.5 to 2 hours) in a randomized
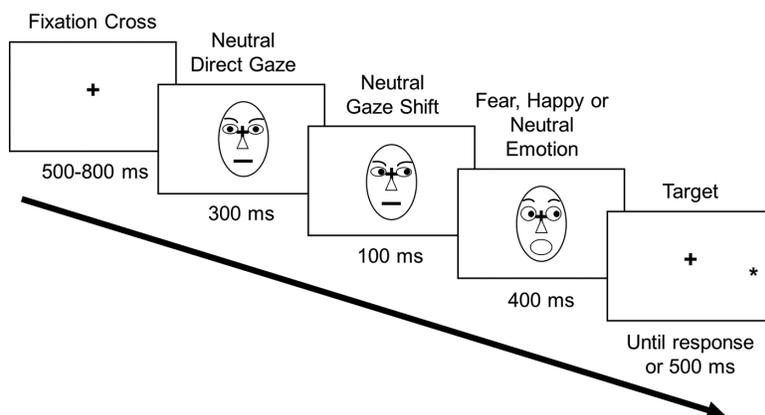

Figure 1. Sample trial sequence. Fearful, happy and neutral faces from the NimStim database (Tottenham et al., 2009) were used in the experiment, represented here with schematics.

order. Participants were encouraged to take breaks between blocks to avoid fatigue. The task was self-paced because participants completed 16 trials at a time before being presented with a break screen. Upon resumption, eye tracking drift correction was performed before starting the next set of trials. Before formal data collection, 24 practice trials were provided to familiarize participants with the detection task.

Statistical analyses

Only correct responses within 2.5 standard deviations of the mean reaction time were used to compute average reaction times for each condition (Van Selst & Jolicoeur, 1994). Incorrect trials were excluded because reaction times in the presence of a task error do not reflect an appropriate orientation of attention. The gaze cueing effect was computed as the difference in reaction times between incongruent and congruent trials.

Statistical analyses were performed with JASP version 0.12.1 (Amsterdam, Netherlands). Accuracy was analyzed with a 3 (eye: dominant eye, non-dominant eye, both eyes) × 2 (group: control, amblyopia) repeated measures analysis of variance (ANOVA). Perception of emotional faces was evaluated using a 3 (emotion: fear, neutral, happy) × 2 (group: control, amblyopia) repeated measures ANOVA on valence and intensity ratings. Reaction times were analyzed with an omnibus 3 (eye: dominant eye, non-dominant eye, both eyes) × 2 (congruency: congruent, incongruent) × 3 (emotion: fear, neutral, happy) × 2 (group: control, amblyopia) repeated measures ANOVA. In cases where Mauchly's test of sphericity was significant, the Huynh-Feldt correction was applied. Post-hoc analyses were conducted on significant interactions using Tukey's correction for multiple comparisons.

Results

A significant main effect of emotion ($F_{2,80} = 310.4$, $p < 0.001$, $\omega^2 = 0.82$) was found for valence ratings. There was no main effect of group ($F_{1,40} = 1.8$, $p > 0.05$) nor an emotion × group interaction ($F_{2,80} = 1.6$, $p > 0.05$). Post-hoc t-tests showed that fearful expressions had a significantly lower (negative) valence rating than both neutral (Table 2; mean difference ± SE -1.48 ± 0.18, $p < 0.001$) and happy (-4.4 ± 0.18, $p < 0.001$) expressions. Neutral expressions had a significantly lower valence rating than happy expressions (-2.9 ± 0.18, $p < 0.001$).

For intensity ratings, significant main effects of emotion ($F_{1.6,65.2} = 81.3$, $p < 0.001$, $\omega^2 = 0.47$) and group ($F_{1,40} = 4.1$, $p = 0.049$, $\omega^2 = 0.04$) but no emotion × group interaction ($F_{1.6,65.2} = 0.4$, $p > 0.05$) were

Measure	Fear	Happy	Neutral
Valence			
Control	3.06 (0.16)	7.22 (0.14)	4.62 (0.12)
Amblyopia	2.74 (0.15)	7.36 (0.18)	4.14 (0.31)
Intensity			
Control	6.37 (0.20)	6.54 (0.14)	4.17 (0.17)
Amblyopia	7.03 (0.15)	6.86 (0.32)	4.76 (0.48)

Table 2. Participants' mean ratings of valence and intensity for each emotional face. Reported as mean rating (standard error of the mean).

found. Participants with amblyopia rated faces to be marginally more intense than participants with normal vision (Table 2; 0.52 ± 0.26, Bonferroni corrected $p = 0.049$). Fearful and happy faces were perceived as more intense than neutral ones (fearful vs. neutral: 2.2 ± 0.2, $p < 0.001$; happy vs neutral: -2.2 ± 0.2, $p < 0.001$), and there was no difference between fearful and happy expressions (0.003 ± 0.2, $p > 0.05$).

Overall target detection accuracy was high in both control (mean ± SE; $96.9\% \pm 0.7\%$) and amblyopia ($97.6\% \pm 0.3\%$) groups. No main effects of eye ($F_{2,80} = 0.3$, $p > 0.05$) nor group ($F_{1,40} = 0.6$, $p > 0.05$) nor an eye × group interaction ($F_{2,80} = 1.6$, $p > 0.05$) were present. Error rates were slightly higher in the control group ($2.1\% \pm 0.5\%$) than the amblyopia group ($1.5\% \pm 0.2\%$), and the percentage of trials with delayed responses were comparable between the two groups (control: $1.0 \pm 0.4\%$; amblyopia: $0.9 \pm 0.2\%$). After trimming reaction times exceeding 2.5 SD of each individual's reaction time to mitigate the influence of outliers, an average of $95.5\% \pm 0.2\%$ (controls) and $96.7\% \pm 0.1\%$ (amblyopia) of the data remained for further reaction time analysis.

A 3 (eye) × 2 (congruency) × 3 (emotion) × 2 (group) analysis on mean reaction time revealed significant main effects of emotion ($F_{1.6,65.5} = 6.1$, $p = 0.006$, $\omega^2 = 0.0007$; see Figure 2A) and eye ($F_{2,80} = 5.2$, $p = 0.008$, $\omega^2 = 0.01$; see Figure 2B) but no effect of group ($F_{1,40} = 1.4$, $p > 0.05$). Other significant interactions included eye × group ($F_{2,80} = 4.8$, $p = 0.011$, $\omega^2 = 0.01$), emotion × group ($F_{1.6,65.5} = 5.6$, $p = 0.009$, $\omega^2 = 0.0006$), and eye × emotion × group ($F_{4.1, 164.6} = 3.2$, $p = 0.013$, $\omega^2 = 0.0004$). However, no significant pairwise comparisons emerged after Tukey correction. A significant interaction of congruency × emotion was present ($F_{2,40} = 20.6$, $p < 0.001$, $\omega^2 = 0.002$) replicating the established emotional gaze cueing effect (Chen et al., 2021; Graham et al., 2010; Lassalle & Itier, 2013; Lassalle & Itier, 2015a; Lassalle & Itier, 2015b; Mathews et al., 2003; McCrackin & Itier, 2018; McCrackin & Itier, 2019; Neath et al., 2013; Putman et al., 2006; Tipples, 2006). Post-hoc analyses revealed that the gaze cueing effect (i.e., the RT difference between
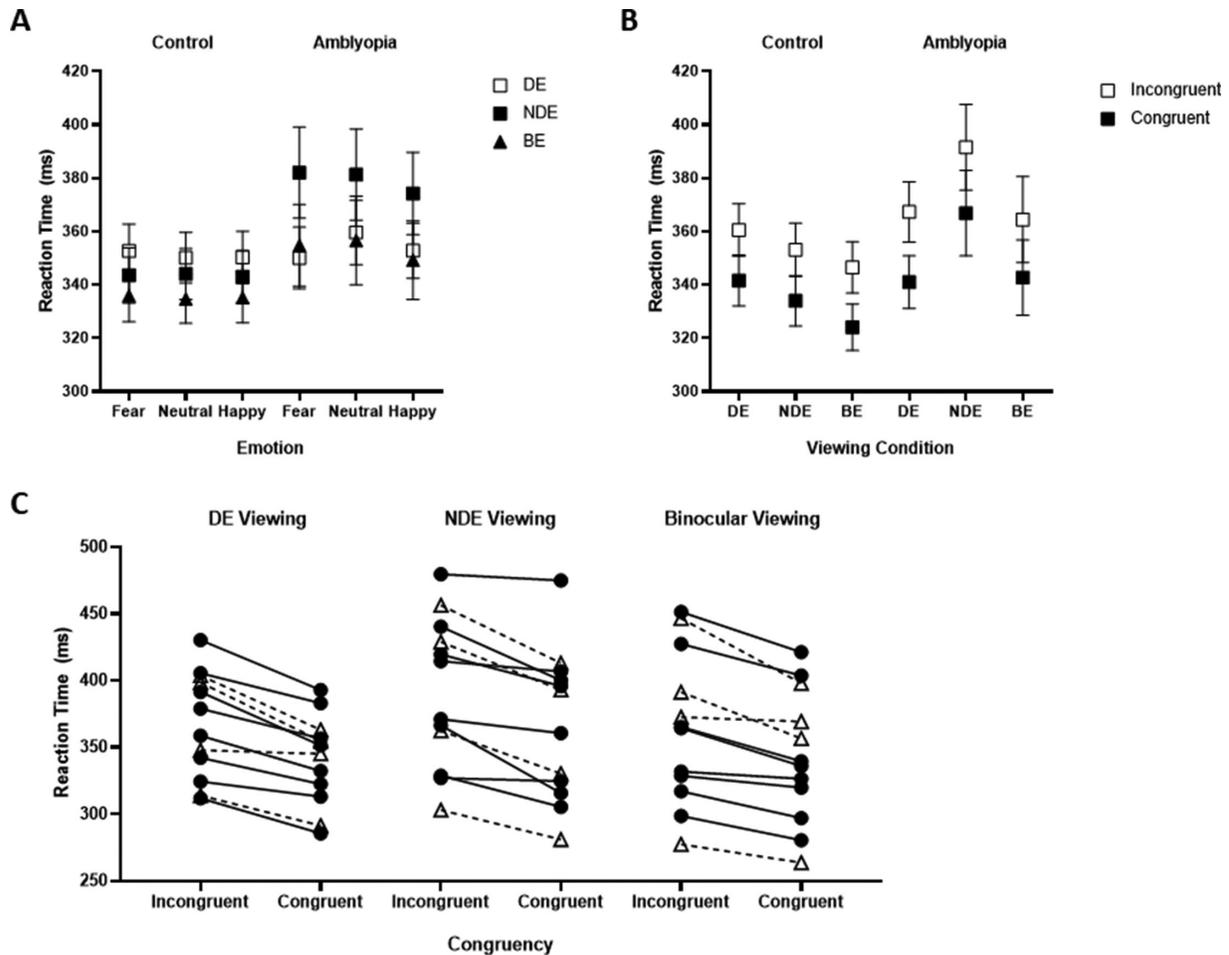
Figure 2. Mean reaction times across emotion (A) and viewing condition (B). (C) Individual reaction time data from the amblyopia group, segregated by amblyopia subtype. Circles (with solid lines) = anisometropic amblyopia; triangles (with dotted lines) = strabismic/mixed amblyopia. DE, dominant/fellow eye; NDE, non-dominant/amblyopic eye; BE, both eyes. Error bars denote standard error.

incongruent and congruent trials) was stronger for fearful than neutral faces (main difference $\pm$ SE 12.2 ± 2.0 ms, Bonferroni corrected $p < 0.001$) and for fearful than happy faces (8.6 ± 2.0 ms, Bonferroni corrected $p < 0.001$); neutral and happy faces did not differ (-3.7 ± 2.0 ms, Bonferroni corrected $p > 0.05$; see Figure 3). Importantly, the interaction of eye $\times$ congruency $\times$ emotion $\times$ group was not significant ($F_{3.9,157.8} = 1.1$, $p > 0.05$), nor was the congruency $\times$ emotion $\times$ group interaction ($F_{2.1,82.4} = 0.79$, $p > 0.05$)[2], suggesting that the emotional cueing effect was similar across groups and eye conditions.[3]

As an exploratory analysis to discern whether there were any differences among subtypes of amblyopia, we separated the amblyopia group into anisometropic ($n = 8$) and strabismic/mixed ($n = 4$) subtypes. A 3 (eye) $\times$ 2 (congruency) $\times$ 3 (emotion) $\times$ 2 (subtype) repeated measures ANOVA showed no main effect of subtype ($F_{1,10} = 0.11$, $p > 0.05$) nor any interaction of subtype with other factors including congruency
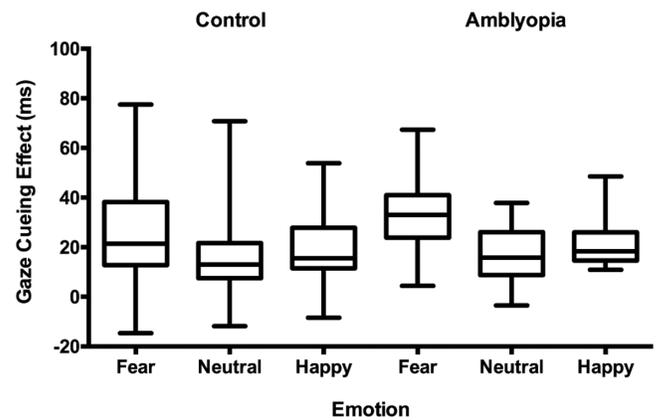

Figure 3. Box plot diagram showing emotional gaze cueing effects for fear, neutral and happy expressions for participants with normal vision ($n = 30$) and amblyopia ($n = 12$). Box boundaries denote twenty-fifth and seventy-fifth percentiles with the line inside box representing the median. Whiskers represent the full range of data points.

$(F_{1,10} = 2.3, p > 0.05)$. Although the congruency $\times$ emotion interaction remained significant $(F_{2,20} = 7.8, p = 0.003)$, it did not interact with amblyopia subtype $(F_{2,20} = 1.47, p > 0.05)$. As seen in Figure 2C, the strabismic/mixed subtype group did not have slower reaction times (mean $\pm$ SE: anisometropia 366.86 $\pm$ 19.45 vs. strabismic/mixed 357.79 $\pm$ 19.45) and trended toward larger gaze cueing effects (anisometropia 19.80 $\pm$ 4.1 vs. strabismic/mixed 28.73 $\pm$ 4.1), although the difference was not statistically significant.

Some participants in the amblyopia group reported previous successful treatment of amblyopia and had an interocular acuity difference less than 0.2 logMAR despite residual functional deficits in stereoacuity. We conducted an independent samples t-test to determine whether the magnitude of the gaze cueing effect was driven by this successfully treated group. We found no significant difference in gaze cueing effects between the successfully treated group (n = 3; mean $\pm$ SE 33.6 $\pm$ 6.5 ms) and the rest of our sample (n = 9; 21.2 $\pm$ 2.9 ms; $t_{10} = -1.98, p = 0.08$). Omission of these participants from the analysis did not change our main findings. Neither the eye $\times$ congruency $\times$ emotion $\times$ group interaction $(F_{4,148} = 0.98, p > 0.05)$ or the congruency $\times$ emotion $\times$ group interaction $(F_{2,74} = 0.2, p > 0.05)$ were significant. The magnitude of the gaze cueing effect appears to be independent of interocular acuity differences $(\rho = -0.11, p > 0.05;$ see Figure 4).

Previous studies have reported larger gaze cueing effects in females than males for neutral expressions (Alwall, Johansson, & Hansen, 2010; Bayliss, di Pellegrino, & Tipper, 2005; Deaner, Shepherd, & Platt, 2007; Feng, Zheng, Zhang, Song, Luo, Li, & Talhelm, 2011; Hayward & Ristic, 2017; McCrackin & Itier, 2019). However, there is no evidence that this difference in gaze cueing effect between sexes varies across emotional expressions (McCrackin & Itier, 2019). Within our sample of 27 females and 15 males, no effect of gender was evident for the gaze cueing effect based on an independent samples t-test (fear: $t_{40} = 0.75, p > 0.05$; neutral: $t_{40} = 0.034, p > 0.05$; happy: $t_{40} = 0.21, p > 0.05$).

Discussion

The present study explored whether amblyopia affects the attention orienting effect generated by the gaze direction of emotional face cues. We first verified the emotional valence of the stimuli to ensure that any attentional capture effects were not limited by low level visual deficits. Despite using a complex attentional task requiring integration of gaze and emotional cues from face processing, our results suggest that orienting covert attention using emotional face cues is not affected by amblyopia across all viewing conditions. Specifically, no
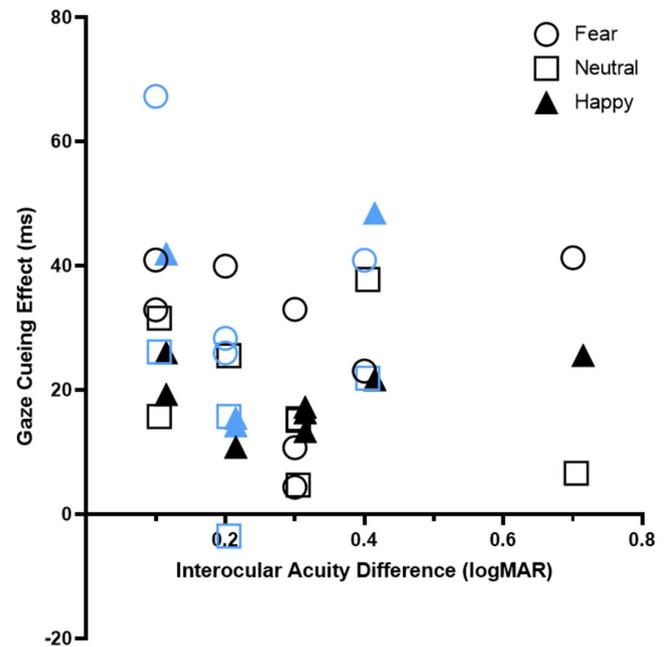

Figure 4. Gaze cueing effect as a function of interocular acuity difference in the amblyopia group across different emotions. Each participant is represented by a shape for each emotional cue condition (open circle = fear, open square = neutral, filled triangle = happy). Black = anisometropic, blue = strabismic/mixed. Shapes are slightly offset to avoid overlapping each other.

deficit in spatial cueing was seen under amblyopic eye viewing, and we did not find an attentional imbalance favoring the fellow eye in amblyopia under monocular viewing conditions. Although we constrain our findings to those with treated, mild and moderate amblyopia, we find a comparable (even nominally larger) gaze cueing effect in our amblyopia group compared to the control group (Chen et al., 2021; Graham et al., 2010; Lassalle & Itier, 2015a; Lassalle & Itier, 2015b; McCrackin & Itier, 2018) and determined that this result was not driven by the subset of participants with treated amblyopia. In particular, fearful facial expressions oriented covert attention more strongly than happy and neutral expressions (Chen et al., 2021; Fox, Mathews, Calder, & Yiend, 2007; Graham et al., 2010; Hietanen & Leppänen, 2003; Lassalle & Itier, 2013; Lassalle & Itier, 2015b; McCrackin & Itier, 2018; McCrackin & Itier, 2019; Tipples, 2006). Additionally, we did not find a correlation between the strength of the gaze cuing effect and severity of amblyopia, similar to other previous studies with their attentional measures (Chow et al., 2018; Farzin & Norcia, 2011; Ramesh et al., 2020; Roberts et al., 2016; Wong-Kee-You et al., 2020).

Regardless of emotion, we found that spatial cueing using gaze cues within face stimuli can orient covert attention in amblyopia. These findings corroborate previous work showing that simple attentional cueing

is effective in amblyopia regardless of viewing eye (Pham et al., 2018; Ramesh et al., 2020; Roberts et al., 2016). Because emotional processing augmented the basic cueing effect, perception of emotional faces may be similar among our control and amblyopia groups. Indeed, subjective ratings of emotional valence and intensity did not differ substantially between our groups of participants. We were limited in this study to less severe cases of amblyopia so that participants would be able to resolve individual facial features. Nevertheless, our results are consistent with previous work demonstrating intact global facial processing as long as stimuli can be fully resolved by the amblyopic eye (Cattaneo et al., 2013; Lerner et al., 2006). Our findings of emotion-specific effects suggest holistic face processing may be unaffected by amblyopia in our sample.

Although we postulate that cortical integration of gaze and emotional cues for the purpose of attention orienting remains intact in mild, moderate, and treated amblyopia, it is also possible that the intact cueing effect is mediated by a different route. A subcortical pathway may expedite face detection and gaze processing, even before detection by cortical routes (Johnson, 2005; Senju & Johnson, 2009; Tamietto & de Gelder, 2010). This pathway involves the superior colliculus, pulvinar and amygdala (Pessoa & Adolphs, 2010). In neurotypical individuals, a stronger functional connection between the pulvinar and amygdala is associated with better recognition of fearful facial expressions (McFadyen, 2019). Neuroimaging of the amygdala in neurotypical individuals reveals residual amygdala activity even when fear-conditioned stimuli are masked (Morris, Ohman, & Dolan, 1999). Through this subcortical route, stimuli continue to be processed despite being perceptually suppressed and this processing occurs in parallel with cortical routes (Morris et al., 1999). A previous report has suggested that motion integration in amblyopia involves intact pulvinar processing and engages a different neural network than individuals without amblyopia (Thompson, Villeneuve, Casanova, & Hess, 2012). These subcortical pathways may mediate the seemingly intact emotional face gaze cueing effect in amblyopia.

Evidence remains mixed as to whether the severity of any attentional deficit differs by amblyopia etiology. Many of the attentional deficits reported in the literature involve individuals with strabismic amblyopia who often have more severe amblyopia (Chow et al., 2018; Hou et al., 2016; Thiel & Sireteanu, 2009; Wang et al., 2017). Under monocular viewing conditions, spatial bias on a line bisection task was more pronounced in strabismic amblyopia than anisometropic amblyopia (Thiel & Sireteanu, 2009). On the other hand, multiple-object tracking under monocular viewing revealed no difference in performance between anisometropic and strabismic amblyopia (Ho et al., 2006). However,

when multiple-object tracking was performed under dichoptic conditions, a tracking deficit was found only for participants with strabismic amblyopia (Chow et al., 2018). Participants with anisometropic amblyopia were equivalent to neurotypical controls (Chow et al., 2018). In another dichoptic attention study, the fellow eye contributed substantially more than the amblyopic eye, with the imbalance greater for strabismic amblyopia than anisometropic amblyopia (Wong-Kee-You et al., 2020). Unfortunately, our limited sample size in this study did not permit us to conduct a subgroup analysis to address this question. In the future, a better understanding of the association between attentional deficits and amblyopia etiology will better inform efforts to recover visual acuity and stereopsis using attention-based amblyopia treatments (Huang, Sun, Luo, Liu, Liu, Mansouri, Wong, Wen, Liu, & Wang, 2014; Li, Ngo, Nguyen, & Levi, 2011; Li, Ngo, & Levi, 2015).

Previous studies have reported that the size of the gaze cueing effect differs between the sexes for neutral expressions. In particular, females demonstrate a larger gaze cueing effects than males (Bayliss, di Pellegrino, & Tipper, 2005; Deaner et al., 2007; Feng et al., 2011; Hayward & Ristic, 2017; McCrackin & Itier, 2019; Moore & Fallah, 2001). There is no evidence that this difference in gaze cueing effect between sexes varies across emotions (McCrackin & Itier, 2019). Exploratory analysis using an independent samples *t*-test did not find a statistically significant difference in gaze cueing effect between males and females in our data, although we cannot draw a strong conclusion based on our limited sample size. Even if there was a difference that we did not capture with our small sample size, the distribution of females was higher in the control group than the amblyopia group, whereby the absence of an attentional deficit in the amblyopia group would not be driven by gender.

The non-dominant eye (NDE) in both groups was exposed to the emotional face stimuli for 12.5% more trials than the dominant eye (DE) as part of the subjective rating procedure at the beginning of the experiment. Although we cannot rule out the presence of a practice effect for the NDE driven by this increased exposure, this is unlikely to be responsible for our results for a number of reasons: (1) The rating procedure did not involve target detection practice to expedite reaction times for the detection of a peripheral stimulus. (2) Cue validity was 50% within the main experiment. Therefore, the effect of prior stimulus exposure would apply equally to both incongruent and congruent trials. (3) Any practice effect would apply to the NDE viewing condition for both groups, and thus our between-group comparison remains valid. Even if it reduced the interocular effect, no monocular difference was evident for the NDE between the groups. (4) We have no reason to believe that any practice effect would

remain monocular because face processing involves cortical areas that are binocular.

Although our main analysis considers the magnitude of attentional orienting effect, we did note the overall increased reaction times for the amblyopia group (despite not being statistically significant). This is likely due to the mild nature of amblyopia among our participants because nine of twelve participants with amblyopia had an amblyopic eye acuity of 0.2 logMAR or better, and reaction time deficits may be correlated with visual acuity (Gambacorta et al., 2018; Hamasaki & Flynn, 1981). Previous studies have found prolonged manual responses when stimuli were viewed with the amblyopic eye as compared to fellow eye or binocular viewing (Gambacorta et al., 2018; Levi et al., 1979; Mackensen, 1958; Pianta & Kalloniatis, 1998; von Noorden, 1961). Increasing stimulus strength to the amblyopic eye can reduce this reaction time difference between the eyes only in anisometropic amblyopia (Gambacorta et al., 2018; Pianta & Kalloniatis, 1998), but an irreducible delay remains for strabismic amblyopia (Gambacorta et al., 2018). Within our small sample of anisometropic and strabismic participants, we did not find any differences among subtypes, because reaction time data from our strabismic amblyopia group fell within the range of the anisometropic amblyopia group (see Figure 2C). Nevertheless, the comparable magnitude of gaze cueing effects for both subtypes suggests that both groups benefit similarly from attentional cueing, although we cannot extrapolate these findings to severe amblyopia. By taking the difference between incongruent and congruent reaction times or a gaze-cueing index as a percentage of overall speed, we are able to exclude any overall reaction time delay inherent to the amblyopia group.

Conclusions

We explored whether amblyopia impairs the development of social attention by examining the orienting of covert attention by emotional face cues. Our results indicate that spatial cueing with emotional cues is unaffected by mild, moderate, and treated amblyopia under monocular and binocular viewing conditions, and that the magnitude of social cueing is similar to neurotypical controls. Future studies should explore attentional cueing in more severe cases of amblyopia. These results place constraints on the range of attentional mechanisms affected by amblyopia and indicate normal processing of emotional face stimuli in mild and treated amblyopia. A better understanding of the attentional mechanisms in amblyopia may help to accelerate the development of new treatments.

Keywords: amblyopia, attention, social cognition, face processing

Footnotes

[1]Development of the MacBrain Face Stimulus Set was overseen by Nim Tottenham and supported by the John D. and Catherine T. MacArthur Foundation Research Network on Early Experience and Brain Development. Please contact Nim Tottenham at tott0006@tc.umn.edu for more information concerning the stimulus set.

[2]A power analysis computed using G*Power (v3.1.9.6) post-hoc revealed that to find a significant group difference in the gaze cueing effect for the non-dominant eye with 95% power, we would require a total sample size of 364 participants, indicating the likely absence of an effect even with larger groups.

[3]Please note that using a gaze-cueing index as a percentage of overall speed ($(RT_{incongruent} - RT_{congruent})/[(RT_{incongruent} + RT_{congruent})/2] \times 100$) to account for longer reaction times in the amblyopia group did not change any of the results (approach used in Chen et al., 2021; Pecchinenda & Petrucci, 2016; Ramon, Busigny, & Rossion, 2010).

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