Editorial Commentary

Binocular treatment of amblyopia: from the laboratory to clinical trials

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Over the last 10 years, numerous psychophysical studies have indicated that binocular mechanisms are structurally intact but functionally suppressed in amblyopia (1-8). Many of these studies have used a contrast balancing approach, whereby the contribution of each eye to binocular vision is equated or "balanced" by presenting higher contrast stimulus elements to the amblyopic eye than the fellow eye (6). Using this approach, the strength of suppression can be quantified by measuring the magnitude of interocular contrast difference required for normal binocular combination. When suppression strength has been correlated with other clinical measures, stronger suppression has been associated with worse stereoacuity and worse amblyopic eye visual acuity indicting a link between the monocular and binocular deficits in amblyopia (5,7).

Current binocular treatments for amblyopia emerged from psychophysical studies of binocular combination and are based on the hypothesis that repeated stimulation of intact binocular mechanisms using contrast balanced stimuli can improve both binocular and monocular vision in amblyopia (9,10). Numerous case-series and laboratory-based studies have reported improved stereopsis, visual acuity and contrast sensitivity in adults and children with amblyopia following binocular treatment in the form of psychophysical tasks, modified videogames or dichoptic movies (9,11-18). Non-human animal studies have also supported the concept of binocular amblyopia treatment (19).

Recently, binocular treatments in the form of modified dichoptic videogames viewed through red/green glasses have been tested within randomized clinical trials. Kelly *et al.* (20) reported that 2 weeks of binocular treatment in the form of an engaging tablet-based videogame called Dig Rush improved visual acuity significantly more that patching in 4–10-year-old children. However, other large-scale clinical trials have found no effect of binocular treatment. Holmes *et al.* (21) observed that binocular treatment induced numerically less visual acuity improvement in 5–12-year-old children than patching and Gao *et al.* (22) found that binocular treatment was no different from placebo for improving visual acuity and stereopsis in a sample starting at 7 years of age with no upper age limit. The very recently reported results of Holmes *et al.* (23) in children aged 7–12 years exhibit a similar pattern of results. Holmes *et al.* (23) observed no difference in visual acuity or stereopsis improvement between a group treated with the Dig Rush videogame and a control group who received only optical treatment. In fact, neither group showed clinically meaningful improvements in any of the outcome measures reported.

What might explain the discrepancy between the initial case-series/laboratory studies and the recent randomized clinical trials? Randomized clinical trials typically control for many more sources of bias than case-series or laboratory studies and therefore are less likely to observe erroneous treatment effects. However, a number of the earlier studies did attempt to account for placebo effects by including controls such as a monocular treatment condition (17). In addition, one well-controlled randomized clinical trial did show a convincing treatment effect (20). Therefore, other factors may also be involved. One such factor is treatment

adherence. The first two large-scale clinical trials of binocular treatment (21,22) used a modified version of the videogame Tetris that failed to engage participants. This resulted in poor adherence. The pattern of adherence in these two randomized clinical trials is different from many of the case-series and laboratory-based studies cited above where participants were closely monitored and therefore achieved 100% adherence. In their recent study, Holmes *et al.* (23) used a more engaging videogame and observed improved adherence, but adherence still did not approach the 100% level of the earlier studies. It is important to note that none of the three negative clinical trials (21-23) observed a dose-response relationship for binocular treatment, which suggests that adherence may not be a critical factor. However, calculating binocular treatment dose may be more complex than simply recording the amount of time that the treatment videogame was active. Outside of controlled laboratory settings, it is impossible to know whether study participants wore the required red green glasses correctly or whether the game was being played by the patient or by another family member. Perhaps more importantly, the treatment may have been split up into small blocks throughout the day or combined with other activities such as watching television or operating a cell-phone. We don't yet understand the impact of these factors on binocular treatment response.

Patient demographics may also have played a role in the results of previous randomized clinical trials. Kelly *et al.* (20), who reported a positive treatment effect, enrolled younger participants (mean age 6.7 years). In contrast, the three negative trials enrolled relatively older participants [Holmes *et al.* 2016, mean age 9.6 years (21); Holmes *et al.* 2019, mean age 8.4–8.6 years (23); Gao *et al.* 2018, mean age 22.1–21.0 years (22)]. This was reasonable based on the promising laboratory results that reported treatment effects in adult participants (4,10). However, older patients with amblyopia may be less likely to exhibit vision improvements (24,25) and therefore the effects of poor or intermittent adherence may be exacerbated. Other unknown factors such as the optimal rate of interocular contrast change and previous treatment for amblyopia may also be more influential in older participants. As stated by Holmes *et al.* (23), the results of the ongoing Pediatric Eye Disease Investigator Group (PEDIG) clinical trial of Dig Rush in younger patients (NCT02983552) will help to shed light on this issue.

The randomized clinical trials reported by Holmes *et al.* (21), Gao *et al.* (22), and most recently by Holmes *et al.* (23) followed gold standard protocols and reflect the real-world engagement of study participants with one of the world's first prescribed videogame treatments. However, the negative results do not necessarily disprove the hypothesis that underpins binocular treatment. In particular, the results may reflect the difficulty of deploying binocular treatment in the home environment. Future home-based studies with more advanced adherence monitoring systems involving gaze tracking and/or supervised in-office randomized clinical trials are required to address these questions.

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Footnote

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Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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