DIG RUSH
PROJECT PROTOCOL

Principal Investigator: Eileen E. Birch PhD
Performance Site: Retina Foundation of the Southwest

Purpose:
Amblyopia is reduced visual acuity in one eye that appears healthy; the visual acuity deficit cannot be corrected with spectacles or contact lenses. Because most types of amblyopia affect visual acuity in one eye, amblyopia is typically considered to be a monocular disease. Amblyopia affects about 3% of the U.S. population and is the most common cause of monocular visual loss in children and young-middle aged adults. The most common treatment is to patch the normal fellow eye to force the child to use the amblyopic eye. Forced monocular use of the amblyopic eye often results in visual acuity improvement.

Amblyopia also affects binocular vision, the ability to use the two eyes together in a coordinated way. Little is known about binocular vision dysfunction in amblyopia. One theory is that amblyopia results when one eye is favored and the visual cortex suppresses the information from the other eye. Others have suggested that suppression may not play a role in amblyopia that results from infantile eye disorders, only in amblyopia that develops later in childhood.

Recently, Robert Hess and colleagues reported that amblyopic adults who repeatedly perform a dichoptic perceptual task or play a dichoptic Falling Blocks game app with reduced fellow eye contrast begin to show improvements in binocular function in 1-5 weeks (Hess et al 2010, 2012). The key features are:

- the images presented to the left and right eyes can be independently controlled
- contrast of the images presented to the eye with normal vision is reduced
- contrast of images presented to the amblyopic eye is 100%

The contrast imbalance allows the amblyopic eye to "break through" suppression so that the two eyes can learn to work together. Importantly, this binocular experience also resulted in improved visual acuity for the amblyopic eye. More recently, we showed that binocular iPad game apps are an effective amblyopia therapy for children, and that the visual acuity gains are maintained for at least 6 months after the cessation of therapy (Li et al 2014a, 2014b).

One limitation of the binocular iPad game approach was that 32-38% of the amblyopic children in our studies had poor compliance or noncompliance with prescribed game play; i.e., they played only 0-4 hours during the entire 4-week therapy period (Li et al 2014a; Birch et al 2015). One of the primary reasons for poor compliance was that the simple game apps that we had available on our iPads (Falling Blocks, Pong, Labyrinth, and Balloons) were not sufficiently appealing to the children. Other children were compliant for an initial 4-week therapy period and achieved significant visual acuity gains, but grew tired of the simple games available and declined to participate in a second 4-week round of binocular iPad game therapy even though they had residual amblyopia and would need to return to patching therapy. Thus, while we were able to demonstrate that binocular iPad game apps were effective, the effectiveness is currently limited by the failure of these simple games to engage the children.

On the other hand, some children who were noncompliant with prescribed binocular iPad game play were simply too busy to fit the time required into their daily routine. Unlike patching therapy, which can be implemented while the child is performing other activities (homework, watching TV, reading), binocular iPad game play requires dedicated time each day to complete therapy. For children with lots of homework, tutoring appointments, sports, and other extracurricular activities, scheduling time for therapy can be a challenge. Whether a more engaging game can solve the problem of noncompliance needs to be investigated.

Another potential advantage of a more engaging binocular iPad game app is that it may provide an arousing and gratifying activity for the child. Playing action video games is associated with increased release of neuromodulators associated with arousal and reward (ACh and dopamine), conditions that have been reported to support brain plasticity (Bavelier et al 2010; Berardi et al 2000; Morishita & Hensch 2008). Therefore, a more engaging active game app may enhance the amblyopic child's therapeutic response to binocular iPad game play.

We propose to evaluate a more engaging, action-oriented binocular iPad game app as a binocular therapy for amblyopic children (*Big Dig*, developed by UbiSoft and provided to us by Amblyotech, Inc).

Specific Aims:

1. To determine whether the *Big Dig* binocular iPad game app is effective in improving visual acuity and reducing interocular suppression in amblyopic children
2. To compare the amount of visual acuity improvement achieved with the *Big Dig* game to the amount achieved with patching
3. To determine whether using the *Big Dig* game alleviates compliance problems with binocular iPad game play in amblyopic children

As in our previous studies, commercially available Apple iPads will be used as the platform for binocular therapy and passive 3D TVs will be used to study suppression. These devices are widely used in family homes and have no known capacity to cause injury. There is no violence in the game. The main goal is to beat the clock and avoid obstacles while collecting gold.

This study can have direct benefits to the participating individuals and society. The therapy procedures aim to improve the vision of children with amblyopia. The study also will provide additional insights regarding the role of interocular suppression in amblyopia and pilot data on the effectiveness of binocular therapy. The data obtained will help us to understand both the mechanism of amblyopia and the potential of a new treatment modality.

Background:

Although patching treatment results in improved visual acuity for 73-90% of amblyopic children, 15-50% fail to achieve normal visual acuity after months or years of treatment (Birch & Stager 2006; Birch et al 2004; Repka et al 2003, 2004, 2005; Rutstein etal 2010; Stewart et al 2004; Wallace et al 2006; Woodruff et al 1994). Even among children who do achieve normal visual acuity with amblyopia treatment, the risk for recurrence of amblyopia is high (Birch 2003; Birch & Stager 2006; Birch et al 1990; 2004, 2005, 2010). Patching treatment is based on the premise that amblyopia is a monocular disorder that can be treated by eliminating the etiologic factor (blur or misalignment) and forcing use of the amblyopic eye (http://www.nei.nih.gov/health/amblyopia). However, recent studies have elucidated a clear link between binocular dysfunction and the complex constellation of deficits that characterizes amblyopia, including visual acuity, vernier acuity, fixation instability, fusional suppression, and risk for residual and recurrent amblyopia (Mansouri et al 2008). The association of binocular dysfunction and the myriad of monocular and binocular deficits in amblyopia has led several authors to propose the hypothesis that amblyopia is a monocular consequence of a primary binocular obstacle to normal visual development (Birch 2013).

In the classic view, it is hypothesized that habitual suppression of one eye eliminates the diplopia or visual confusion that results from strabismus or anisometropia and causes a reduction in the number of binocularly-driven cortical excitatory neurons. However, recent evidence refutes this hypothesis; although binocular interaction does not normally occur in amblyopia, it can occur when fellow-eye contrast is

reduced (Mansouri et al 2008). Recent physiological evidence also suggests that weak, noisy signals from the amblyopic eye can contribute to binocular vision if suppression by the fellow eye is reduced by signal attenuation, such as reduced stimulus contrast (Sengpiel et al 2006; Bi et al 2011). In addition, the lack of binocular responsiveness of V1 neurons in amblyopia is reversible when interocular suppression is removed by ionophoretic applications of bicuculline, which blocks GABAergic inhibition (Sengpiel et al 2005). Taken together, the psychophysical and physiological data support the hypothesis that active suppression renders a structurally intact binocular visual system functionally monocular in amblyopia.

Reduced fellow eye contrast to equate the visibility for the amblyopic and fellow eyes allows at least some amblyopic adults to experience binocular vision (Mansouri et al 2008; Baker et al 2007). In small cohorts of amblyopic adults and schoolchildren, repeated practice with dichoptic perceptual judgment or an iPod dichoptic Falling Blocks game with reduced fellow eye contrast yielded reduction in the strength of interocular suppression and modest visual acuity improvement after just 1-5 weeks (Hess et al 2010, 2012, 2014; Knox et al 2011; Li et al 2012). Recently, we showed that the same binocular therapy approach (reduced fellow eye contrast) could be adapted for home use by amblyopic children, using four simple anaglyphic (red-green dichoptic) games presented on a larger iPad display (Li et al 2014; Birch et al 2014). These games were effective in improving visual acuity, and the visual acuity gains were maintained for at least 6 months after the cessation of therapy (Li et al 2014a, 2014b).

One limitation of the binocular iPad game apps was that 32-38% of the amblyopic children in our studies had poor compliance or noncompliance with prescribed game play; i.e., they played only 0-4 hours during the entire 4-week therapy period (Li et al 2014a; Birch et al 2014). One of the primary reasons for poor compliance was that the simple game apps that we had available on our iPads (Falling Blocks, Pong, Labyrinth, and Balloons) were not sufficiently appealing to the children. To overcome this limitation, we propose to evaluate a more engaging, action-oriented binocular iPad game app as a binocular therapy for amblyopic children (*Big Dig*, developed by UbiSoft and provided to us by Amblyotech, Inc).

Concise Summary of Project:
In this study we use a new, more engaging binocular iPad game, *Big Dig*, to determine whether practice with a binocular iPad games app, with reduced fellow eye contrast, can improve visual acuity and reduce interocular suppression in children with amblyopia. Parents will be offered a chance to view the video game before allowing their children to participate.

Participants will include 56 children with anisometropia, strabismus, combined mechanism, or deprivation amblyopia, age 4-10 years. The participants will be randomly assigned to patch 2 hours daily patching (standard-of-care treatment) or to play the iPad *Big Dig* game app 1 hour per day 5 days per week for 2 weeks. Half of the children will have had no prior treatment for amblyopia and the other half will have had prior patching treatment; these two subgroups will be randomized separately. A blocked randomization order will be provided in sealed envelopes by our consultant statistician.

Vision will be tested at baseline and at 2-weeks. At the 2-week visit, the patching group will be crossed over to play the iPad *Big Dig* app 1 hour per day 5 days per week for 2 weeks and return for an outcome visit in 2 weeks. Children playing the *Big Dig* app will be given the option to continue for an additional 2 weeks at each visit; visits be scheduled every 2 weeks until visual acuity reaches 0.0 logMAR (20/20), or the child or parents no longer want to continue with the *Big Dig* game (maximum 8 weeks).

- Visit 1 (baseline)
- Visit 2 at 2 weeks (primary outcome to compare *Big Dig* vs patching)
- Visit 3 (required for patching group only for crossover assessment)
- Up to 3 additional visits at 2-week intervals (optional visits to track improvements in vision with continued *Big Dig* game play*)*.

At each visit, we measure visual acuity, stereoacuity, interocular suppression, and fixation stability. We will also download the iPad binocular game app log that tracks time spent playing the game app to provide an objective measure of compliance. We will provide a loaned iPad and glasses with red and green filters for the duration of therapy.

Study Procedures:

- Review of age, birth data and medical history to determine eligibility.
- Measurement of visual acuity in order to determine eligibility and, if eligible, to provide a baseline measurement.
- Measurement of stereoacuity, interocular suppression, and fixation stability to provide a baseline measurement.
- The enrolled participants will play the *Big Dig* binocular iPad game app while wearing red-green filter glasses to separate images to each eye or wear a patch over the fellow eye (standard-of-care treatment).
- Visual acuity, stereopsis, interocular suppression, and fixation stability every two weeks during the study period.

Criteria for Inclusion of Subjects:

1. Children age 4-10 years
2. Female and male
3. Amblyopia with amblyopic eye visual acuity 20/40-20/125, fellow eye visual acuity 20/16-20/25, and interocular difference in visual acuity of 3 lines or more.
4. Anisometropic (with or without microtropia) fully accommodative esotropia (no tropia present with glasses), or deprivation amblyopia
5. No strabismus greater than 5 prism diopters
6. Wearing glasses (if needed) for 8 weeks or no change in visual acuity with glasses wear for 4-6 weeks.
7. Must be able to demonstrate understanding and ability to play the *Big Dig* game app during the enrollment visit.
8. Signed informed consent obtained

Criteria for Exclusion of Subjects:

1. Prematurity ≥8 weeks
2. Coexisting ocular or systemic disease
3. Developmental delay
4. Poor ocular alignment (strabismus >5 prism diopters)

Sources of Research Material:

Some information about participants is gathered by questionnaire (names, patients' names, address, phone number, gender/race/ethnic group, date of birth, due date, health status, family history of eye disorders). Other data are gathered at the time of routine clinical examinations (refractive error, diagnosis, treatment history). Visual acuity, stereoacuity, interocular suppression, fixation stability data, game play iPad log files, and handwritten calendar logs are gathered during study visits are solely for research purposes.

Recruitment Methods and Consenting Process:

1. Pediatric ophthalmologists who have previously collaborated with RFSW in Dallas area will be sent a

description of the study rationale and design along with eligibility criteria. We will also introduce them to the study at our monthly regional pediatric ophthalmology research meeting. They will be asked to refer children who meet study criteria to RFSW. A referral sheet will be given to the parents by ophthalmologists with contact information if they wish to obtain more details about the study. At the beginning of the visit in RFSW, the research staff member will explain the study to child's parents, review the consent form, and answer their questions. After review of the consent form and answering all questions, if the parents agree to participate, they will be asked to sign a consent form. They will receive a copy of the consent form. We will also explain the study to the child and ask their parents to discuss the study with them.

2. Potential subjects will also be identified, based on the inclusion criteria, from our existing research database of patients and normal controls. These individuals will be contacted through phone or e-mail with a brief description of the study and an invitation to participate.

Potential Risks:

There are no risks of physical injury associated with participation in the study. The risks are similar to those encountered in playing video games. Minimal eyestrain may occur.

Subject Safety and Data Monitoring:

No significant risks are anticipated for any of the proposed testing procedure. The risks involved in this study are minimal to none when compared to the potential benefits. The PI, co-investigators and research personnel will monitor the subject safety problems, data integrity and will report any adverse events to the IRB immediately.

Procedures to Maintain Confidentiality:

1. All information collected from the subject will be transferred to the case report file and the master database. Data files collected in this study will be stored in a password-protected computer in a locked laboratory.
2. Only study personnel have the access code to the computer. All data are coded by patient number to protect privacy. Certain organizations may look at and/or copy the medical records for protecting the rights and welfare of human research subjects recruited to participate in this study, research, quality assurance, and data analysis. The organizations include:
    - The UT Southwestern Institutional Review Board
3. De-identified data will be shared with Amblyotech at the end of the study, to allow the developer to assess effectivenses of this new binocular iPad game amblyopia therapy.

Potential Benefits:

The participants may or may not benefit from participation in this study. Society in general will benefit from our developing a better understanding of the role that suppression plays in amblyopia. This knowledge can guide efforts to rehabilitate vision in amblyopia. Because our previous studies, which have employed a similar approach to amblyopia therapy, have shown improvement in visual acuity, there is a possibility of direct benefit to the individual subjects who participate. If the results of the study are favorable, then it has the potential to be prescribed in a clinical or home setting to benefit many amblyopic patients.

Biostatistics:

Sample size:

The primary outcome is visual acuity at the 2-week visit. Based on our prior studies (Li et al 2014a, 2014b; Birch et al 2014) and a recent study conducted by Hess et al (2014), we anticipate that binocular iPad game play for 2 weeks will result in at least 0.11±0.10 logMAR improvement in visual acuity. Based on patching studies by the PEDIG network (Repka et al 2003, 2004, 2005), we anticipate that patching

treatment for 2 weeks will result in 0.00±0.10 logMAR improvement in visual acuity. For $\alpha = 0.05$ and $1-\beta = 0.80$, the required sample size is 13 per group. Based on our historical loss to follow-up, we plan to enroll 14 children per group, i.e., 28 children total. This sample size is also sufficient to detect a difference in proportions of children who have visual acuity improvement of at least 0.1 logMAR of 70% versus 10%.

In a second phase of the study, we will continue to enroll and randomize children toward the goal of enrolling 28 additional children (56 total), including 28 with prior amblyopia treatment and 28 with no prior amblyopia treatment. This larger cohort will provide sufficient sample size to conduct exploratory analyses of the effect of baseline factors (age at enrollment, baseline visual acuity, stereoacuity, suppression, age at diagnosis, history of prior amblyopia treatment, and ocular alignment).

Analysis:

- Comparisons of binocular iPad game versus patching groups' visual acuity outcome at 2 weeks will be conducted by t-test.
- The proportion of children whose visual acuity improves by 0.1 logMAR or more in the binocular iPad game versus patching groups and their 95% confidence intervals will be calculated.
- Secondary analysis will compare binocular iPad game versus patching groups' stereoacuity outcome at 2 weeks will be conducted via Mann Whitney U test (stereoacuity is a nonparametric outcome because measurement includes a "nil" outcome category).
- Secondary analysis will compare binocular iPad game versus patching groups' depth of interocular suppression and fixation stability outcomes at 2 weeks will be conducted via t-tests.
- Compliance logs from the iPads will be tabulated and summarized with descriptive statistics.
- Secondary analysis will compare crossover iPad game play visual acuity outcome at 4 weeks versus baseline and patching visual acuity outcome at 2 weeks by paired t-tests.
- Exploratory analysis will be conducted to examine whether any of the measured baseline factors affected the amount of visual acuity improvement observed with binocular iPad game or patching.