The use of stereovision-tests in pediatric vision screening

PhD thesis

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1. Introduction

Amblyopia, also known as „lazy eye" is a disorder originating from the abnormal early development of the visual system, which is mostly irreversible in adulthood. In developed countries, where the infectious eye diseases are less common, amblyopia is the leading cause of severe visual impairment. Worldwide prevalence varies between 0,2-5,3%. In Hungary, it is between 2-3%, according to the latest available data from 2009. Early recognition is crucial, since children before the age of 7 respond better to treatment, thus vision can potentially be spared, or the degree of amblyopia can be reduced.

As a neuro-ophthalmological disorder, amblyopia interferes with several aspects of daily life as well. It can affect visuo-motor skills (e.g. eye-hand coordination), it can limit career options, and free time activities, such as sports. Adults and elderly also suffer from the consequences, as amblyopia causes instability in movement and balance. Furthermore, if the healthy eye is affected by glaucoma or trauma, the patients become practically blind, which leads to a significant decrease in the quality of life.

The goal of this doctoral thesis was the clinical testing of a dynamic random dot stereogram „E" (DRDSE) generating software developed by our laboratory, which will hopefully contribute to the screening of amblyopia and amblyogenic conditions (such as hyperopia, strabismus convergens, anismetropia, etc.), thus fostering the early recognition and treatment.

2. Methods

Bela Julesz (1928-2003), a Hungarian-born American neuroscientist laid down the principles of random dot stereograms in the 1950s and introduced the term cyclopean vision in 1971. The cyclopean eye is a „virtual third eye" located between the two eyes, whose main role is to synthesize the information coming from the right and left eyes, in this way creating a three-dimensional perception. Random dot stereograms are cyclopean stimuli, which stimulate only this „third eye"; when observing with only with the left or right eye (monocular observation), one can only see a set of random, meaningless dots. The requirement for cyclopean vision is the compatible information coming from the two eyes, which can be influenced by the above mentioned amblyogenic factors. These conditions usually lead to the impairment of binocular vision. These individuals can not perceive stereograms properly and they do not experience a three-dimensional sensation.

The principle of random dot stereograms is the following: a group of randomly arranged dots is shifted horizontally and the original space of these dots is filled with further random dots. The disparity of the shifted part changes, which is processed in the visual cortex as three-dimensional information. The fusion – which is essential for this process – starts to develop in infancy through various visual stimuli. Based on this observation, there is a certain level of maturity and age, when these tests can be performed. Using Julesz's method, a number of stereograms were created and are widely used in the ophthalmological practice, which form an integral part of the everyday clinical vision screening.

The well-known Lang I and II stereograms are most commonly used in the Hungarian practice. These A5-size plastic cards represent simple figures (mostly animals) with different disparity, and – it is assumed – these can only be identified if the stereovision is intact. It has to be highlighted that if the examined subject moves either her head or the plastic card, these binocular figures could be seen monocularly, thus creating a false impression of stereovision. Because of these circumstances, the evaluation of the Lang test can be fairly subjective, which raises numerous methodological concerns, that are described in detail in my PhD thesis. We chose the Lang test as the control test for our study due to its availability and popularity in the clinical practice.

The EuvisionTab® software (an innovation of our laboratory) has a module, which applies the principles of dynamic random dot stereograms and is suitable for the screening of stereovision. Technically, this module is a random dot stereogram generator, where the setup parameters can be set by the examiner. In this present study we tested a dynamic RDS (random dot stereogram) with a disparity-coded Snellen E optotype (DRDSE), generating the letter „E" in four orientations (left, right, up, down). The orientation of the letter „E" may only be determined with intact stereovision, while wearing red-green glasses. The stimulus was projected on a Samsung Galaxy Tab 10.1 tablet.

The disparity value was 420", the Snellen E optotype line thickness was under 2' visual angle from 25-30 cm viewing distance. Dot density was 1% with 3% uncorrelated noise, with a picture refreshment rate of 10 Hz. Before showing the 9+2 Snellen E letters to the subjects, we projected 8 other RDSE letters with easier parameter settings, in order to familiarize the children with the stimulus and the task. These letters were static (non-refreshing) or

dynamic with higher disparity values or higher dot density. The results of these 8 letters have not been evaluated, they served merely as exercise before moving on to the main task.

3. Objectives

Goals of the preliminary studies:

1. Determine testability and target population
2. Minimize monocular artefacts, and improve the stimulus

Goals of the clinical (main) study:

1. Recognize and eliminate typical errors of the stereotests widely used in clinical practice

2. Testability of the dynamic random dot stereotest „E", and comparison with the Lang test

3. Compare the sensitivity of DRDSE and the Lang test

4. Validate DRDSE in the screening of amblyopia and amblyogenic conditions

5. Develop a state of the art, easy to use software and screening protocol

4. Results

Results of the preliminary studies:

The testability study performed on a large sample size clearly demonstrated that 100% of children above the age of 3 can understand and perform the task, which was the determination of the „E" letter orientation, after a short (2-5 minutes) training session alone or in a group.

We also verified, that the success rate in testability increased with age in the screened population. This information provided the baseline when we determined the age group involved in the clinical (main) study.

The protocol designed to minimize the monocular artefacts proved that the reduction in dot density from 50% to 1% significantly reduced the monocular hit ratio, but did not affect the binocular recognizability of the stimulus (when viewing with both eyes, through red-green glasses). Since at the 1% dot intensity the monocular and binocular hit ratios did not differ significantly from the random hit ratio, we can conclude that with this dot density (1%), the monocular hit is a random effect. In the clinical study we used 1% dot density.

Results of the clinical (main) study:

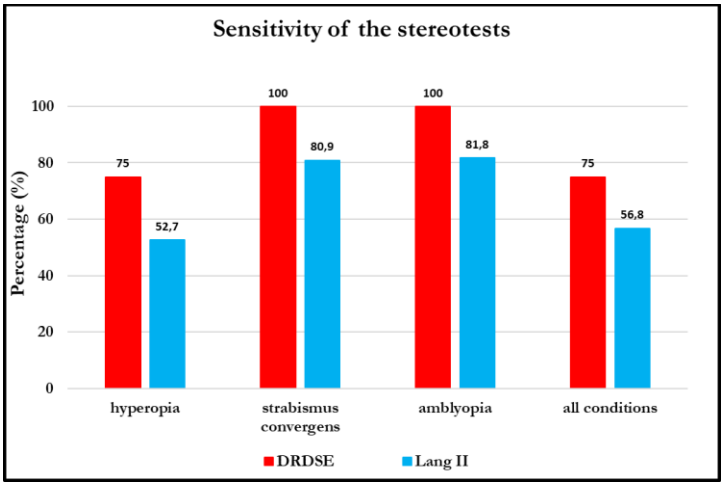
In order to establish the optimal pass/fail threshold for the DRDSE (that is, how many „E" letters should be correctly identified out of 9) to reach the highest possible sensitivity and specificity, receiver-operating characteristic curve (ROC curve) analysis was performed. ROC-analysis was conducted with every diagnosis which we intended to screen: hyperopia, strabismus convergens, amblyopia, anisometropia and as a fifth group, all

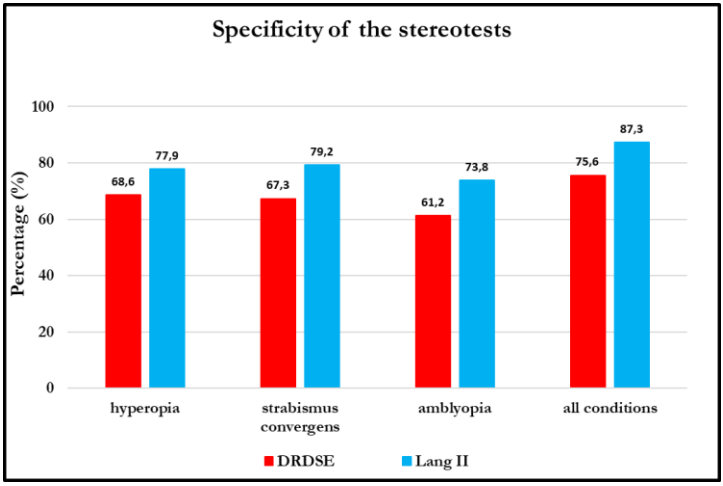
conditions together. DRDSE showed statistical significance in every group except anisometropia. The area under the curve in this case indicated the test's ability to draw a distinction between healthy individuals and patients with the studied ophthalmological conditions. In this case, DRDSE is unsuitable for screening anisometropia. When determining the pass/fail threshold for DRDSE, a „5 correct answers out of 9" proved to be statistically suitable for the screening of hyperopia, amblyopia, strabismus convergens and „all conditions". That is, a person presenting any of the above mentioned conditions will most likely fail DRDSE.

Fisher's exact test was carried out to evaluate which amblyogenic condition could be screened with the Lang test. The results demonstrated that the Lang II stereotest shows statistical significance in the screening of amblyopia, strabismus convergens and „all conditions".

To answer the question whether the screening accuracy of DRDSE and Lang differ from each other the chi-square test was applied. The null hypothesis was that the performance of the two tests are the same. The Chi.square test was applied to the group „all conditions". The resulting p-value of 0,035 (significance level p=0,001) indicated keeping the null hypothesis. We can conclude that the results of the two tests do not differ significantly from each other. In practice it means that DRDSE is at least as effective as Lang II test.

The following bar graphs represent the comparison of the sensitivities and specificities of the two tests, with exact percentages above each bar.


Sensitivity of the stereotests
Percentage (%)
100
80
60
40
20
0
75
52,7
100
80,9
100
81,8
75
56,8
hyperopia
strabismus convergens
amblyopia
all conditions
DRDSE
Lang II


Specificity of the stereotests
Percentage (%)
100
80
60
40
20
0
68,6
77,9
67,3
79,2
61,2
73,8
75,6
87,3
hyperopia
strabismus convergens
amblyopia
all conditions
DRDSE
Lang II

5. Discussion

In the present study we investigated the EuvisionTab® vision screening software's stereovision test. This novel, innovative software, which was designed for large-scale pediatric vision screening could be a milestone in the early recognition of amblyopia and amblyogenic conditions.

The ideal test is fast, easy to use, and has both high sensitivity and specificity at the same time. For screening tests, the cost-effectiveness and sensitivity are the key requirements. Poor sensitivity means a high rate of false negative cases, which increases the number of unrecognized pathologic conditions. This is ethically unacceptable. On the other hand, low specificity leads to overreferral, which places more load and pressure on the professional healthcare system. Although both measures are important for the overall efficacy, poorer specificity could be forgiven but no compromise is allowed in sensitivity. It is more acceptable to refer a child to ophthalmologist unnecessarily, than to miss any amblyopic or strabismic patient.

Many attempts have been made to investigate the efficacy of stereotests in vision screening, with the objective that they could simplify and speed up the examination. The additional information about the stereopsis status could modify the referral protocol, which nowadays mostly relies on visual acuity. This practice originates from the most common definition of amblyopia which emphasizes the decrease in monocular visual acuity, despite the fact that the decreased visual acuity is not the cause, but the direct consequence of abnormal binocular vision development. Some studies do not recommend using stereotests with low specificity and sensitivity as standalone tests for vision screening. Also, stereotests may fail to identify conditions where there is no significant loss in binocular vision, such as myopia, since symmetric

myopia alone is not a typical amblyogenic condition. These shortcomings can potentially be mitigated by constructing a stereotest with the highest possible sensitivity and specificity.

The sensitivity of DRDSE for amblyopia and strabismus convergens was 100%, the highest among all commercially available stereotests. Its lower specificity could be explained by the following theories.

The exceptional sensitivity of the test can be explained by its level of difficulty. Low-density RDS requires global stereopsis to recognize the embedded disparity coded images. The RDS density was 1% with 3% uncorrelated noise, which is probably close to the detection threshold for children. In addition to low dot density, the test was dynamic with a refresh rate of 10 Hz. The dynamically refreshing dots may add more difficulty in the perception of the disparity-coded image. The high sensitivity, which is a considerable advantage of the stimulus might go hand in hand with its disadvantage (i.e., low specificity): it is a rather difficult task even for emmetropes to accomplish. Since the pass threshold of DRDSE has been carefully optimized with the ROC analysis, it cannot be further lowered without a dramatic decrease in sensitivity. In order to reduce the level of difficulty, we may need to design different screening sets with increased dot density and/or reduced noise level, in favor of elevating the specificity of DRDSE, while preserving high sensitivity.

Co-existing but potentially non-amblyogenic ophthalmologic conditions may hinder stereopsis and increase the number of false positive cases. Astigmatism (n = 6) and myopia (n = 8) were the most frequent refractive errors in our sample. We calculated a mean diopter for myopic patients (o.d. mean, − 2.1D and SD 1.8; o.s. mean, − 2.0D and SD 1.9). Based on this

information, we suspect that a certain degree of myopia alone or combined with astigmatism might lead to a decrease in stereovision. The effect of astigmatism on stereopsis is especially severe when the difference in the angles between the two eyes is more than 45°. In our dataset, only two patients had 40° or greater difference, which is insufficient for drawing meaningful conclusions. Despite this fact, our results are in accord with the findings of international literature: Yang et al. and Kulkarni et al. demonstrated in their recent large-scale studies a correlation between myopia, astigmatism, and reduced stereopsis.

We managed to prove with statistical analysis that sensitivity of DRDSE is higher and its specificity is lower than of the Lang II, which test is widespread in the Hungarian clinical practice. To eliminate the main limitation of the DRDSE method – which is the weaker specificity -, more clinical studies with different stereo sets are needed. There is a currently active cooperation with Spanish reseachers to address this problem.

Larger-scale screenings are needed, involving hundreds of children, to validate DRDSE - which is the other limitation of this present study. Despite these limitations, we can conclude that the EuvisionTab® vision screening software fits in the trend of the 21st century stereovision-research, which – after further research and improvement – would potentially become a screening tool for everyday use.

To sum up the most important findings of this clinical study, we conclude that the DRDSE test can be completed in about 5–7 min (including the explanation of the task to the children) and is easy to use (after a short training) for non-professional examiners such as teachers, parents, district

nurses, or social workers. As for the technical background, a tablet with the appropriate software and red-green spectacles are required.

6. Acknowledgements

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7. Publications

7.1. Article related to this thesis

Budai, A., Czigler, A., Mikó-Baráth, E. G. Jandó et al. (2019) Validation of dynamic random dot stereotests in pediatric vision screening. Graefes Arch Clin Exp Ophthalmol, 257:413–423 **IF: 2,249**

7.2 Article unrelated to this thesis

E. Mikó-Baráth; K. Markó; **A. Budai**; B. Török; I. Kovacs; G. Jandó (2014) Maturation of Cyclopean Visual Evoked Potential Phase in Preterm and Full-Term Infants. Investigative Ophthalmology & Visual Science, Vol.55, 2574-2583 **IF: 3,660**

Cumulative impaxct factor: 5,909

7.3. Abstracts related to this thesis (citable)

1. Csizek, Zs ; David, P Piñero ; Mikó-Baráth, E ; **Budai, A** ; Pedro, Ruiz Fortes ; Carlos, Javier Hernández Rodríguez ; Roberto, Soto Negro ; Jandó, G: New stereotest – sensitivity and specificity.Medical Conference for PhD Pécs, Magyarország : Pécsi Tudományegyetem Doktorandusz Önkormányzat, (2019)

2. Zsófia Csizek, David P. Piñero, Eszter Mikó-Baráth, **Anna Budai**, Pedro Ruiz Fortes, Carlos Javier Hernández Rodríguez, Roberto Soto Negro, Gábor Jandó: New stereotest – sensitivity and specificity. 42st European Conference on Visual Perception (ECVP)

2019 Leuven. Perception, 48 (2_suppl), 1–236. DOI: 10.1177/0301006619863862

3. Eszter Mikó-Baráth, **Anna Budai**, David Pinero, Janka Juszt, Vanda Nemes, András Czigler and Gábor Jandó: Comparison of a tablet based and chart projector visual acuity tests. 41st European Conference on Visual Perception (ECVP) 2018 Trieste. Perception, 48 (1_suppl), 1-233. DOI: 10.1177/0301006618824879
4. **Anna Budai**, Andras Czigler, Petra Juhasz, Vanda Nemes, Agota Pusztai and Gabor Jando: The evaluation of dynamic stereotests in the screening of amblyopia – a clinical study. 39th European Conference on Visual Perception (ECVP) 2016 Barcelona. Perception, 45(2_suppl), 1–383. DOI: 10.1177/0301006616671273
5. Csizek Zs, Fülöp D, Nemes V, **Budai A**, Mikó-Baráth E, D'Orlando F, Caporusso G; Agostini T, Jandó G: Feasibility of dynamic stereovision tests in amblyopia screening. IBRO Workshop: Debrecen, Magyarország, 2014.01.16 -2014.01.17. Paper P186.
6. Katalin Markó, Eszter Mikó-Baráth, **Anna Budai**, Tímea Dani, Selim Sevinc, Márton Gyenge, Mónika Schwöller, Zsuzsanna Pámer, Zsolt Bíró, Gábor Jandó: Comparison Of Dynamic Random Dot E Stereo Test And Lang II Test: Testability And Reliability In Preschool Children ARVO Annual Meeting 2011 Florida, Amerikai Egyesült Államok, 2011.05.01-2011.05.05. Paper 2512/D827.
7. Mikó-Baráth E; Markó K; **Budai A**; Dani T; Sevinc S; Gyenge M; Schwoller M; Pamer Z; Bíró Z; Jandó G, Screening of binocular function with static- and dynamic random dot E stereograms in preschool population, (poszter), MITT XIII. konferenciája, Budapest, 2011. január 20-22. http://mitt2011.elte.hu/Posters/P6/P6.19.pdf

7.4. Oral presentations related to this thesis

1. Csizek, Zsófia; Mikó-Baráth, Eszter ; **Budai, Anna** ; David, P Piñero ; Pedro, Ruiz Fortes ; Carlos, Javier Hernández Rodríguez ; Roberto, Soto Negro ; Jandó, Gábor: Új sztereoteszt alkalmazhatósága – szenzitivitás és specificitás; Huszonegyedik Magyar Látás Szimpózium (2019)

2. **Budai Anna:** A tompalátásról és szűréséről – múlt, jelen, jövő. Orvos-és egészségtudományok I. szekció, XX. Tavaszi Szél Doktorandusz Konferencia, Miskolc (2017)
3. **Budai Anna:** Dinamikus sztereotesztek értékelése az amblyopia szűrésében – egy klinikai vizsgálat eredményei. 19. Magyar Látásszimpózium, Szeged (2017)
4. Csizek Zsófia, Fülöp Diána, **Budai Anna:** Statikus és dinamikus sztereotesztek alkalmazása óvodáskorú gyerekek látásszűrésében. I. helyezés, Országos Tudományos Diákköri Konferencia Orvos-és Egészségtudományi Szekció, Budapest (2015)
5. **Budai Anna:** A random pont sztereotesztek értékelése a klinikai gyakorlatban. II: helyezés. Idegtudományi Centrum II. TDK – és PhD – konferenciája, Pécs (2015)
6. **Anna Budai:** Screening of amblyopia in preschool children – first results of a clinical study. 47th Annual Meeting of HMAA, Sarasota, Florida,USA (2015)
7. **Budai Anna:** A gyermekkori tompalátás korszerű szűrése – egy klinikai vizsgálat első eredményei. Tavaszi Szél Doktorandusz Konferencia, Eger (2015)

8. **Anna Budai**, Zsófia Csizek,Diána Fülöp: Visual screening of preschool children- case presentation, 46th Annual Meeting of HMAA, Sarasota, Florida, USA (2014)
9. Csizek Zsófia, Fülöp Diána, **Budai Anna**: Vizuális kiváltott válasszal előre jelezhető a tompalátás? II. helyezett, Országos Tudományos Diákköri Konferencia, Szeged (2013)
10. **Budai Anna**, Csizek Zsófia, Fülöp Diána: Vizuális kiváltott válasszal előre jelezhető a tompalátás? Legjobb magyar nyelvű előadás díja (Istvan Mechtler Award) Magyar-Amerikai Orvosszövetség Konferenciája, Balatonfüred (2013)
11. **Anna Budai**, Zsófia Csizek, Diána Fülöp: Can visual evoked potential predict amblyopia? 45th Annual Meeting of HMAA, Sarasota, Florida,USA (2013)
12. **Budai Anna**, Csizek Zsófia, Fülöp Diána: DRDS-E, mint új típusú gyermekkori látásszűrő vizsgálat: monokuláris artefaktok kiküszöbölése. I. helyezés, Házi TDK Konferencia, Pécs (2012)
13. **Anna Budai:** New methods in the screening of stereovision in preschool children. Magyar-Amerikai Orvosszövetség Konferenciája, Balatonfüred (2011)
14. **Budai Anna**: Egy újfajta térlátás-vizsgálati módszer klinikai alkalmazása - esetbemutatás. Grastyán Endre Nemzetközi és Interdiszciplináris Konferencia, Pécs (2011)
15. **Budai Anna**, Dani Timea: A dinamikus véletlen pont sztereogramok jelentősége a kisgyermekkori látásszűrésben. I. helyezés, Házi TDK Konferencia, Pécs (2011)
16. **Budai Anna**, Dani Timea: A dinamikus véletlen pont sztereogramok jelentősége a kisgyermekkori látásszűrésben. III.

helyezés, Országos Tudományos Diákköri Konferencia Orvos-és Egészségtudományi Szekció, Debrecen (2011)

17. **Budai Anna:** Alkalmas-e a random pont E sztereogram a tompalátás korai szűrésére? Jánossy Ferenc Emlékkonferencia, Budapest (2011)
18. **Budai Anna**, Dani Timea: A térlátás vizsgálata 7 év alatti gyermekeknél, az amblyopia szűrése. Legjobb előadó díja, Grastyán Endre Nemzetközi és Interdiszciplináris Konferencia, Pécs (2010)

7.5. Other presentations related to this thesis

1. Csizek, Zs; Mikó-Baráth, E; **Budai, A**; Szabó-Guth, K; Pusztai, Á; Csutak, A; Piñero, DP; Jandó, G: Innovative medical diagnostic device: detection of amblyopia. Paper: 2670 (2020)

2. Csizek, Zs; Mikó-Baráth, E; Piñero, DP; **Budai, A**; Szabó-Guth, K; Hegyi, P ; Pusztai, Á ; Csutak, A ; Jandó, G: Mobile devices in vision screening: examination of stereovision. Paper: 395 (2020)

3. David Pablo Piñero, Eszter Mikó, Pedro Ruiz, **Anna Budai**, Carlos Javier Hernández, Zsofia Csizek, Roberto Soto, Gabor Jandó: Sensibilidad y especificidad de un nuevo test de estereopsis en tablet para el screening de la ambliopía. OPTOM Meeting Valladolid, Spanyolország (2019)
4. **Anna Budai**, András Czigler, Petra Juhász, Gábor Horváth, Eszter Mikó-Baráth, Ágota Pusztai, Gábor Jandó: Capacidad de screening en el ámbito de la ambliopía de un nuevo test de estereopsis dinámica. 25. Congreso Internacional de Optometría, Contactología y Óptica oftálmica, Madrid, Spanyolország (2018)
5. Guth, K; **Budai, A**; Szabó, I; Jandó, G
   Modernkori informatika a látásszűrés szolgálatában.
   Tavaszi Szél Konferencia 2017: Nemzetközi Multidiszciplináris Konferencia Budapest, Magyarország: Doktoranduszok Országos Szövetsége (2017)
6. Guth, K; **Budai, A**; Szabó, I; Jandó, G: Látásszűrés az informatika segítségével. Tavaszi Szél = Spring Wind 2017 [tanulmánykötet] 2. Budapest, Magyarország: Doktoranduszok Országos Szövetsége, (2017)

7. **Budai A**, Czigler A, Juhász P,Horváth G, Mikó-Baráth E, Pusztai Á, Jandó G: Comparing random dot stereotests with the Lang test in the ophthalmological practice. FENS Regional Meeting, Pécs (2017)
8. Mikó-Baráth E, **Budai A**, Fülöp D, Nemes V, Kerekes J, Juszt J, Guth K, Horváth G, Szabó I, Buzás P, Jandó G: Increasing the sensitivity of a new, web-based amblyopia screening application. FENS Regional Meeting, Pécs (2017)
9. **Budai Anna**, Czigler András, Juhász Petra, Nemes Vanda, Pusztai Ágota, Jandó Gábor: Dinamikus sztereotesztek értékelése az amblyopia szűrésében. Magyar Farmakológiai, Anatómus, Mikrocirkulációs és Élettani Társaságok Közös Tudományos Konferenciája, Pécs (2016)
10. **Anna Budai**, András Czigler, Petra Juhász, Zsófia Csizek,Vanda A. Nemes, Gábor Jandó: Screening of amblyopia in preschool children – first results of a clinical study. IBRO Workshop, Budapest (2016)
11. **Budai Anna**, Juhász Petra, Csizek Zsófia, Dr. Mikó-Baráth Eszter, Dr. Nemes Vanda, Dr. Jandó Gábor: A dinamikus random pont sztereoteszt szerepe óvodáskorú gyermekek amblyopia-szűrésében. Magyar-Amerikai Orvosszövetség Konferenciája,Balatonfüred, (2015)
12. **A.Budai**, Zs.Csizek, D.Fülöp, E.Mikó-Baráth, V. Nemes, F.D'Orlando, G. Caporusso, T. Agostini, G.Jandó:Feasibility of dynamic stereovision tests in amblyopia screening. 1st Innovation in Science 2014 – Doctoral Student Conference, Szeged (2014)
13. **A.Budai**, Zs.Csizek, D.Fülöp, E.Mikó-Baráth, V. Nemes, F.D'Orlando, G. Caporusso, T. Agostini, G.Jandó: Psychophysical dynamic stereovision tests in amblyopia

screening. Trieste Symposium on Perception & Cognition, Trieszt, Olaszország (2014)

14. Eszter Mikó-Baráth, Katalin Markó, **Anna Budai**, Timea Dani, Selim Sevinc, Márton Gyenge, Mónika Schwöller, Zsuzsanna Pámer, Zsolt Bíró, Gábor Jandó: Screening of binocular functions with static- and dynamic random dot E stereograms in preschool population, MITT-Congress (2011)
15. Mikó-Baráth E, **Budai A**, Dani T, Gyenge M, Jandó G: Screening of stereovision in preschool children, MÉT kongresszus (2010)

7.6 Theses, grants

1. **Budai Anna:** A dinamikus random pont sztereogramok jelentősége a kisgyermekkori látásszűrésben. I. helyezés, Dékáni pályamunka pályázat, Pécs (2013)
2. **Budai Anna:** A dinamikus véletlen pont sztereogramok jelentősége a kisgyermekkori látásszűrésben. Eötvös Loránd Hallgatói Ösztöndíj (2013)
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