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ORIGINAL

Evaluation the effectiveness of the cognitive rehabilitation therapy model for improvement executive functions in high- functions autistic children, by using neuroimaging, neuropsychological and molecular genetics technique

Evaluación de la eficacia del modelo de terapia de rehabilitación cognitiva para la mejora de las funciones ejecutivas en niños autistas de altas funciones, mediante el uso de técnicas de neuroimagen, neuropsicológicas y de genética molecular

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Abstract

Background: Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized mainly by difficulty in social communication and impaired executive performance. Executive functions are cognitive multi-dimensional capabilities required for complex behaviors. In recent years, serious efforts have been made better to understand certain executive deficiencies in children with ASD. Herein, we used a D-KEFS-based training program to increase the executive performance of autistic children on the Wisconsin card sorting test (WCST). Also, we evaluated children's brain activity using electroencephalography (EEG) during the training course and their expression profile of BDNF, CREB1, and FOXP2 genes, which are associated with neural development.
Methods: Twenty autistic children referred to clinics and mental counseling centers were enrolled in this non-randomized before-after trial compared to twenty normal children. The WSCT as pre and post-test was used to evaluate the training program's effectiveness on executive functions. Blood samples were obtained for gene expression, and all subjects were evaluated with a five-minute closed-eye EEG. The D-KEFS training program was conducted for patients for five weeks.
Results: improvement of executive functions after the training program and increase in expression level of BDNF and CREB1 genes in autistic subjects showed in results. Also theta and bdelta waves were increased in cortical areas of children with autism after five weeks training.
Conclusion: The study results showed that cognitive rehabilitation therapy might improve executive functions in children with ASD, probably through gene expression and neural activity alterations.

Key words: Autism spectrum disorder (ASD), cognitive rehabilitation therapy (CRT), Delis-Kaplan executive function system (D-KEFS), Wisconsin Card Sorting Test (WCST), BDNF, CREB1, FOXP2, gene expression, electroencephalography (EEG).

Resumen

Antecedentes: El trastorno del espectro autista (TEA) es un trastorno del neurodesarrollo caracterizado principalmente por la dificultad en la comunicación social y el deterioro de las funciones ejecutivas. Las funciones ejecutivas son capacidades cognitivas multidimensionales necesarias para los comportamientos complejos. En los últimos años, se han hecho serios esfuerzos para comprender mejor ciertas deficiencias ejecutivas en los niños con TEA. En este caso, utilizamos un programa de entrenamiento basado en el D-KEFS para aumentar el rendimiento ejecutivo de los niños autistas en la prueba de clasificación de tarjetas de Wisconsin (WCST). Además, evaluamos la actividad cerebral de los niños mediante electroencefalografía (EEG) durante el curso de entrenamiento y su perfil de expresión de los genes BDNF, CREB1 y FOXP2, asociados al desarrollo neuronal.
Métodos: Veinte niños autistas remitidos a clínicas y centros de asesoramiento mental se inscribieron en este ensayo no aleatorio de antes y después en comparación con veinte niños normales. Se utilizó el WSCT como pre y post test para evaluar la eficacia del programa de entrenamiento en las funciones ejecutivas. Se obtuvieron muestras de sangre para la expresión génica, y todos los sujetos fueron evaluados con un EEG de ojos cerrados de cinco minutos. El programa de entrenamiento D-KEFS se llevó a cabo para los pacientes durante cinco semanas.
Resultados: se observó una mejora de las funciones ejecutivas tras el programa de entrenamiento y un aumento del nivel de expresión de los genes BDNF y CREB1 en los sujetos autistas. También las ondas theta y bdelta aumentaron en las áreas corticales de los niños con autismo después de cinco semanas de entrenamiento.
Conclusión: Los resultados del estudio mostraron que la terapia de rehabilitación cognitiva podría mejorar las funciones ejecutivas en los niños con TEA, probablemente a través de la expresión de genes y las alteraciones de la actividad neuronal.

Palabras clave: Trastorno del espectro autista (TEA), terapia de rehabilitación cognitiva (TRC), sistema de función ejecutiva Delis-Kaplan (D-KEFS), test de clasificación de tarjetas de Wisconsin (WCST), BDNF, CREB1, FOXP2, expresión génica, electroencefalografía (EEG).

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder diagnosed by symptoms based on (1) deficits in communication and social connections and (2) repetitive, stereotyped behaviors[1]. This condition has been considered a spectrum due to vast, heterogeneous manifestations. For instance, cognitive and verbal disabilities are more severe and profound in some patients than others, and therefore, some have better intellectual and communication abilities[2,3]. In other words, autistic children are known as non-verbal children. ASD often interferes with the development of social and communication skills[1].

In the year 2019, the prevalence of autism has been estimated at 1 in 160 children, globally[4]. Generally, ASD is four times more frequent in males than females[5]. The ASD prevalence increased in recent decades; for instance, it was increased in the united states from 5-4 per thousand in 1990 to one in 50 in 2013[6].

Generally, ASD is associated with cognitive and psychological problems, such as mental retardation, attention deficit-hyperactivity disorder (ADHD), irritability, and anxiety. Inability to understanding and recognizing emotions is one of the most prominent features of ASD and is probably one of the main problems in their social relationships[7]. These problems make it very difficult to be present in the community as an active, self-reliant, and successful person, which poses serious challenges for their parents, teachers, and caregivers[1].

The exact underlying etiopathogenesis of ASD is still unclear, but several mechanisms have been proposed in recent years, including genetic and neurologic alterations[8]. Mounting evidence argues that a single factor does not cause ASD, but the interaction between environment and genetic factors may be responsible[7,9-11]. Today, ASD is considered a deficit in neurobiological development, strengthened by evidence stressed on its biological background and proposed etiopathogenesis related to neonatal period[10,12-14]. The cognitive and behavioral defects of ASD can be seen in 18-24-month-olds, but a definite diagnosis can be made at the age of three, which means that these traits are evident in the early years of life[9].

Several genetic factors have been introduced in ASD, including alterations in X, 7, 12, and 22 chromosomes. Point mutations in genes, including GluR6, PTEM, WNT2, and FMR1, in addition to epigenetic modifications, alter gene expression[15]. For instance, ASD has been reported in 15-60% of patients with fragile X syndrome, which is attributed to the fmr1 gene deletion or variants 15. Further, neurobiological evidence demonstrated abnormal frontal lobe function, the executive function's main structure[16-18]. Also, ADS cognitive function deficits in ASD, often attributed to anterior cingulate cortex (ACC) function, a region responsible for storing information and impulse control[19]. Although cognitive functions are not attributed to a single region, various regions are involved in different executive functions.

Treatment options for ASD symptoms are very limited and mainly designed to better control the disease, but well-designed educational interventions may improve these symptoms and increase their communications[20]. Accordingly, cognitive rehabilitation therapy improves the executive functions of autistic children effectively[15]. Cognitive rehabilitation is a complex method design to increase understanding, comprehension, attention, learning, recall, and problem-solving in individuals with neuropsychological disorders, such as ASD[21].

In recent years, grave attempts have been made to improve individual executive performance in ASD children[22], but most research focused on communication issues, and executive functions' promotion was less considered[23]. Although previous studies have examined the differences between autistic children, efforts continue to provide a novel treatment strategy focused on executive functions in ASD children. This study aimed to evaluate educational interventions' effectiveness to increase executive functions in autistic children, and its influence on underlying neurobiology.

Materials and methods

Subjects

We designed this non-randomized controlled before-and-after study on twenty children diagnosed with autism (study group) and twenty matched non-autistic healthy children at the age between 6-12 years-old (control group) in Tehran, Iran in 2018, aiming evaluation the cognitive rehabilitation intervention on psychoneurological and genetic profiles of executive functions. The study protocol was approved by Informed consent from parents or legal guardians was obtained.

The inclusion criteria for cases was the Intelligence Quotient (IQ) score >70. The exclusion criteria were as followed: **1.** History of any narcotic, recreational drugs, or alcohol consuming abuse in both the study and control groups and their parents. **2.** Any mental or intellectual problem in both study and control groups. The IQ test was obtained to exclude subjects with intellectual problems in control and subjects with IQ scores less than or equal to 70 in the study group. **3.** Any psychologic problems in the control group were screened with a non-structured psychiatric interview performed by the study psychiatrist. **4.** Any physical problem or disability, which can be a potential confounding factor. **5.** Coincide ASD and ADHD. **6.** Significant experienced physical or emotional trauma in the last four months due to the gene expression profile's potential effect.

Delis-Kaplan Executive Function System (D-KFES) training programs

The training program was planned to improve executive functions based on D-KFES in the study group. The training program duration was five weeks, including playing sessions for 15 minutes per day. The playing session was done in a quiet room with minimal auditory and visual disturbance in the examiner's presence.

This program consisted of three types of tests; Trail Making Test, to improve the flexibility of thinking; Color-Word Test, improve the ability of fast respond; and Sorting Test to improve the planning, memory, attention, and problem-solving abilities.

The Delis-Kaplan Executive Function System (D-KEFS) is a standard assessment tool to evaluate a wide range of verbal and non-verbal executive functions. D-KEFS includes nine independent subtests that comprehensively assess children and adults' executive functions.

Wisconsin Card Sorting Test (WCST)

The WCST is a neuropsychological assessment tool used to measure problem-solving skills, classification, abstract thinking, concept formation, and cognitive flexibility, all attributed to the frontal lobe function. Both healthy subjects and patients (before and after the intervention) were assessed with WCST[1]. An expert trainer explained the method for each participant to perform the test. Participants must match the number of shown cards to one of four card categories. The matching can be done by shape, color, or number. After 10 consecutive correct matchings, the rule of matching changes and shift to a new rule of matching. After each matching set was completed, it was called the "completing set." The matching rules change up to 5 sessions. We measured three outcomes of WCST in this study: the number of preserved errors (PE), the number of completing sets (NOC), and the total of errors (ΣE).

Gene expression analysis in blood

We used peripheral blood samples from subjects and stored in EDTA tubes at 4ºC. RNA extracted from blood by usisng commercial RNA etraction kits and cDNA synthesed from RNA samples. The expression of FOXP2, CREB1, and BDNF as target genes and the GAPDH gene as a refrence gene was examined with Real-time polymerase chain reaction (Real time PCR).

Table I: Primer sequences used for Real time PCR assessment.

Forward Primer BDNF	5'CTGTAGTCGCCAAGGTGGTT3'
Reverse Primer BDNF	5'AAGTGCTAGGAAGAGCCGTG3'
Forward primer GAPDH	5'AAGGGCCCTGACAACTCTTT3'
Reverse primer GAPDH	5'CTCCCCTCTTCAAGGGGTCT3'
Forward primer FOXP2	5'TGGCATTAAACATGGAGGGC3'
Reverse primer FOXP2	5'TTTGGAAGTGTTGGAGGAGGT3'
Forward primer CREB1	5'CCCGAAGAAACCCGAAGGTCT3'
Reverse primer CREB1	5'GGCCGCGCACGGAAAC3'

RNA extraction, cDNA synthesis and Real time PCR procedure were conducted based on previous study[24]. Primer sequences of genes were presented in **table I.**

Electroencephalography (EEG)

The EEG recording was used to evaluate the training program (intervention) impact on cortical activities. We compared the EEG results with gene expression results for a possible relationship between EEG pattern and gene expression. Twenty-one channels of EEG were recorded with a Negar amplifier in an isolated faraday room using Ag/AgCl electrodes in the linked-ear montage. The sampling rate was 256 Hz and a 40 Hz low-pass filter was applied. EEG was recorded using a nineteen channel Electrocap® and electrodes impedance was kept under 10 kΩ. Linked-ear montage was used for recording. EEG cancelation was minimized in this montage. Five minutes of EEG was recorded in eyes closed condition. Artifact rejection was performed by using z-score based algorithm, applied by Neuroguide software (www.appliedneuroscience.com). The algorithm works based on amplitude and frequency. The acceptable z-scores were selected between -1.96 and +1.96 by 95% accuracy. The average of signal remaining was 184 seconds after the automatic artifact rejection. Finally 60 artifact free signal segments with length of 3 seconds. The selection was performed from entire signals and the test-retest and split half tests for all EEG channels were remained over 0.9.

Statistical analysis

We used SPSS software v. 22.0 (IBM Corp. USA). The level of statistical significance is considered a p-value of less than 0.05. Descriptive data are expressed as mean ± SD (range), and the level of statistical significance was set at $P<0.05$. One-way ANOVA analysis was used for multiple group comparisons, statistical differences. Pearson correlation test was used for asseements of relations between variables.

Results

In the present study, 20 children (15 boys and 5 girls) with the confirmed diagnosis of ASD (the study group) and 20 sociodemographicly matched non-psychitric children were enrolled as the study populationwith age range 0f 8±4 years and 8±2 years, respectively. Also, the IQ score was 91±4 in the study group and 108±10 in the control group. There was no statistically significant difference regarding sex, age, and IQ score. Data were presented in **table II**.

Table II: Demographic data and IQ score of the study population.

Group		Patient	Control	p-value
Age		8±4.3	8±2.5	0.44
Gender	Male Female	15 boys 5 girls	14 boys 6 girls	0.58
IQ score		91±4	108±10	0.33

Table III: The results of Wisconsin test in control and study (before and after the training program).

No. of Comparisons	Group	Number of completed sets (NOC)		Preserved error (PE)		Total of errors (ΣE)	
		Mean	p-value	Mean	p-value	Mean	p-value
1	Control Study (before)	2.9 1.9	0.01	12.2 27.6	0.02	31.3 60.4	0.01
2	Control Study (after)	2.9 2.2	0.01	12.2 20.3	0.02	31.3 52.3	0.29
3	Study (before) Study (after)	1.9 2.2	0.04	27.6 20.3	0.18	60.4 52.3	0.03

Table IV: Results of BDNF, CREB1 and FOXP2 genes expression comparison between control and Autistic children (before and after the training program) groups.

Gene	Comparisons	Ratio (fold change)*	p-value
BDNF	Autistic children (before) vs. Control Autistic children (after) vs. Control Autistic children (before) vs. Autistic children (after)	0.55 0.89 0.66	0.01 0.03 0.04
CREB1	Control vs. Autistic children (before) Control vs. Autistic children (after) Autistic children (before) vs. Autistic children (after)	0.62 0.78 0.54	0.02 0.04 0.04
FOXP2	Control vs. Autistic children (before) Control vs. Autistic children (after) Autistic children (before) vs. Autistic children (after)	0.89 0.95 0.93	0.09 0.24 0.21

* by 2-ΔΔCT method.

WCST results

We used WCST to examine higher-level cognitive abilities in the control and the study group (before and after the intervention). The result of the WCST is summarized in **table III**. The results of WCST showed that all three outcomes (i.e., NOC, PE, and ΣE) were significantly lower in the study group before the treatment compared to the control group ($p<0.01$). However, the ΣE in the study group significantly decreased after the training program, compared to before the training program ($p=0.03$, **table III**).

Gene expression

mRNA level of FOXP2, CREB1, and BDNF genes evaluated by using Real-time PCR. The results of gene expression comparison inmcluding flod changes and statistical analysis presented in **table IV**.

EEG study

The frequency band analysis of EEG results showed low frequency of Dleta, Theta and Alpha in ASD group compared with control group. After the treatment increase in frequency of Dleta, Theta and Alpha were observed in ASDs. Correlation study between the gene expression results and EEG studies show a significant correlation between theta frequency and expression of BDNF and CREB1 among the study group. Data were presented in **table V**.

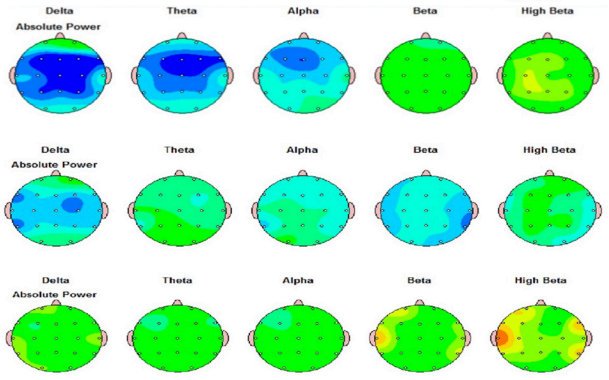
Table V: Correlation study of gene expression results and EEG frequency band.

Waves	CREB1	FOXP2	BDNF
Alpha	R: 0.15 p value: 0.34	R: 0.41 p value: 0.07	R: 0.18 p value: 0.63
Beta	R: 0.28 p value: 0.39	R: 0.18 p value: 0.33	R:- 0.18 p value: 0.53
Theta	R: 0.78 p value: 0.002	R: 0.12 p value: 0.43	R: 0.44 p value: 0.02
Delta	R: 0.29 p value: 0.19	R: 0.21 p value: 0.17	R:- 0.32 p value: 0.2
High Beta	R: 0.35 p value: 0.16	R: 0.42 p value: 0.09	R: -0.27 p value: 0.11

Discussion

The global incidence of ASD was progressed in recent decades[4], and a better understanding of the disease's neurobiological complexities seems indispensable, aiming to improve the treatment interventions[6]. Typically, ASD is a heterogeneous disease, with a complex interaction between environmental and genetic factors[20,25,26]. Hence, there is no definite treatment, and current strategies mainly aim to control the condition and increase the quality of life and communication with the environment. In the present study, we explored the cognitive rehabilitation strategy's effects based on the D-KEFS, and assessed the outcome with psychological, electrophysiological and molecular assessments.

Figure 1: Fourier analysis of three groups, first line from the above is ASDs before treatment, second line refer to ASDs after treatment and last line from the above is referring to normal children.



Executive functions are high-cognitive and metacognitive functions that carry a set of higher abilities, consisted of self-control, inhibition, self-initiation, strategic planning, cognitive flexibility, and impulse control. These functions are compromised in neuropsychological and neurodevelopmental disorders, including ASD. Cognitive rehabilitation is shown might be effective in such diseases. Kenworthy et al. revealed that early educational rehabilitation in autistic children could improve sociability, flexibility, and problem solving[27]. Rezaei et al. demonstrated that emotional control education might increase social cognition and executive reaction in children with ASD[28]. Studies have shown that D-KEFS-based training programs, designed to increase cognitive and behavioral performance, can increase the executive performance in schizophrenic and ADHD patients (ref). However, the program's effectiveness in children with autism has not been studied. Hence, neuropsychological tests are widely recognized as reliable and valid tools for executive assessment.

Previously, Brady et al. explored the executive functions in autistic adolescents using D-KEFS and revealed that despite the normal and acceptable executive functions in this group, their performance significantly differed compared to non-autistic, matched control[29]. Boyer et al. examined adolescents' planning skills with ADHD using all D-KEFS subtests and showed that only 1% of the study subjects had impaired planning functionality[30]. Herein, we applied WCST in the present study to evaluate the D-KEFS-based training program's effectiveness. The WCST results showed that the training program could improve the executive function in children with ASD compared to matched control groups and results before the training program. The EEG showed only modest alterations in cortical activities than before the training program.

Different brain regions, including the prefrontal area and parietal cortex, are involved in various cognitive functions (such as attention, perception, unconscious processing, working memory, and decision making). Solomon et al. studied the connection between brain regions and executive functions in ASD using functional magnetic resonance imaging (fMRI) studies. Their study demonstrated that functional connectivity between frontoparietal regions was lower than matched controls. Just et al. studied regions associated with inhibition in autistic adolescents compared to matched controls and found that these areas were hypoactive in autistic subjects[19].

In recent decades, studies are shifted toward the neurobiological basis of cognitive disorders. Mounting evidence emphasized the role of environmental factors, such as pollutions, infectious disease, and alcohol or substance abuse during the neonatal period. Several hypotheses about the neurobiology of ASD have been proposed, such as inflammatory or immune system responses, consequently affecting the cognitive and behavioral functions[6,20,31,32]. Other hypotheses.

With the advantage of microarray and DNA sequencing methods, exploring the connection between genes and diseases emerged. Up to now, several genetic candidates have been introduced for ASD, but they are not currently used in routine clinical settings[2,33-37]. Abbasi et al. showed that NRG1 expression is associated with working memory, inhibition, and consciousness in autistic children[38]. Numerous genes are proposed in the brain's cognitive functions, such as BDNF, CREB1, and FOXP2. The BDNF is a known factor implicate in neuroplasticity. The CREB1 is a member of transcription factors associated with learning and memory, and the FOXP2 is a known genetic factor involved in language development and verbal communication skills in humans. We explored the training program's effectiveness on BDNF, CREB1, and FOXP2 gene expression.

Previous reports demonstrated the association between cognitive disorders and candidate genes' expression status, such as BDNF[12,29,39-42]. However, the rehabilitation program's effect on gene expression is not well-studied. Although these genes' expression was lower in the study group before and after the intervention compared to healthy subjects, the expression level significantly increased after the intervention. This observation may be correlated with improved executive functions in the study group.

Our study could be considered as pilot study for a potential treatment for Autistic children with cognitive disabilities. There were several limitations in present study including lack of samples, short training time and lack of comprehensive cognition testings.

Conclusion

We evaluated cognitive rehabilitation's effectiveness in autistic children with psychologic tests in conjugation with genetic and electrophysiological assessments. The results showed that improvement with cognitive training program might be associated with modifications in genes and neural activity, which indicates a strong influence of the environment on patients with ASD's neurobiology. Our results can help signify the educational program's role in disease management.

Author Contributions

Fazlollah Shahraki, was the study designer. He was involved in clinical and laboratory data collection and analysis of data. he was also participated in writing the manuscript.

Peyman Hassani-Abharian was the head of the research team. He was involved in clinical and laboratory data collection, data analysis and editing the manuscript.

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Interests conflict

The researchers declare that they have no conflict of interest.

References

1. Fletcher-Watson S, McConnell F, Manola E, McConachie H. Interventions based on the Theory of Mind cognitive model for autism spectrum disorder (ASD). *Cochrane database of systematic reviews*, 2014.

2. Gross C. Defective phosphoinositide metabolism in autism. *Journal of neuroscience research*. 2017; 95: 1161-73.

3. Jiujias M, Kelley E, Hall L. Restricted, repetitive behaviors in autism spectrum disorder and obsessive-compulsive disorder: a comparative review. *Child Psychiatry & Human Development*. 2017; 48: 944-59.

4. Elsabbagh M, Divan G, Koh YJ, Kim YS, Kauchali S, Marcín C, et al. Global prevalence of autism and other pervasive developmental disorders. *Autism research*. 2012; 5: 160-79.

5. Christensen DL, Baio J, Braun KV, Bilder D, Charles J, Constantino J, et al, Lee LC 2018. Prevalence and characteristics of autism spectrum disorder among children aged 8 years-autism and developmental disabilities monitoring network, 11 sites, United States, 2012. *MMWR Surveillance Summaries*. 2016; 65: 1.

6. Ghaffari MA, Mousavinejad E, Riahi F, Mousavinejad M, Afsharmanesh MR. Increased serum levels of tumor necrosis factor-alpha, resistin, and visfatin in the children with autism spectrum disorders: a case-control study. *Neurology research international*, 2016.

7. Gepner B, Deruelle C, Grynfeltt S. Motion and emotion: A novel approach to the study of face processing by young autistic children. *Journal of autism and developmental disorders*. 2001; 31: 37-45.

8. Zhang R, Zhang H-F, Han J-S, Han S-P. Genes related to oxytocin and arginine-vasopressin pathways: associations with autism spectrum disorders. *Neuroscience bulletin*. 2017; 33: 238-46.

9. Ronemus M, Iossifov I, Levy D, Wigler M. The role of de novo mutations in the genetics of autism spectrum disorders. *Nature Reviews Genetics*. 2014; 15:133-41.

10. Girault JB, Piven J. The neurodevelopment of autism from infancy through toddlerhood. *Neuroimaging Clinics*. 2020; 30: 97-114.

11. Olsson NC, Flygare O, Coco C, Görling A, Råde A, Chen Q, et al. Social skills training for children and adolescents with autism spectrum disorder: a randomized controlled trial. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2017; 56: 585-92.

12. Bishop D. Genes, cognition and communication: insights from neurodevelopmental disorders. *Annals of the New York Academy of Sciences*. 2009; 1156: 1.

13. Barkoski JM, Busgang S, Bixby B, Bennett D, Schmidt R, Barr DB, et al. Prenatal phenol and paraben exposures in relation to child neurodevelopment including autism spectrum disorders in the MARBLES study. *Environmental research*. 2019; 179: 108719.

14. Mc Partland JC, Jeste SS. Connectivity in context: emphasizing neurodevelopment in autism spectrum disorder. *Biological psychiatry*. 2015; 77: 772-4.

15. Jacquemont ML, Sanlaville D, Redon R, Cormier-Daire V, Lyonnet S, Amiel J, *et al.* Array-based comparative genomic hybridisation identifies high frequency of cryptic chromosomal rearrangements in patients with syndromic autism spectrum disorders. *Journal of medical genetics*. 2006; 43: 843-9.

16. Carper R A, Moses P, Tigue ZD, Courchesne E. Cerebral lobes in autism: early hyperplasia and abnormal age effects. *Neuroimage*. 2002; 16: 1038-51.

17. Fujii E, Mori K, Miyazaki M, Hashimoto T, Harada M, Kagami S. Function of the frontal lobe in autistic individuals: a proton magnetic resonance spectroscopic study. *The Journal of Medical Investigation*. 2010; 57, 35-44.

18. Scott-Van Zeeland AA, Abrahams BS, Alvarez-Retuerto AI, Sonnenblick LI, Rudie JD, Ghahremani D. Altered functional connectivity in frontal lobe circuits is associated with variation in the autism risk gene CNTNAP2. *Science translational medicine*. 2010; 2: 56ra80-56ra80.

19. Just MA, Cherkassky VL, Keller TA, Kana RK, Minshew NJ. Functional and anatomical cortical underconnectivity in autism: evidence from an FMRI study of an executive function task and corpus callosum morphometry. *Cerebral cortex*. 2007; 17: 951-61.

20. Theoharides T, Tsilioni I, Patel A, Doyle R. Atopic diseases and inflammation of the brain in the pathogenesis of autism spectrum disorders. *Translational psychiatry*. 2016; 6: e844-e844.

21. Wolters G, Stapert S, Brands I, Van Heugten C. Coping styles in relation to cognitive rehabilitation and quality of life after brain injury. *Neuropsychological rehabilitation*. 2010; 20: 587-600.

22. Chan AS, Cheung MC, Han YMY, Sze SL, Leung WW, Man HS, *et al*. Executive function deficits and neural discordance in children with autism spectrum disorders. *Clinical Neurophysiology*. 2009; 120:1107-15.

23. Mazzocco MM, Myers GF. Complexities in identifying and defining mathematics learning disability in the primary school-age years. *Annals of dyslexia*. 2003; 53: 218-53.

24. Haghighatfard A, Andalib S, Amini Faskhodi M, Sadeghi S, Ghaderi AH, Moradkhani S, Rostampour J, Tabrizi Z, Mahmoodi A, Karimi T. Gene expression study of mitochondrial complex I in schizophrenia and paranoid personality disorder. *The World Journal of Biological Psychiatry*. 2017;1-14.

25. Yui K, Tanuma N, Yamada H, Kawasaki Y. Decreased total antioxidant capacity has a larger effect size than increased oxidant levels in urine in individuals with autism spectrum disorder. *Environmental Science and Pollution Research*. 2017; 24: 9635-44.

26. Frustaci A, Neri M, Cesario A, Adams JB, Domenici E, Bernardina BD, et al. Oxidative stress-related biomarkers in autism: systematic review and meta-analyses. *Free Radical Biology and Medicine*. 2012; 52: 2128-41.

27. Kenworthy L, Anthony LG, Naiman DQ, Cannon L, Wills MC, Luong-Tran C, et al. Randomized controlled effectiveness trial of executive function intervention for children on the autism spectrum. *Journal of Child Psychology and Psychiatry*. 2014; 55: 374-83.

28. Rezaei A, Kazemi MS. The Effect of Emotional Regulation Training on Social Cognition and Executive Functions of Children with Autism Spectrum Disorder. *Quarterly Journal of Child Mental Health*. 2017; 4: 82-91.

29. Brady DI, Saklofske DH, Schwean VL, Montgomery JM, Thorne KJ, McCrimmon AW. Executive functions in young adults with autism spectrum disorder. *Focus on Autism and Other Developmental Disabilities*. 2017; 32: 31-43.

30. Boyer BE, GeurtsHM , Van der Oord S. Planning skills of adolescents with ADHD. *Journal of attention disorders*. 2018; 22: 46-57.

31. Xu N, Li X , Zhong Y. Inflammatory cytokines: potential biomarkers of immunologic dysfunction in autism spectrum disorders. *Mediators of inflammation*, 2015.

32. Fantuzzi G. Adipose tissue, adipokines, and inflammation. *Journal of Allergy and Clinical Immunology*. 2005; 115: 911-9.

33. Kushima I, Aleksic B, Nakatochi M, Shimamura T, Okada T, Uno Y, et al. Comparative analyses of copy-number variation in autism spectrum disorder and schizophrenia reveal etiological overlap and biological insights. *Cell reports*. 2018; 24: 2838-56.

34. Wang ET, Taliaferro JM, Lee JA, Sudhakaran IP, Rossoll W, Gross C, et al. Dysregulation of mRNA localization and translation in genetic disease. *Journal of Neuroscience*. 2016; 36: 11418-26.

35. Mokhtari B, Karimzadeh F. A review on the Authism with the most approach on the critical biomarkers. *Razi Journal of Medical Sciences*. 2018; 24: 35-46.

36. Shen L, *et al*. in *Reviews on Biomarker Studies in Psychiatric and Neurodegenerative Disorders*, Springer 2019; 207-33.

37. Bjørklund G, Meguid NA, El-Ansary A, El-Bana MA, Dadar M, Aaseth GJ, *et al*. Diagnostic and severity-tracking biomarkers for autism spectrum disorder. *Journal of Molecular Neuroscience*. 2018; 66: 492-511.

38. Abbasy S, Shahraki F, Haghighatfard A, Ghasemzadeh- Qazvini M, Towfigh-Rafiei, S, *Noshadirad* E, *et al*. Neuregulin1 types mRNA level changes in autism spectrum disorder, and is associated with deficit in executive functions. *EBioMedicine*. 2018; 37: 483-8.

39. Ricci S, Businaro R, Ippoliti F, Vasco V R Lo, Massoni F, Onofri E, *et al*. Altered cytokine and BDNF levels in autism spectrum disorder. *Neurotoxicity research*. 2013; 24: 491-501.

40. Ferrer A, Labad J, Salvat-Pujol N, Barrachina M, Costas J, Urretavizcaya M, *et al*. BDNF genetic variants and methylation: effects on cognition in major depressive disorder. *Translational psychiatry*. 2019; 9: 1-10.

41. Post RM. Role of BDNF in bipolar and unipolar disorder: clinical and theoretical implications. *Journal of psychiatric research*. 2007; 41: 979-90.

42. Najmabadi H, Hu H, Garshasbi M, Zemojtel T, Abedini SS, Chen W, *et al*. Deep sequencing reveals 50 novel genes for recessive cognitive disorders. *Nature*. 2011; 478: 57-63.