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АУТИЗМ И НАРУШЕНИЯ РАЗВИТИЯ

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по итогам VII Международной научно-практической конференции «Аутизм. Вызовы и решения»
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EDITOR'S NOTE

КОЛОНКА ГЛАВНОГО РЕДАКТОРА

Dear Readers,

Since 2013, Center on the Challenges of Autism: education, research, assistance, protection of rights with the participation of international experts in the field of support to people with autism spectrum disorders annually organizes the International Conference Autism. Challenges and Solutions. Stephen Edelson (USA), Executive Director of the Autism Research Institute, is the permanent co-chairman of the conference committee. In 2018, both the Center on the Challenges of Autism» and the editorial board of the Journal «Autism and Developmental Disorders» (Russia), which is pu blished by the Federal Resource Center for Organization of Comprehensive Support to Children with ASD of MSUPE, mutually decided to cooperate in the context of publication of thematic journal issues. In 2019—2020, the Autism Research Institute became a partner of this initiative. Stephen Edelson took over as the guest thematic science editor. The result of this work is the current issue of the Journal.

MSUPE and the editorial staff of the Journal «Autism and Developmental Disorders» (Russia) highly appreciate the partnership with the Center on the Challenges of Autism and the Autism Research Institute and express deep gratitude to Ekaterina Men and Stephen Edelson for their personal contribution to the development of present issue of the Journal. This issue collected scientific materials from various fields of autism research — neurobiology, autism treatment, ASD in adults.

The editorial express special gratitude to the Temple Grandin, professor of the University of Colorado, who "opened the doors" of perception of the changes that have occurred in the world during the pandemic by a person with autism. An interview with professor Grandin highlighted issues related to the difficulties faced by a person with autism in connection with the current changes, and what are the ways to overcome such difficulties.

The well-coordinated teamwork of the people who took part in the preparation of the present issue, colored with positive emotions and satisfaction from professional cooperation, is of particular value for the editorial of the Journal.

The editorial board expresses readiness for further cooperation with the Autism Research Institute and the Center on the Challenges of Autism in order to integrate the experience of the Russian and international scientific community in the field of autism-related research and the support to individuals with ASD.

The editorial also thank the expert reviewers and consultants whose comments, providing valuable feedback to authors and editors, have led to improvements in the articles published in this issue.

A.V. Khaustov

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GUEST EDITOR NOTE

КОЛОНКА ТЕМАТИЧЕСКОГО РЕДАКТОРА

Dear Readers,

This special issue highlights several of the lectures presented at the 7th annual "*Autism. Challenges and Solutions*" conference in Moscow, Russia. In previous years, well-established researchers and clinicians worldwide had an opportunity to share their expertise with individuals on the autism spectrum, their family members, and professionals throughout Eastern Europe. Due to the rapid spread of the COVID-19 virus, this year's conference was held online over a one-month period.

Today there are numerous challenges in the autism community and relatively few evidence-based solutions or treatments. Research is paramount to finding solutions. In addition to the importance of research, these solutions need to be accessible and affordable to all individuals on the autism spectrum — and not just some.

We all want the very best for those on the autism spectrum, and peer-reviewed research studies provide a channel for real solutions. With the publication of original studies along with replication by independent research teams, solutions should be available in clinical, therapeutic, and educational settings. However, there is usually a considerable delay between published findings and their real world application. A greater awareness of research on effective treatments is necessary to expedite implementation of appropriate treatments.

Russian scientists are well-respected throughout the world, and the journal of Autism and Developmental Disorders — Russia (ADD-R) has followed the tradition of publishing quality studies for 18 years. Researchers throughout the world are welcome to submit their research studies to ADD-R.

Finally, we would like to dedicate this issue to Ekaterina Men who founded and directs the efforts of *Autism. Challenges and Solutions*. Her tireless dedication, hard work, and perseverance have made, and continues to make, a significant impact in Russian and other eastern European autism communities.

S.M. Edelson

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Employment in Autism: Reflections on the Literature and Steps for Moving Forward

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Reflecting an address given at the Autism Challenges and Solutions International Conference in Moscow in April 2019, this paper reviews selected studies within the author's program of research as well as selected literature addressing pathways to employment for adults with autism. A range of employment support programs are considered, representing promising approaches. Attention is given to environmental elements that appear to have a bearing on individual employment experience and outcomes. These elements point to a person in environment approach which is increasingly supported by emerging evidence. This approach is conveyed as the employment ecosystem, with constituent elements that include the individual (employee or potential employee), family, employer, co-workers, work setting, community services, and embedded labor, health and disability policy. These various components of the ecosystem offer relevance in terms of understanding employment options and experiences of autistic adults. Recommendations for advancing this field are offered.

Keywords: autism spectrum, autistic, employment, quality of life, ecosystem.

Funding. Funding is gratefully acknowledged from Autism Speaks, Social Sciences and Humanities Council of Canada, and the Sinneave Family Foundation.

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Трудоустройство людей с РАС. Анализ исследований и шаги для дальнейшего развития

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Эта статья написана по итогам VII Международной научно-практической конференции «Аутизм. Вызовы и решения» (Москва, апрель 2019 г.). В ней представлен обзор некоторых работ в рамках исследовательской программы автора, а также избранные обзорные статьи, посвященные созданию возможностей для трудоустройства взрослых с расстройствами аутистического спектра (РАС). Рассмотрен ряд программ с перспективными подходами по повышению занятости людей с ограниченными возможностями. Особое внимание уделяется элементам окружающей среды, оказывающим влияние на полученный опыт и достигнутый результат трудоустройства. Элементы указывают на использование подхода на основе учета интересов человека в окружающей среде, эффективность которого все чаще подтверждается новыми данными. Этот подход выражается в экосистеме занятости, компонентами которой являются сам человек (работник или потенци-

альный работник), его семья, работодатель, коллеги, рабочая обстановка, социальные службы и политика в отношении труда, здоровья и инвалидности. Для понимания вариантов трудоустройства и соответствующего опыта взрослых с РАС имеют значение все компоненты экосистемы. В работе предложены рекомендации для развития данной сферы.

Ключевые слова: аутистический спектр, аутичный, трудоустройство, качество жизни, экосистема.

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Reflecting a presentation offered at the *Autism Challenges and Solutions International Conference* in Moscow on April 8, 2019, this paper reviews selected research addressing employment experiences and outcomes for adults with autism. Promising support interventions in the field are considered, with employment being positioned as reflective of an array of contributing elements within the broader community and system at large.

Background

Several recent systematic reviews have examined employment programs and interventions for adults with autism. Taylor et al. [17] examined vocational interventions for individuals with autism aged 13 to 30 years, and found only a few studies, with the authors noting them as being poor quality. A synthesis review by Nicholas et al. [8] also found a limited number of studies and concerns over methodological quality, but noted the literature addressing supported employment in community settings appeared promising. A subsequent systematic review by Hedley et al. [3] on employment programs for adults with ASD also raised concerns with study quality, with studies generally reporting positive outcomes.

Despite this emerging evidence demonstrating means to support employment in the autistic population, there continues to be overall low employment rates and reported dissatisfaction about employment prospects among autistic individuals themselves [9]. As an example, the Canadian employment rate for adults with autism is unacceptably low at only 14.3% for individuals over 15 years of age [19]. Of further concern, those who are employed are often engaged in short-term and low-paying jobs, and some may not find their work to be meaningful or satisfying [7; 12; 16].

In seeking improved employment prospects, a recent roundtable discussion consisting of expert stakeholders in the autism employment field [11], addressed proposed steps forward. Discussants recommended a strengths-based approach to employment support by acknowledging what each autistic individual offers, and their preferences, goals, and support needs to reach their potential-all while aiming to change the environment to nurture employment success. Suggested aims were the development of inclusive communities and workplaces, and recognition of how employment connects to the individual's life and wellbeing, and the importance of developing careers as opposed to focusing merely on job acquisition [11].

Khayatzadeh-Mahani et al. [6] reported similar findings, noting barriers for autistic individuals such as not being exposed to work as early as their peers, a lack of employer knowledge about autism, stigma, insufficient capacity, and non-helpful workplace policy. Recommendations included the alleviation of potential disincentives to work, increased employment opportunities, and more employment education in high school. Of top priority among participants, Khayatzedeh-Mahani and colleagues [6] identified the need to address, "employers' knowledge, capacity, attitudes, and management practices" [6, p. 4]. The authors recommended employer training aimed at building knowledge around inclusion, with a suggestion to commence this training in school, which could also have a broader societal impact.

Nicholas and Klag [12] called for shifts in the focus of employment supports and related policy. They noted that many support programs focus on obtaining employment as a sign of success, which often includes shorter term employment. Despite initial positive outcomes, this can potentially lead to future concerns such as a potential cycle of short-term employment that may be seen as less desirable by future

employers [12]. Furthermore, this cycle of *on-and-off-again* employment can leave gaps in an individual's income. Seeking longer-term employment is suggested, including sculpting jobs to an individual's strengths and interests, engaging employers and coworkers in employment support, and an earlier introduction to employment opportunities. Nicholas and Klag further suggested that services need to offer greater focus on building individual capacity in soft skills (e.g., social reciprocity), and be sufficient enough to alleviate reliance on family members who currently may feel compelled to provide employment-related support due to a lack of services. Finally, a more holistic view of employment is invited, with the ultimate goal of attaining a 'good life' in terms meaningful to the autistic individual [12].

In qualitative interviews with young adults with autism and their parents, the importance of addressing family involvement along with other intersecting systems such as schools, service providers, and employers was raised by participants [1]. Anderson et al. [1] found that, "many barriers to employment had less to do with a young adult's characteristics and more to do with larger systems and external realities, including prejudice, organizational inflexibility ('we do not just hire for little niches'), and lack of services" [1, p. 11], including a need to examine young people's experiences in high school and how these experiences could be improved.

Despite advances in employment opportunities and support for people with autism, gaps and challenges exist in this field, and high unemployment rates remain. This paper documents promising developments in the literature, and highlights a broader *ecosystem* approach. Specific aims of the paper are to: 1) explore selected employment support initiatives, and 2) examine the emerging ecosystem perspective within employment in autism. Below is a review of selected literature, along with research reflections related to employment among youth and adults with autism. We seek to amplify core elements of employment and employment support that may increase the likelihood of autistic adults finding and maintaining employment.

What is the Employment Ecosystem? An Analogy for Navigating Employment

An *ecosystem* is defined as "a biological system composed of all the organisms found in a particular physical environment, interacting with it and with each other" [2]. In our program of research, participants have conveyed employment somewhat akin to a walking path on a steep ascending slope that is overgrown with encroaching foliage as well as bumps and crevices on the pathway. At one point long ago before its metaphorical and hypothetical development, there presumably was no path; rather, it was created through mutual effort on the part of many over time — by intention, design and toil which cumulatively opened space to traverse the challenging terrain. Yet the path, as constructed in this analogy, may be less than ideal; even largely impassable hence, potentially unfunctional.

Extending this image to the real and often arduous *uphill journey* to employment access and sustainability, autistic adults in our research have often conveyed the path to employment as daunting and anxiety-producing. For too many adults, the path is hewn with barriers akin to large rocks, deep crevasses and bumps that can render it impassable, with meaningful work seemingly unattainable. Un- or underemployment is borne out by population-based statistics internationally. Our pressing task, as advocates, employers, service providers and researchers, is to innovate ways to overcome and decrease barriers on the path to and within employment.

Accentuating the urgency for rapid advancement in employment access for autistic adults, the first-hand experiences of autistic adults, their family members and service providers in Canada were collated and reported elsewhere [9]. In that study, participants conveyed the need for further resources and service shifts related to greater employment access and integration in their community, including the need for ancillary resources (e.g., transportation, mental health support, housing). Our research to date, as well as that of others in the field, has identified similar needs for enhanced employment-based service to autistic youth and adults along with additional elements such as community and workplace supports — all integral for sustained employment success. Below are some examples of promising employment support initiatives reported in the literature and discussed in the Moscow session, followed by a reflection on broader community factors that cumulatively may advance employment options for adults with autism.

Promising Employment Support Programming

As reported and reviewed by others [3; 10], we briefly reflect on international examples described in the literature; two programs from the United States, one program from the United Kingdom, and one program from Canada:

Based in the United States, the TEACCH Program® offers training and job coaching in the environment in which employment is occurring. Over a period of approximately 10 years, over 100 individuals were served, with 96 placed in jobs and an 89% job retention rate [5].

Project SEARCH® is an internship program for youth in the final year of high school that offers a range of supports including environmental support. It has been offered at multiple sites in North America. Eighty-eight percent of the youth evaluated in these reviews went on to competitive employment versus 6% of youth who received basic services according to a more standard education plan called an *Individualized Education Plan* [13; 18].

Based on an early report from the United Kingdom in 2005, the National Autistic Society (NAS) Prospects Program reflects a supported employment service model. A 68% success rate was reported, through job placement in 192 jobs over an 8-year period, along with employer capacity building [4].

An integrated support approach was implemented by a Canadian program entitled, Employment*Works* (EW), an employment support resource aimed at improving job readiness for individuals with autism, while also supporting the capacity of employers and communities [10]. Positive program outcomes included individual skill development, capacity building among employers, and bolstered engagement and receptiveness of coworkers. Autistic individuals and their coworkers/employers were engaged together in onsite experiences and mutual learning, and these relationships were reported to be pivotal to capacity building. Engagement of employers in the program reportedly led to shifts in thinking, and provided the space to confront preconceived negative notions and stereotypes, which led to increased intention to hire autistic individuals [10].

Cumulatively, the reported outcomes of the various initiatives across world regions demonstrate that working with individuals and colleagues in the aim of supporting employment appears promising, although in some cases, more robust evaluation is advised [3; 8; 17].

Seaman and Cannella-Malone [14] reviewed vocational skills-based interventions that offer employment-related skills that enable individuals with autism to become more ready for employment. They described 3 groups or types of intervention. The first group was focused on pre-employment services (all 3 interventions were based at universities, and not at workplaces). The second reviewed group of 14 studies consisted of programs that supported capacity in completing tasks of work, and of these, 13 studies used technology such as handheld devices that electronically cued or reminded the individual about aspects for success in the workplace. Of these studies, 7 studies were based at universities/schools while 7 were in workplaces. The third group in Seaman and Cannella-Malone's [14] review consisted of 4 studies that focused on job retention, with several using technology applications. An important distinctive feature of this work is its focus not only on *finding* a job, but also *keeping* a job.

Gaps in employment support based on this review were noted [14]. Specifically, there was an identified lack of pre-employment skill development (e.g., core skills, resume writing, interviewing, occupational focus, motivation) and fewer resources that support job retention. A challenge for many people with autism that warrants greater support in service delivery was reported as the navigation of social interaction such as social reciprocity and engaging in dialogue [14]; indeed, requisite skills in many jobs.

In summary, we are learning from emerging studies and secondary reviews of the literature, that acquiring the skills for success in the workplace for some with autism requires a range of supports and other structures. Time to try varying jobs and workplace experiences may allow greater opportunity to consider what types of employment or employment sectors and fields, best suit and appeal to the individual. This collective work cautions against individuals being slotted into a particular job; and rather, supports an approach of methodically planning and sculpting jobs based on who the individual is and in what role and setting they may vocationally thrive.

While substantial gains have been made in the last decade, there seemingly is a long way to go. Attaining substantial and sustained gains in employment rates for this population will likely not only require the work of employment support personnel, but also a range of mutually supportive ecosystem components applying collective effort.

Dr. Paul Shattuck and Anne Roux [15] astutely argued, "Unemployment is not just an individual predicament, it is a social problem. Social problems cannot be solved entirely through a focus on modifying individual behaviors and abilities, although this is certainly an important pursuit. We also need to examine the social environment and the impact of interventions targeting a community or policy level" [15, p. 246].

As conveyed in this literature, proactive action at individual, employer, community and societal levels is invited. If parts *of the whole* are lacking, it is suspected that the path to sustained and generative employment may be that much more challenging — just as the rocks and debris on the metaphoric ascending pathway can block and impede steps forward.

Stakeholders on the Path to Employment

As illustrated in *figure*, the employment ecosystem has increasingly been identified in recent research [1; 6; 10]. It variably consists of the job seeker or employee as well as community resources, employment support assistants, employers, coworkers, and informal supports including family members and the community. Beyond these individual and community-level factors, the suite of education, labor and disability policy and societal values within a jurisdiction, may foster or conversely impede a pro-employment, inclusive context. It seems that if we are to substantially increase job access and retention, we need to pay attention to the complementarity versus dissonance of needs relative to resources within a given jurisdiction. As noted at the bottom of *fig.*, elements of time and context (e.g., earlier exposure to employment options, economic conditions, geopolitical considerations, housing sufficiency and affordability) may impose facilitative and/or impeding influencers that may have a bearing on employment prospects. As an example, at the time of the writing of this manuscript, the COVID-19 pandemic had dramatically impacted countries around the world. Consequent closure of many workplaces and services, as well as requirements of social distancing and other pandemic-related restrictions, are vivid examples of a global contextual condition, with impacts on employment prospects and experiences for autistic individuals and others.

The layered and intersecting components of the employment ecosystem lead us to conclude that the achievement of employment is not *just getting a job*. Rather, it entails contributing factors such as people, services, systems and broader conditions that play a role in the achievement of sustained em-

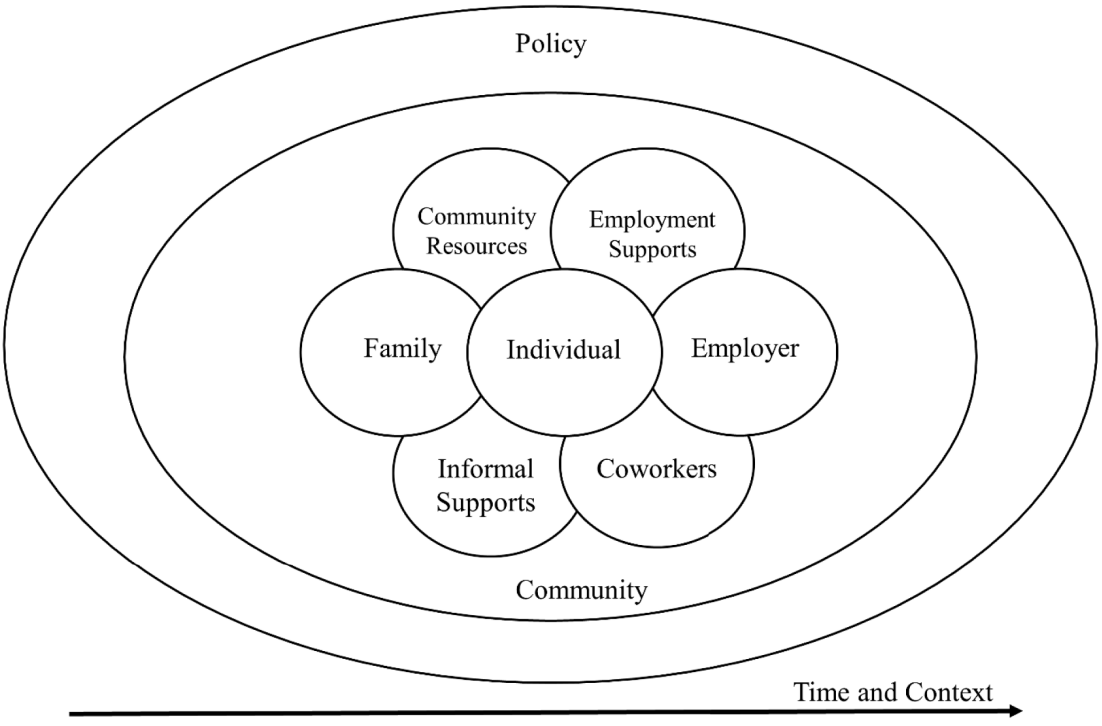

Fig. The Ecosystem: Components Nurturing Employment

ployment (or lack thereof). Adding to these components, social and ancillary conditions associated with the Social Determinants of Health, such as poverty, transportation challenges, a lack of social support, and co-existing mental health or health issues, may impede prospects of employment, thereby warranting concerted supportive strategies at individual, community and population levels [12].

Some Considerations and Recommendations in Moving Forward

This research invites action at individual, community and societal levels. At the individual support level, sufficiency of resources for employment access and career planning as well as assistance *in the workplace* for autistic youth and adults are needed. Within the employment sector, training of employers and co-workers may heighten understanding and ultimately work opportunity for autistic employees. Pro-diversity organizational and societal policy may need bolstering to ultimately achieve infrastructure supporting inclusive employment. Proactive policy and resources such as health and mental health coverage and services to encourage wellness and quality-of-work-life are important features of a sustained inclusive employment workforce.

Research Implications

Emerging from this review, greater engagement with autistic youth and adults seems warranted in better understanding their *first-person* needs and priorities for advancing inclusive employment, supportive work environments and broad-based systemic change. Examining autistic adults' work and life journeys both in moving toward, and within, employment, importantly may amplify facilitative and impeding factors that ultimately can be proactively calibrated in practice and program supports. We need to develop valid measures and methods for evaluating the various intersecting elements of the employment ecosystem. Granular analysis is further recommended, including sample distinctions across the autism phenotype (as well as potential co-existing conditions), employment/industry sectors, and support approaches/models.

Many potential research questions remain unanswered. For instance, we need to better understand specific mechanisms that advance outcomes, including how they may be linked with contextual elements such as region (e.g., locale, urban versus rural region), economic conditions, culture and policy structure. There is yet limited research that focuses on how employment supports and services moderate outcomes. In considering the impact of employment on well-being, potential questions for further inquiry emerge such as, 'how do employment services affect employee identity, self-esteem and quality of life?'. It is anticipated (and hoped) that advancing this line of research may assist in supporting autistic individuals' quality of life by determining *if* and if so, *how* employment and the range of possible supports therein, can enrich one's life course.

Interventional and longitudinal studies are needed that address employment support initiatives and trajectories across varying industry/employment sectors. Lastly, population-based impacts from the employment of autistic people are needed in determining economic and other societal outcomes (e.g., gross domestic product [GDP], population-level attitudes and values) which in turn, may heighten awareness and justify further proactive employment opportunity.

Conclusion

Research in this field suggests that meaningful and long-term employment is an important aim, yet one that may be challenging, anxiety-producing and/or elusive for many adults with autism. Employment supports are recommended to be catalytic in seeking broad level inclusion of autistic individuals in employment and community at large via ecosystem transformation. As we move forward, building partnerships amongst private and public sector stakeholders seems pivotal to sustainable change. Multi-level strategy development is invited in the aim of individual, workplace, community and societal capacity building. Advances over the last decade demonstrate that employment prospects can be improved for adults with autism. However, formidable shifts are yet needed. Working together to improve employment possibilities emerges as an endeavor worthy of pursuit in the aim of advancing outcomes and quality of life for autistic adults.

References

1. *Anderson C., Butt C., Sarsony C.* Young adults on the autism spectrum and early employment-related experiences: Aspirations and obstacles. *Journal of Autism and Developmental Disorders*, 2020. Advance online publication. DOI:10.1007/s10803-020-04513-4
2. Ecosystem / Oxford English Dictionary Online Edition [Web resource]. URL: https://www.oed.com/view/Entry/59402 (Accessed 25.05.2020).
3. *Hedley D., Uljarevic M., Cameron L., Halder S., Richdale A., Dissanayake C.* Employment programmes and interventions targeting adults with autism spectrum disorder: A systematic review of the literature. *Autism*, 2017, vol. 21, no. 8, pp. 929—941. DOI:10.1177/1362361316661855
4. *Howlin P., Alcock J., Burkin C.* An 8 year follow-up of a specialist supported employment service for high-ability adults with autism of Asperger syndrome. *Autism*, 2005, vol. 9, no. 5, pp. 533—549. DOI:10.1177/1362361305057871
5. *Keel H.J., Mesibov G.B., Woods A.V.* TEACCH-Supported employment program. *Journal of Autism and Developmental Disorders*, 1997, vol. 27, no. 1, pp. 3—9. DOI:10.1023/a:1025813020229
6. *Khayatzadeh-Mahani A., Wittevrongel K., Nicholas D.B., Zwicker J.D.* Prioritizing barriers and solutions to improve employment for persons with developmental disabilities. *Disability and Rehabilitation*, 2019, vol. 11, pp. 1—11. DOI:10.1080/09638288.2019.1570356
7. *Levy A., Perry A.* Outcomes in adolescent and adults with autism: A review of the literature. *Research in Autism Spectrum Disorders*, 2011, vol. 5, no. 4, pp. 1271—1282. DOI:10.1016/j.rasd.2011.01.023
8. *Nicholas D.B., Attridge M., Zwaigenbaum L., Clarke M.* Vocational support approaches in autism spectrum disorder: A synthesis review of the literature. *Autism*, 2015, vol. 19, no. 2, pp. 235—245. DOI: 10.1177/1362361313516548
9. *Nicholas D.B., Zwaigenbaum L. Zwicker J., Clarke M., Lamsal R., Stoddart K., Carroll C., Muskat B., Spolestra M., Lowe K.* Evaluation of employment support services for adults with autism spectrum disorder. *Autism*, 2018, vol. 22, no. 6, pp. 693—702. DOI:10.1177/1362361317702507
10. *Nicholas D.B., Mitchell W., Dudley C., Clarke M., Zulla R.* An ecosystem approach to employment and autism spectrum disorder. *Journal of Autism and Developmental Disorders,* 2018, vol. 48, no. 1, pp. 264—275. DOI:10.1007/s10803-017-3351-6
11. *Nicholas D.B., Hedley D., Randolph J.K., Raymaker D.M., Robertson S.M., Vincent J.* An expert discussion on employment in autism. *Autism in Adulthood*, 2019, vol. 1, no. 3, pp. 1—8. DOI:10.1089/aut.2019.29003.djn
12. *Nicholas D.B., Klag M.* Critical reflections on employment among autistic adults. *Autism in Adulthood*, 2020. Advance online publication. DOI:10.1089/aut.2020.0006
13. *Schall C.M., Wehman P., Brooke V., Graham C., McDonough J., Brooke A., Ham W., Rounds R., Lau S., Allen J.* Employment interventions for individuals with autism: The relative efficacy of supported employment with or without prior Project SEARCH training. *Journal of Autism and Developmental Disorders*, 2015, vol. 45, no. 12, pp. 3990—4001. DOI:10.1007/s10803-015-2426-5
14. *Seaman R.L., Cannella-Malone H.I.* Vocational skills interventions for adults with autism spectrum disorder: A review of the literature. *Journal of Developmental and Physical Disabilities, 2016, vol. 28*, no. 3, pp. 479—494. DOI:10.1007/s10882-016-9479-z
15. *Shattuck P.T., Roux A.M.* Commentary on employment support research. *Autism*, 2015, vol. 19, no. 2, pp. 246—247. DOI:10.1177/1362361313518996
16. *Taylor J.L., Seltzer M.M.* Employment and post-secondary educational activities for young adults with Autism Spectrum Disorders during the transition to adulthood. *Journal of Autism and Developmental Disorders*, 2011, vol. 41, no. 5, pp. 566—574. DOI:10.1007/s10803-010-1070-3
17. *Taylor J.L., McPheeters M.L., Sathe N.A., Dove D., Veenstra-VanderWeele J., Warren Z.* A systematic review of vocational interventions for young adults with Autism Spectrum Disorders. *Pediatrics, 2012, vol. 130*, no. 3, pp. 531—538. DOI:10.1542/peds.2012-0682
18. *Wehman P. Schall C.M., McDonough J., Kregel J., Brooke V., Molinelli A., Ham W., Graham C.W., Erin Riehle J., Collins H.T., Thiss W.* Competitive employment for youth with autism spectrum disorders: Early results from a randomized clinical trial. *Journal of Autism and Developmental Disorders*, 2014, vol. 44, no. 3, pp. 487—500. DOI:10.1007/s10803-013-1892-x
19. *Zwicker J.D., Zaresani A., Emery J.C.H.* Describing unmet needs among adults with a developmental disability: An examination of the 2012 Canadian Survey on Disability. *Research in Developmental Disabilities*, 2017, vol. 65, pp. 1—11. DOI:10.1016/j.ridd.2017.04.003

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Impact of Employment on the Quality of Life and Job Satisfaction of Autistic Workers

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The current research sought to understand the relationship between job satisfaction and quality of life in employed individuals with Autism Spectrum Disorder (ASD). The research focuses on participants involved in a supported employment program for individuals with ASD, the DXC Technology Dandelion Program. We examined the sustained impact of participating in the supported employment program on quality of life and job satisfaction, via a longitudinal survey of the employees with ASD. Quality of life was assessed with the World Health Organization Quality of Life Brief, and intrinsic and extrinsic job satisfaction were assessed with the Minnesota Satisfaction Questionnaire (Short Form). Results indicated small but statistically non-significant (using an adjusted significance level of .001) changes in both quality of life and job satisfaction across a 12-month period. Results are discussed in terms of how to further improve the employment program and support employees with ASD.

Keywords: autism spectrum disorder, disability, job satisfaction, quality of life, supported employment, adults, vocation.

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Влияние трудоустройства на качество жизни и удовлетворенность работой у людей с РАС

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В представленном исследовании рассматривалась взаимосвязь между удовлетворенностью работой и качеством жизни трудоустроенных людей с расстройствами аутистического спектра (РАС). Участники исследования — люди с РАС, задействованные в программе трудоустройства людей с ограниченными возможностями Dandelion DXC Technology. В рамках лонгитюдного исследования авторы оценивали, как участие в программе трудоустройства людей с ограниченными возможностями влияет на качество жизни и удовлетворенность работой сотрудников с РАС. Качество жизни оценивалось в соответствии с Кратким опросником ВОЗ для оценки качества жизни (World Health Organisation Quality of Life Brief), а внутренняя и внешняя удовлетворенность работой оценивалась по сокращенной версии Миннесотского опросника удовлетворенности (Minnesota Satisfaction Questionnaire (Short Form)). Результаты показали статистически незначимое (уровень значимости p = 0,01) изменение качества жизни и удовлетворенности работой в течение 12 месяцев. Данные результаты в дальнейшем используются для улучшения программы по трудоустройству и поддержке сотрудников с РАС.

Ключевые слова: расстройства аутистического спектра, инвалидность, удовлетворенность работой, качество жизни, трудоустройство людей с ограниченными возможностями, взрослые, призвание.

Финансирование. Исследования, на которые ссылается настоящая работа, были проведены при поддержке DXC Technology и Департамента социального обеспечения при правительстве Австралии. Содержание настоящей работы является исключительно ответственностью авторов и не было утверждено или одобрено компанией DXC Technology или Департаментом социального обеспечения при правительстве Австралии.

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The Organisation for Co-operation and Development (OECD, 2010) [37], revealed that the average employment rate for persons with a disability is approximately 40%, compared to 75% for persons without a disability. People with Autism Spectrum Disorder (ASD) face some of the highest rates of underemployment and unemployment of all disability groups, with employment rates ranging from 14% in Canada to 32% in the United Kingdom [31; 35; 41]. In Australia, the estimated employment rate of people with ASD is 28% [11], although the requirements for being included in this statistic are low, and can include as little as working a few hours a week. This study explored the sustained impact of participating in a supported employment program within the Information and Communications Technology (ICT) sector, through an examination of the relationship between well-being and quality of life on employees with ASD.

ASD is a neurodevelopmental disorder characterized by persistent deficits in social communication and social interaction, restricted and repetitive patterns of behaviors, and hyper- or hyporeactivity to sensory input [9]. Symptoms typically appear in early childhood with much of the extant research focused on early detection and treatment. However, ASD is a lifelong disorder and individuals with ASD are a growing segment of the workforce; in the United States each year 50,000 individuals with ASD transition into adulthood [35]. Challenges and barriers that underlie poor employment outcomes in ASD include difficulty navigating traditional recruitment and selection practices that often favor individuals with strong social skills [30; 33], and features of contemporary organizations including open-plan work environments, expectations that employees be effective in teams, and are flexible and adapt to change [12]. Individuals with ASD therefore often require specific supports to be successful at work [33; 35]. Without these supports, negative work experiences can lead to lower job satisfaction [25] and shorter job tenure and uneven work history, further undermining job prospects and quality of life [6].

The World Health Organization [46] defines quality of life as “individuals’ perceptions of their

position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" [46, p. 6]. Thus, quality of life is a subjective evaluation of well-being across several domains that is calibrated against the individual's personal, cultural and situational expectations. To the extent that employment is important to an individual, it should contribute to higher quality of life. Indeed, there is ample evidence to indicate that employment does improve well-being in myriad ways [44]. Individuals with ASD often report a strong desire to work [8], but as noted above they often face challenges to finding and maintaining employment, which may contribute to the lower quality of life reported in this population [43].

One job-specific indicator of well-being is job satisfaction [44], which refers to a positive evaluation of a job or its characteristics [28]. Job satisfaction predicts a range of positive outcomes including improved work performance, lower absenteeism, and lower turnover [25]. Prior research on job satisfaction among individuals with disabilities is relatively sparse. Employees with disabilities may report high job satisfaction when the organizational culture is responsive and fair [36], and when employees with disabilities have workplace support and flexibility [2]. The limited research on job satisfaction among individuals with ASD suggests that job satisfaction may be high when starting work, but may decline over time if jobs are not stimulating [22]. Given the relative paucity of research examining employment among individuals with ASD, and employment's relationship to quality of life and job satisfaction for these individuals, the purpose of this research is to examine the relationship between job satisfaction and quality of life of individuals with ASD employed in a supported work program.

Supporting meaningful employment

Supported employment programs can help to ensure individuals with intellectual disabilities or other conditions, such as mental illness or ASD, participate fully in the work environment [7]. Support can ensure that the nature of the job does not disadvantage the person with a disability [39]. Although individuals with ASD present with specific deficits associated with their diagnosis, at the same time, many individuals also exhibit atypical or high intellectual ability [16], or specific skills and interests that make them well suited to certain occupations and roles [12]. Individuals with ASD also tend to be reliable, trustworthy and conscientious employees, often completing work to a high standard [15; 22; 26]. Thus, both organizations and individuals with ASD would benefit from employing and supporting individuals with ASD [5]. However, there is a lack of empirical research regarding employment supports for adults with ASD [19].

The present research included people with ASD employed within the DXC Technology Dandelion Program, which is a supported employment program for individuals with ASD within Australia. The Dandelion Program is intended to fill a skills gap—there is a significant worldwide skills gap within the ICT field [10] — while simultaneously providing individuals with ASD a pathway to meaningful employment. Some individuals with ASD have skills and interests, such as extraordinary memory, concentration and pattern recognition, which are ideal for certain ICT roles [12]. Thus, the program seeks to leverage the skill and interest profile of individuals with ASD to meet this business need, provides significant workplace supports to accommodate the diverse needs of individuals with ASD, and aims to prepare them for longer-term employment.

In the Dandelion Program trainees with ASD are employed in areas including software testing, data analytics, cybersecurity, and records management. DXC Technology have made significant changes to the organizational context [39] to support employees with ASD, such as revising human resource protocols. For example, the recruitment and selection process has a reduced focus on candidates' past experience and interpersonal skills and instead focuses on the candidates' ability to demonstrate specific skills and to work together. Individuals work in teams of 10 to 14; each team is supported by specially trained staff and work alongside other ICT professionals.

The lack of suitable employment is a likely barrier to quality of life among adults with ASD [21; 34]. The little research that has directly addressed this issue suggests that supported employment may improve quality of life. Garcia-Villamisar, Wehman, Wehman and Navarra [13] found that individuals with ASD in supported employment showed an increase in quality of life over a 5-year period. However, this study has been critiqued elsewhere due to methodological limitations [18]. Renty and

Roeyers [32] focused on the impact of ASD support and disability characteristics on quality of life, but they also noted that adults with ASD who participated in daytime activities, including employment, reported a significantly higher quality of life than those without such engagement.

Job satisfaction is a context-specific indicator of well-being and quality of life [44], and research on job satisfaction among individuals with disabilities, or ASD, is also generally sparse. However, as highlighted, organizational factors such as a fair organizational culture [36] and workplace support and flexibility [2] may be related to greater job satisfaction for individuals with disabilities. Research on temporal patterns of job satisfaction has demonstrated that newcomer job satisfaction fluctuates over time, peaking in the 'honeymoon' phase shortly after starting the job and declining thereafter in a 'hangover' phase [4]. Consistent with this 'hangover' effect, some research on employees with ASD suggests that their job satisfaction tends to decrease over time, partly due to boredom [22]. However, it is unclear whether a similar pattern of decreasing job satisfaction would emerge for employees with ASD who work on challenging tasks with ongoing support and flexibility.

The present study explored the impact of participation in the DXC Technology Dandelion Program through an examination of the relationship between quality of life and job satisfaction of the trainees with ASD engaged in the program. Based on prior literature and our own qualitative research [17], we predicted that participants would report relatively high job satisfaction at the onset of the program, and that job satisfaction and quality of life would be associated. Though prior research suggests that quality of life improves over the course of employment [13; 32], research on job satisfaction suggests that it declines over time [4; 22]. Variables were measured over a 12-month period to examine whether the trajectory is more consistent with employment increasing quality of life or more consistent with it decreasing job satisfaction and thus, quality of life.

Method

Participants

Twenty trainees (19 male, Mage = 23.85, SD = 5.61, Range = 18—44 years) participated in the study. Two additional trainees did not consent to participate in the study, and one individual withdrew following the first data collection point after he was informed that he had not passed a 6-month probation period and his contract was discontinued. Participants' education level varied and included Bachelor's degree (30%), Diploma (30%), completed secondary school (30%), and did not complete secondary school (10%). The majority of participants lived with one or more parent (80%), 15% lived alone, and one individual lived with a spouse. Prior to starting in the program 5% were employed full-time, 50% had part time jobs (M = 9.75, SD = 6.43, Range = 4—25 hrs/week), and 45% were unemployed. Evidence of ASD diagnosis was provided when individuals applied for the program, and none reported an intellectual disability.

Procedure

The research was approved by the La Trobe University Human Research Ethics Committee and participants provided informed consent. We report results from three administrations at 6-month intervals (Baseline, 6-months, 12-months). Demographic information and employment history were collected at baseline.

Measures

WHO Quality of Life-Brief [46] is a 26-item self-assessment of quality of life across four domains: Physical health (7 items related to activities of daily living, dependence on medicinal substances and medical aids, energy and fatigue, mobility, pain and discomfort, sleep and rest, work capacity); Psychological (6 items related to bodily image and appearance, negative feelings, positive feelings, self-esteem, spirituality/religion/personal beliefs, thinking/learning/memory and concentration); Social relationships (3 items related to personal relationships, social support, sexual activity); and Environment (8 items related to financial resources, freedom/physical safety and security, health and social care: accessibility and quality, home environment, opportunities for acquiring new information and skills, participation in and opportunities for recreation/leisure activities, physical environment, transport); as well as two additional items assessing overall quality of life and general health. Responses are given on 5-point scales and raw scores are transformed to a 0-100 scale, with higher scores indicating a higher perception of quality of life. The WHOQOL-BREF

is widely used in samples with ASD [43] and has been found to be both a valid and reliable measure of quality of life with Cronbach's alphas ranging from .55 to .87 [38].

Minnesota Satisfaction Questionnaire Short Form (MSQ-SF) is a 20-item self-report measure of job satisfaction [45]. Respondents indicate how satisfied they are with particular aspects of their job, such as "being able to keep busy all the time" and "the freedom to use my own judgement". Items are rated on a 5-point Likert-type scale (1 "very dissatisfied with this aspect of my job", 2 "dissatisfied with this aspect of my job", 3 "can't decide if I'm satisfied or dissatisfied with this aspect of my job", 4 "satisfied with this aspect of my job" and 5 "very satisfied with this aspect of my job"). The MSQ-SF provides two factor scales consisting of Intrinsic Satisfaction (score range 12—60) and Extrinsic Satisfaction (score range 6—30), with lower scores indicating a lower level of satisfaction. The MSQ-SF is widely reported in the literature, including with samples of employees with disabilities [45], with reliability coefficients ranging from 0.77 to 0.92 [23].

Results

Initial screening showed no missing data, no presence of outliers for any of the scales, and that data were normally distributed. Significance levels for multiple comparisons were adjusted to .01 to minimize the chance of a Type I error [40]. Pearson's correlations were used to explore the relationships between intrinsic and extrinsic job satisfaction and quality of life (QOL) over a 12-month period (*table*). Potential relationships between age and the study variables were examined first. Participant age was generally not found to correlate significantly with QOL or job satisfaction at any time-point ($r = .06—.42$, all $p > .05$), with the exception of baseline intrinsic ($r = .72$, $p < .001$) and extrinsic ($r = .65$, $p < .001$) job satisfaction, which were both positively associated with age. Given lack of significant results at other time-points, or with QOL, this finding was not examined further. While the study scales were mostly significantly correlated between time points, no significant associations were identified between QOL and job satisfaction.

A repeated measures analysis of variance (ANOVA) applying the Greenhouse-Geisser correction was used to explore change in quality of life, and intrinsic and extrinsic job satisfaction over the study period. As can be seen from *table*, there was a trend for an increase in quality of life scores from baseline to 6-months, followed by a decrease from 6—12 months, and a trend for a decrease of both intrinsic and extrinsic job satisfaction scores across three time points. However, these trends were not found to be statistically significant: WHOQOL-BREF, $F(1.41, 26.70) = .596$, $p = .501$, $\eta p2 = .03$; Intrinsic Job Satisfaction, $F(1.94, 36.87) = 2.94$, $p = .067$, $\eta p2 = .134$; Extrinsic Job Satisfaction, $F(1.64, 31.15) = 3.63$, $p = .046$, $\eta p2 = .161$. There were no significant changes on the WHOQOL-BREF domain scores: Physical Health, $F(1.67, 31.63) = .183$, $p = .794$, $\eta p2 = .01$, Psychological Health, $F(1.82,34.55) = .92$, $p = .40$, $\eta p2 = .046$, Social Relations, $F(1.63,30.95) = .109$, $p = .858$, $\eta p2 = .006$, and Environment, $F(1.65, 31.36) = .374$, $p = .651$, $\eta p2 = .019$.

Table

Means, standard deviations, and correlations of study variables over 12-months

Variable	Mean	SD	1.	2.	3.	4.	5.	6.	7.	8.
1. WHOQOL-BREF Baseline	65.62	18.08								
2. WHOQOL-BREF 6-months	69.37	15.43	**.509***							
3. WHOQOL-BREF 12-months	66.87	20.39	**.519***	**.893****						
4. MSQ Intrinsic Time Baseline	48.10	3.94	-.014	-.12	-.267					
5. MSQ Intrinsic Time 6-months	47.85	3.34	.03	.136	.010	**.460***				
6. MSQ Intrinsic Time 12-months	46.30	3.81	.32	.265	.177	**.554***	**.586****			
7. MSQ Extrinsic Time Baseline	25.70	2.47	.037	.074	-.064	**.812****	**.484***	**.579****		
8. MSQ Extrinsic Time 6-months	24.60	2.98	.143	.118	-.038	**.621****	**.859****	**.709****	**.732****	
9. MSQ Extrinsic Time 12-months	24.25	2.79	.293	.310	.175	**.487***	.431	**.911***	**.548***	**.663****

*$p < .05$, **$p < .01$

Discussion

The current research explored the impact of participating in the DXC Technology Dandelion Program, a supported employment program for individuals with ASD, through an examination of the relationship between job satisfaction and quality of life (QOL). Our results suggest participating in the program does not lead to significant or sustained improvements (nor decrements) in QOL over a 12-month period, a finding we have replicated elsewhere with regards to mental health [18]. Trainee job satisfaction tended to be high over time relative to normative samples [45]; however, we did observe a slight, albeit non-significant drop in satisfaction from baseline to 6-months, and this drop was sustained at 12-months. This is consistent with Hillier et al.'s [22] observation that employees with ASD rated their job satisfaction to be relatively high, but job satisfaction ratings tended to decrease over time as employees with ASD also rated their jobs less challenging, as well as the more general 'hangover' effect observed in the literature on job satisfaction [4]. In the current sample, the jobs that the trainees perform do vary (e.g., different software iterations) and may align with tendencies of individuals with ASD (e.g., attention to detail, repetition). However, the overall job may still become less interesting over time. Further, trainees may become more aware of some of the more mundane aspects of working in ICT (e.g., occasional technology failures that limit work periods or 'slower' periods). Anecdotal evidence from conversations with support staff suggest that the trainees with ASD may find these setbacks to be especially frustrating, which may contribute to the slight drop in their job satisfaction [17]. Further research is needed to examine the longer-term trend in job satisfaction for individuals with ASD.

Quality of life remained fairly stable over time, and consistent with levels reported in other samples with ASD [43], though it should be noted that previous research has also found that quality of life tends to be somewhat lower among individuals with ASD compared to the general population [43]. Given that employment has been related to improved quality of life for individuals with ASD in other studies [18], it is somewhat surprising that quality of life did not change over time in the present research. It could be that the sample was too small or that the period of employment was not long enough to detect changes. It is also possible that the participants with ASD lacked sufficient insight into how their quality of life had changed. However, other researchers have noted a 'disability paradox' such that individuals with disabilities may be unlikely to view their quality of life negatively [1; 47]. This paradox might be understood in terms of a capabilities approach to disability. Mitra [29] explains that 'capabilities' refer to the range of practical opportunities available to a person (i.e., potential disability) whereas 'functionings' refer to the specific capabilities that the person chooses to pursue (i.e., actual disability). An individual's capability set is affected by personal and situational characteristics (e.g., social and political environment), thus employment may alter the capability set of individuals with ASD and, subsequently, the person's functionings and how the individuals adapt and focus their attention. Consistent with this framework, comments from participants [17] suggests that employment changed trainees outlook and perspective, for example, providing them with a sense of purpose.

Turning to the correlation results, there was a significant positive relationship between job satisfaction and age at baseline, suggesting older individuals were more likely to report higher job satisfaction scores than younger employees; however, this effect was not evident in 6- and 12- month data. Age was also not found to be significantly associated with quality of life. We did not identify significant relationships between quality of life and job satisfaction, contrary to our hypothesis [44]. This finding was likely affected by the lack of overall change in scores over time, but was somewhat unexpected nonetheless. This finding suggests a disconnect between quality of life and job satisfaction in the present sample. Specifically, employed people with ASD may discriminate between satisfaction at work and broader aspects of their lives; that is, satisfaction at work may not generalize to broader life improvements, such as those captured by our current measure.

It is also important to consider that employment may not be associated with improved mental health outcomes in people with ASD [18]. For example, previous research has found that greater independence, including employment, in adults with ASD is associated with greater likelihood of experiencing poor mental health outcomes [3]. Our results suggest the relationship between employ-

ment, including satisfaction at work, ASD, and psychological wellbeing, assessed through quality of life, is likely to be complex and non-linear. A more nuanced examination of these constructs is required, utilizing longitudinal designs and broad-based, multiple assessment of the constructs in question. In addition, inclusion and control of external, non-employment related constructs will be required to better identify the nature of the relationship between, and contribution of, employment to health and wellbeing, and quality of life, in people with ASD.

Practical Implications and Limitations

Our findings are limited by our use of measures not specifically designed for use with people with ASD, although recent research supports the use of the WHOQOL-BREF in people with ASD [27]. Nevertheless, it is important to consider whether participants had sufficient understanding of the questions related to quality of life, or sufficient insight to be able to adequately report change in quality of life over time. Our previous research [17] does suggest that participants have sufficient insight into their lives, and are able to report on this in an interview setting, although this may not translate to survey questionnaires as employed here. Future research would benefit from a mixed-method approach, employing both qualitative and quantitative methodology. In employment research specifically, different measures have been used [13], making it difficult to directly compare previous results with the findings reported here. Our previous research suggests that the DXC Technology Dandelion Program has significant strengths and potential benefits for participants [17]. However, these qualitative improvements reported previously are not supported by the present study, which failed to capture significant improvement in quality of life as participants progressed through the program. We suggest there are ways in which the Dandelion Program could be improved. This could be through targeted training and personalization based on the individual abilities and level of experience of the trainees with ASD; e.g., the program mandates a slow and gradual adjustment into the workplace, which may not be necessary for all individuals with ASD. Indeed, advocates for the autistic community often stress their diversity and the 'different, not less' ways that autistic individuals demonstrate achievement [14; 31; 42]. Further research with larger samples and diverse support programs would be useful to explore how such customization could be achieved. In particular, the current study would have benefitted from the inclusion of a comparison or control group, as well as qualitative reports (although see [17] for qualitative findings) to better consider the granularity of the mixed findings related to job satisfaction and quality of life. Our recent research [18] has identified significant mental health concerns amongst employees with ASD, suggestive of additional impacts of stress that may further affect quality of life. Tackling mental health and well-being amongst employees with ASD within the workplace is an important next step.

Another issue to consider in the DXC Technology Dandelion Program, and other supported work programs, is that it requires individuals to disclose their disability. Indeed, a confirmed diagnosis of ASD is the only requirement to apply for the program, and participants' disclosure is not limited to confidential human resource paperwork as the purpose of the program is widely known throughout the organization. As the Dandelion Program and similar autism at work programs become more widely publicized, future disclosure may be implicit on the employee's CV. Individuals with ASD vary in their willingness and enthusiasm to disclose their diagnosis [24], and one participant explicitly noted in other research [17] that he had been unwilling to disclose to previous employers. Future research should examine the consequences of such disclosure for employees' well-being and future work experiences.

Conclusion

There is a paucity of research on employment among individuals with ASD [19; 31], but it is a growing part of the workforce [20]. Over a period of 12-months we found relative stability over time in both quality of life as well as intrinsic and extrinsic job satisfaction, with no significant change over time identified. In contrast to our hypothesis, we failed to identify statistically significant relationships between quality of life and job satisfaction suggesting a disconnect between these two constructs in the present sample. Our findings challenge the

assumption that employment is a desirable outcome in and of itself, without giving consideration to potential risks, pitfalls, and layers of employment in ASD that are not yet well-understood or articulated in the literature. By locating employment in the context of one's overall well-being, these concepts, along with finding ways to nurture employment in terms of broader aims of overall quality of life, and effective means to build job satisfaction in one's employment experience, offer promise for research and practice advancement. Finally, it is imperative to further understand how organizations can support individuals with ASD in the workplace, and how to help them develop long-lasting and meaningful careers that are satisfying and positively affect their quality of life.

References

1. *Albrecht G.L., Devlieger P.J.* The disability paradox: High quality of life against all odds. *Social Science & Medicine*, 1999, vol. 48, no. 8, pp. 977—988. DOI: 10.1016/S0277-9536(98)00411-0
2. *Baumgärtner M.K., Dwertmann D.J.G., Boehm S.A., Bruch H.* Job satisfaction of employees with disabilities: The role of perceived structural flexibility. *Human Resource Management*, 2015, vol. 54, no. 2, pp. 323—343. DOI: 10.1002/hrm.21673
3. *Bishop-Fitzpatrick L., Hong J., Smith L.E., Makuch R.A., Greenberg J S., Mailick M.R.* Characterizing objective quality of life and normative outcomes in adults with Autism Spectrum Disorder: An exploratory latent class analysis. *Journal of Autism and Developmental Disorders*, 2016, vol. 46, no. 8, pp. 2707—2719. DOI: 10.1007/s10803-016-2816-3
4. *Boswell W.R., Shipp A.J., Payne S.C., Culbertson S.S.* Changes in newcomer job satisfaction over time: Examining the pattern of honeymoons and hangovers. *Journal of Applied Psychology*, 2009, vol. 94, no. 4, pp. 844—858. DOI: 10.1037/a0014975
5. *Bury S.M., Hedley D., Uljarević M., Gal E.* The autism advantage at work: A critical and systematic review of current evidence. *Research in Developmental Disabilities*, 2020, vol. 105. DOI: 10.1016/j.ridd.2020.103750
6. *Carr S.E.* Quality of life in emerging adults with autism spectrum disorder. *Dissertation Abstracts International: Section B: The Sciences and Engineering*, 2015, vol. 76.
7. *Cavanagh J., Bartram T., Meacham H., Bigby C., Oakman J., Fossey E.* Supporting workers with disabilities: A scoping review of the role of human resource management in contemporary organisations. *Asia Pacific Journal of Human Resources*, 2015, vol. 55, no. 1, pp. 6—43. DOI: 10.1111/1744-7941.12111
8. *Chen J.L., Leader G., Sung C., Leahy M.* Trends in employment for individuals with Autism Spectrum Disorder: A review of the research literature. *Review Journal of Autism and Developmental Disorders, vol. 2,* pp. 115—127. DOI: 10.1007/s40489-014-0041-6
9. Diagnostic and statistical manual of mental disorders (5th ed.). Washington: Publ. American Psychiatric Association, 2013. 991 p. ISBN 978-0-89042555-8.
10. Digital Skills and Jobs Coalition / European Commission [Web resource]. 2020. URL: https://ec.*europa*.eu/digital-single-market/en/news/bridging-digital-talent-gap-towards-successful-industry-university-partnerships-workshop (Accessed 03.09.2020).
11. Disability, Ageing and Carers, Australia: Summary of Findings, 2018 / Australia Bureau of Statistics [Web resource]. 2019. URL: https://www.abs.gov.au/ausstats/abs@.nsf/mf/4430.0 (Accessed 03.09.2020).
12. *Donovan S.* Entrepreneur Thorkil Sonne on what you can learn from employees with autism. *Harvard Business Review*, 2008, no. 9, p. 32.
13. *Garcia-Villamisar D., Wehman P., Navarra M D.* Changes in the quality of autistic people's life that work in supported and sheltered employment: A 5-year follow-up study. *Journal of Vocational Rehabilitation*, 2003, vol. 17, no. 4, pp. 309—312.
14. *Grandin T.* Different... not less: Inspiring stories of achievement and successul employment from adults with autism, Asperger's, and ADHD. Arlington: Publ. Future Horizons, 2012. 407 p. ISBN 978-1-93527460-5.
15. *Hagner D., Cooney B.F.* "I do that for everybody": Supervising employees with Autism. *Focus on Autism and Other Developmental Disabilities, 2005, vol. 20,* no. 2, pp. 91—97. DOI: 10.1177/10883576050200020501
16. *Happe F., Frith U.* The weak coherence account: detail-focused cognitive style in autism spectrum disorders. *Journal of Autism and Developmental Disorders*, 2006, vol. 36, no. 1, pp. 5—25. DOI: 10.1007/s10803-005-0039-0
17. *Hedley D., Cai R., Uljarević M., Wilmot M., Spoor J R., Richdale A., Dissanayake C.* Transition to work: Perspectives from the autism spectrum. *Autism*, 2018, vol. 22, no. 5, pp. 528—541. DOI: 10.1177/1362361316687697
18. *Hedley D., Uljarević M., Bury S.M., Dissanayake, C.* Predictors of mental health and well-being in employed adults with autism spectrum disorder at 12-month follow-up. *Autism Research*, 2019, vol. 12, no. 3, pp. 482—494. DOI: 10.1002/aur.2064
19. *Hedley D., Uljarević M., Cameron L., Halder S., Richdale A., Dissanayake, C.* Employment programmes and interventions targeting adults with autism spectrum disorder: A systematic review of the literature. *Autism*, 2017, vol. 21, no. 8, pp. 929—941. DOI: 10.1177/1362361316661855
20. *Hedley D., Uljarević M., Hedley D.F.E.* Employment and living with Autism: Personal, social and economic impact. In *Halder S., Assaf L.C. (eds.)* Inclusion, Disability and Culture: An Ethnographic Perspective Traversing Abilities and Challenges. New York: Publ. Springer, 2017. 390 p. ISBN 978-3-31955223-1. DOI: 10.1007/978-3-319-55224-8_19
21. *Hendricks D.* Employment and adults with autism spectrum disorders: Challenges and strategies for success. *Journal of Vocational Rehabilitation*, 2010, vol. 32, no. 2, pp. 125—134. DOI: 10.3233/JVR-2010-0502

22. *Hillier A., Campbell H., Mastriani K., Izzo M.V., Kool-Tucker A.K., Cherry L., Beversdorf D.Q.* Two-year evaluation of a vocational support program for adults on the autism spectrum. *Career Development for Exceptional Individuals*, vol. 30, no. 1, pp. 35—47. DOI: 10.1177/08857288070300010501
23. *Hirschfeld R.R.* Does revising the intrinsic and extrinsic subscales of the Minnesota Satisfaction Questionnaire Short Form make a difference? *Educational and Psychological Measurement*, 2000, vol. 60, no. 2, pp. 255—270. DOI: 10.1177/00131640021970493
24. *Johnson T.D., Joshi A.* Dark clouds or silver linings? A stigma threat perspective on the implications of an autism diagnosis for workplace well-being. *Journal of Applied Psychology*, 2016, vol. 101, no. 3, pp. 430—449. DOI: 10.1037/apl0000058
25. *Judge T.A., Klinger R.* Job satisfaction: Subjective well-being at work. In *Eid M., Larsen R.J. (eds.)* The science of subjective well-being. New York: Publ. Guilford Press, 2008. Pp. 393—413. ISBN 978-1-59385581-9.
26. *Krzeminska A., Austin R., Bruyere S., Hedley D.* The advantages and challenges of neurodiversity employment in organizations. *Journal of Management and Organization*, 2019, vol. 25, no. 7, pp. 453—463. DOI: 10.1017/jmo.2019.58
27. *Lawson L.P., Richdale A.L., Haschek A., Flower R L., Vartuli J., Arnold S.R., Trollor J.N.* Cross-sectional and longitudinal predictors of quality of life in autistic individuals from adolescence to adulthood: The role of mental health and sleep quality. *Autism, 2020, vol. 24,* no. 4, pp. 954—967. DOI: 10.1177/1362361320908107
28. *Locke E.A.* The nature and causes of job satisfaction. In *M.D. Dunnette (Ed.)* Handbook of industrial and organizational psychology. Chicago: Publ. Rand McNally, 1976. Pp. 1297—1343.
29. *Mitra S.* The capability approach and disability. *Journal of Disability Policy Studies*, 2006, vol.16, no. 4, pp. 236—247. DOI: 10.1177/10442073060160040501
30. *Muller E., Schuler A., Burton B.A., Yates G.B.* Meeting the vocational support needs of individuals with Asperger Syndrome and other autism spectrum disabilities. *Journal of Vocational Rehabilitation*, 2003, vol. 18, pp. 163—175.
31. *Nicholas D.B., Hedley D., Randolph J.K., Raymaker D.M., Robertson S.M., Vincent J.* An expert discussion on employment in autism. *Autism in Adulthood*, 2019, vol. 1, no. 3, pp. 162—169. DOI: 10.1089/aut.2019.29003.djn
32. *Renty J.O., Roeyers H.* Quality of life in high-functioning adults with autism spectrum disorder. *Autism*, 2006, vol. 10, no. 5, pp. 511—524. DOI: 10.1177/1362361306066604
33. *Richards J.* Examining the exclusion of employees with Asperger Syndrome from the workplace. *Personnel Review*, 2012, vol. 41, no. 5, pp. 630—646. DOI: 10.1108/00483481211249148
34. *Robertson S.M.* Neurodiversity, quality of life, and autistic adults: Shifting research and professional focuses onto real-life challenges. *Disability Studies Quarterly*, 2010, vol. e30, no. 1. DOI: 10.18061/dsq.v30i1.1069
35. *Roux A.M., Shattuck P.T., Cooper B.P., Anderson K.A., Wagner M., Narendorf S.C.* Postsecondary employment experiences among young adults with an autism spectrum disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, 2013, vol. 52, no. 9, pp. 931—939. DOI: 10.1016/j.jaac.2013.05.019
36. *Schur L., Kruse D., Blasi J., Blanck P.* Is disability disabling in all workplaces? Workplace disparities and corporate culture. *Industrial Relations: A Journal of Economy and Society*, 2009, vol. 48, no. 3, pp. 381—410. DOI: 10.1111/j.1468-232X.2009.00565.x
37. Sickness, disability and work: Breaking the barriers: A synthesis of findings across OECD countries. Paris: Publ. OECD, 2010. 165 p. ISBN 978-9-26408884-9.
38. *Skevington S.M., Lotfy M., O'Connell K.A.* The World Health Organization's WHOQOL-BREF quality of life assessment: Psychometric properties and results of the international field trial: A report from the WHOQOL group. *Quality of Life Research*, 2004, vol. 13, no. 2, pp. 299—310. DOI: 10.1023/B:QURE.0000018486.91360.00
39. *Stone D.L., Colella A.* A model of factors affecting the treatment of disabled individuals in organizations. *Academy of Management Review*, 1996, vol. 21, no. 2, pp. 352—401. DOI: 10.2307/258666
40. *Tabachnick B.G., Fidell L.S.* Using multivariate statistics. 5th ed. Needham Heights: Publ. Allyn & Bacon, 2007. 980 p. ISBN 978-0-20545938-4.
41. *Taylor J.L., Henninger N.A., Mailick M.R.* Longitudinal patterns of employment and postsecondary education for adults with autism and average-range IQ. *Autism*, 2015, vol. 19, no. 7, pp. 785—793. DOI: 10.1177/1362361315585643
42. *Urbanowicz A., Nicolaidas C., den Houting J., Shore S.S., Gaudion K., Girdler S., Savarese R.J.* An expert discussion on strengths-based approaches in autism. *Autism in Adulthood*, 2019, vol. 1, no. 2, pp. 82—89. DOI: 10.1089/aut.2019.29002.aju
43. *Van Heijst B.F., Geurts H.M.* Quality of life in autism across the lifespan: a meta-analysis. *Autism: The international journal of research and practice*, 2015, vol. 19, no. 2, pp. 158—167. DOI: 10.1177/1362361313517053
44. *Warr P.* Well-being and the workplace. In *D. Kahneman, E. Diener, N. Schwarz (Eds.)* Well-being: The foundations of hedonic psychology. New York: Publ. Russell Sage Foundation, 1999. Pp. 392—412. ISBN 978-0-87154423-0.
45. *Weiss D.J., Dawis R.V., England G.W., Lofquist L.H.* Manual for the Minnesota Satisfaction Questionnaire / Industrial Relations Center. Minneapolis: Publ. University of Minnesota, 1967. 119 p.
46. WHOQOL-BREF: Introduction, administration, scoring, and generic version of the assessment. Geneva: World Health Organization, 1996. 32 p.
47. World report on disability / WHO; World Bank. Geneva: World Health Organization, 2011. ISBN 978-92-4-156418-2.

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Autism: Multidisciplinary Evaluation and Treatment. The LADDERS Model

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Autism Spectrum Disorder (ASD) is a developmental disorder characterized by impaired social interaction, delayed and disordered communication skills and isolated areas of interest. There is a growing appreciation that ASD is more complex than previously appreciate and in many cases, involves multiple organ systems beyond the brain. Those affected require intensive therapeutic services as well as skilled medical diagnosis and supervision. This paper describes a multidisciplinary clinical model in which the many services and interventions needed by ASD patients can be provided in a single site, reducing fragmentation of care and providing skilled diagnostic care and ongoing supervision.

Keywords: autism, behavior, medical co-morbidities, coordinated care.

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Аутизм. Мультидисциплинарная оценка и терапия. Модель LADDERS

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Расстройства аутистического спектра (РАС) — это нарушения развития, характеризующиеся трудностями в социальном взаимодействии, дефицитом и задержкой развития коммуникативных навыков, а также ограниченными интересами. В настоящее время растет понимание того, что РАС — более сложное состояние, чем считалось ранее; во многих случаях оно связано не только с мозгом, но и с другими системами органов. Люди с данными расстройствами нуждаются в интенсивной терапевтической помощи, а также в квалифицированной диагностике и наблюдении. В статье описана мультидисциплинарная клиническая модель, в рамках которой большое количество услуг и вмешательств, необходимых пациентам с РАС, может быть предоставлено в одном учреждении, что уменьшит разобщенность процессов оказания медицинских услуг и позволит обеспечить квалифицированную диагностику и постоянное наблюдение.

Ключевые слова: аутизм, поведение, сопутствующие заболевания, скоординированная помощь.

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Infantile autism is a behaviorally defined disorder first described by Leo Kanner in 1943 [8]. Since its original description, it has become apparent that the disorder is clinically, etiologically and biologically heterogeneous. Despite these differences, it is generally agreed that the core features of the disorder consist of a triad of clinical characteristics including impaired social interaction, delayed and disordered language and isolated areas of interest [5]. Additional features can include reduced eye contact, stereotypic and repetitive behaviors, sensory processing dysfunction and an insistence on sameness. Symptoms can range from mild to very severe. Until recently, it was believed that most individuals on the autism spectrum cognitively functioned in the mentally retarded range. However, current data suggests that fewer than half of those affected have a significant cognitive deficit [10].

Since its original description, the prevalence of the Autism Spectrum Disorders has been increasing, possibly in part due to improved recognition, expanded access to services and broadening of defining diagnostic features. According to the Centers for Disease Control and Prevention (CDC), autism is estimated to affect 1 in 59 children in the United States today [1; 2]. In many cases, ASD can be reliably diagnosed by the age of 2 years but some associated developmental delays are often evident earlier in life [9].

Since the 1980s, much of the research related to ASD has been devoted to the investigation and understanding of the underlying neurobiological mechanisms related to the clinical characteristic features of the disorder. Research approaches have included studies of gross and microscopic anatomy, neuroimaging, metabolic and genetic assessments, neurochemical and immunological mechanisms and studies of cellular connectivity. Although much progress has been, we still have much to learn.

Coincident with the expansion of basic science research has been the broadening of clinical investigations. As a result, there is now increasing evidence that ASD is a much more complex disorder than previously appreciated and may involve not only the brain but, in many cases, multiple organ systems. There is a growing body of literature documenting disorders such as gastrointestinal dysfunction, sleep disorders, metabolic abnormalities, urinary tract and hormonal involvement, allergies, obesity, osteoporosis, enlarged tonsils and adenoids, and PANDAS to name a few. Until the past 5-10 years, many of these disorders had been overlooked, possibly because many ASD patients can be difficult to examine. Many are non-verbal and cannot express their pain and discomfort or accurately localize their discomfort. Still others may present with symptoms that are not easily recognized as signals for underlying medical conditions by the average practitioner such as episodic disruptive behaviors that may signal discomfort [3].

In addition to their multiple medical disorders, children, adolescents and adults on the autism spectrum present with developmental challenges that require specialized and intensive interventions including speech and language services, occupational therapy, physical therapy, applied behavior analysis (ABA), social skills intervention, access to assisted technology, special education approaches and transitional planning into adulthood including secondary education opportunities and vocational exploration. From the perspective of the average family, locating and providing needed interventions for their autistic child or young adult can be confusing and often extremely stressful.

The Birth of the LADDERS Program

In the 1960s, federally supported programs were established in the United States during the Kennedy administration designated as University Affiliated Programs (UAPs) [7; 12]. Each academically associated UAP provided a multidisciplinary team designed to evaluate individuals with developmental disabilities, including those residing in mental institutions, with the goal of moving these clients from these settings out into the community. These programs involved a broad range of professional disciplines including Neurology, Psychiatry, Nursing, Audiology, Speech Pathology, Psychology, Occupational Therapy, Physical Therapy, Social Work, Special Education and a Vocational Specialist. Team members each evaluated the same patient over a two-week period after which results were shared within the team, discussed with the client's family and plans made for community placement. Not only was this an exceptional evaluation opportunity for the patient and his/her family, but the program provided a valuable teaching model for team members, each of whom was able to learn from their colleagues. It was against the background of the UAP model that the concept of LADDERS (Learning And Developmental Evaluation and Rehabilitation Services) was created.

LADDERS began in the late 1980s, initially centered in a rehabilitation hospital in Cambridge, Massachusetts. In contrast to the UAP model, the LADDERS approach included not only the evaluation of the patient, but also program planning, direct therapy on site, and ongoing follow-up. Initially, the program was focused on the assessment and provision of services for students with learning differences (Learning Disabilities). However, the client population began to change during the early 1990s as the result of the then growing body of research being conducted in autism and with the increased awareness of this disorder. Thus, from that point forward, the focus of the program rapidly changed to a center dedicated to the diagnosis and treatment of children, adolescents and adults with autism. During the mid-2000s, the program came under the administration of one of the major teaching hospitals in eastern Massachusetts, a relationship that helped to foster the education of doctors in training as well as undergraduate and graduate students, and provided a rich environment for interdisciplinary clinical research.

The Expansion of the LADDERS Program

By 2003, the majority of LADDERS patients were being referred from sites throughout all of the New England states as well as New York and New Jersey. 90% of these patients carried a diagnosis of ASD, with the remaining patients presenting with other types of learning and developmental disabilities. Patients were typically referred by primary care physicians, educators, therapists, family members and Early Intervention Agencies. Initially, the focus of a first-time referral was to the medical staff and was devoted to making or confirming a specific diagnosis. Later, however, an equal number of requested assessments were directed toward the therapeutic staff with requests to define the patient's therapeutic and educational needs and to help families locate needed quality services near their respective homes. The provision of direct on-site therapies, including speech and language intervention, Occupational Therapy and Physical Therapy were also added. Ongoing monitoring of the patient's progress then became an integral part of the program in order to insure that the services provided were effectively meeting each patient's needs and allowing each client to make meaningful progress.

Program Structure

A patient referred to LADDERS was initially processed by an Intake Coordinator who conducted a telephone interview, usually with the parent, in order to identify the reason for the referral in order to be able to direct the patient to the appropriate provider. An initial appointment was scheduled and an Intake Packet was mailed to the family requesting past medical and developmental history as well as copies of previous medical and educational records. Typically, the patient would be first seen by one of the clinic physicians who, based on the information provided and the physical and neurological evaluation, would determine what laboratory studies and medical and therapy assessments would be needed to define the patient's diagnosis and therapeutic needs. Upon completion of these evaluations, the physician would meet with the patient's parents/caregiver to review the findings and recommendations, and provide appropriate resources for therapies and interventions. Following the initial assessments, ongoing periodic monitoring was provided, with follow-up visits typically scheduled every 3—6 months.

The LADDERS Team

Although LADDERS began its life under the administration of a rehabilitation hospital, it later became overseen by a joint agreement between an acute care academic teaching hospital and a rehabilitation facility. Specialty areas supported by the acute care academic hospital included Developmental Pediatrics, Adult and Child Neurology, Internal Medicine, Adult and Child Psychiatry, Neuropyschology, Social Work, Family Resource Coordinator/Patient Navigator, Gastroenterology and Education Specialist.

Disciplines supported by the Rehabilitation Hospital included Occupational Therapy, Physical Therapy, Speech and Language Pathology, Nutrition/Feeding Specialist and Assisted Technology/Communication Device Specialist.

A clinical program such as LADDERS cannot reasonably support every potential discipline that any one patient might need on site. It is therefore important that quality community based therapeutic and medical resources must be identified with whom this program could collaborate. Further, such resources cannot be only identified locally, but since many patients have been referred from throughout

the northeast region of the United States and beyond, resources need to be sought near where any specific patient resides. Seeking and identifying skilled resources becomes the job of the Family Resource Coordinator/Patient Navigator in collaboration with other clinic providers [6]. The identification of skilled medical and therapeutic care and educational programs on behalf of the patient is as important as making the initial diagnosis. Without quality intervention and treatment programs, the chances that the patient can and will make the progress of he/she is capable remains uncertain.

In addition to identifying appropriate therapeutic sites near a patient's home, needed community based medical resources are many. Individuals on the autism spectrum can experience many of the health conditions impacting their typically developing peers. However, it is essential to identify resources experienced in working with the autistic population because these individuals can present with symptoms not easily recognized by the average medical provider or specialist. Some of these resources include Medical Genetics, Sleep Disorders, Allergy, Urology/Nephrology, Endocrinology, Otolaryngology, Developmental Optometry, Ophthalmology, Audiology, Dental care, Orthopedics, Behavioral Psychology, Infectious Disease, Educational Advocacy, Educational Law and Social Skills agencies.

The LADDERS Program now

In 2003, the concept of the multidisciplinary program/medical home for individuals on the autism spectrum was presented at a conference in Seattle, Washington. Following this presentation and with the aide of philanthropic resources, it was elected to create a collaboration of similar programs throughout the United States. As a result, the Autism Treatment Network (ATN) was established under the guidance of the Northwest Autism Foundation in Portland, Oregon with the goal of creating a network of academically based multidisciplinary centers that would develop mutually agreed upon protocols focused on the documentation and assessment of prevalence, presenting clinical features and treatment of comorbid medical conditions across the autism spectrum. Later, in 2008, the ATN came to be incorporated into the work of Autism Speaks, currently the largest autism advocacy organization in the United States. Although the ATN has undergone changes in collaborators, personnel and funding over time, the program continues to thrive under the auspices of Autism Speaks and now includes 12 sites, two in Canada with the remaining 10 programs located throughout the United States [4].

Despite its changes and growth over time, the goals of the ATN have remained consistent and include, 1) the establishment of scientifically sound and meaningful standards of healthcare for those on the autism spectrum, 2) the establishment of evidence based data with regard to medically related conditions in autism, 3) the provision of a forum for collaborative hypothesis-driven clinical research across the network and 4) the provision high quality care for those on the autism spectrum by identifying and implementing best practices [11]. Over the past several years, the ATN, with the support of Autism Speaks, has created and maintained a clinical patient registry, which now includes close to 7000 children with autism. This registry has gathered follow-up data allowing a review of changes over time in some of the characteristics and health care needs of ASD children. This data has been made available to both internal and external investigators, resulting in doctoral dissertations and peer-reviewed publications [11].

Medical Comorbidities

With advances in clinical care, there has come the appreciation that many children, adolescents and adults on the autism spectrum experience medically significant disorders that may negatively impact their developmental progress and behavior, but which frequently go undetected. Many of these conditions are treatable, and when identified and addressed, can improve developmental trajectory and quality of life for both the patient and his/her family/caregivers. Some of the more common medical conditions include seizures, sleep disorders, gastrointestinal dysfunction, obesity, metabolic conditions, hormonal imbalances, and psychiatric disorders including anxiety, attention deficit disorders, obsessive compulsive disorders and depression. Additional conditions that are now receiving increased attention include osteoporosis, otitis media, bladder and renal disorders, hypertension, diabetes, dental pain and immune disorders. In many cases, more commonly in those patients who are non-verbal, these disorders many present in an atypical manner, often with the patient demonstrating disruptive behaviors including aggression,

self-injury and screaming. There is a growing recognition that many of these behaviors may reflect pain and discomfort in a patient who cannot verbally express his/her distress or accurately localize the cause of their discomfort. Thus, there is an increasing consensus that any patient presenting with unexplained disruptive behaviors merits a detailed medical assessment before assuming that these behaviors are "just part of their autism"/

Multidisciplinary Programs — the benefits and challenges

The creation and development of multidisciplinary centers focused on the evaluation, treatment and advocacy for individuals on the autism spectrum provides a numbers of advantages and resources, both for families as well as providers. Although ASD is becoming an increasingly common disorder, there are still situations in which the diagnosis of autism is missed or overlooked. This most often occurs in the very young child, in individuals with "high functioning autism" and in females, many of whom have been labeled with a variety of psychiatric conditions. The availability of high quality, skilled autism centers can provide a site where families and caregivers can confidently seek and obtain accurate assessments and scientifically sound recommendations for interventions and services. Further, once a diagnosis and recommendations are made, a multidisciplinary site can provide additional evaluations and needed therapeutic interventions in the same location, thus preventing fragmented care. Offering ongoing multiple services for families in the same site reduces stress on parents/caregivers, while increasing opportunities for therapists and medical staff to communicate with each other and to carry over strategies and interventions across disciplines, thereby enhancing treatment approaches and effectiveness.

Ongoing educational opportunities for staff is a critically important feature of a multidisciplinary program. Many physicians do not receive an in-depth exposure to speech pathology or occupational and physical therapy as it relates to the evaluation and treatment of individuals with special needs as part of their training. The availability of other disciplines evaluating the same patient teaches providers on the team to appreciate and learn from the insights of others, a very valuable lesson, and often allows them to see what they may have missed as part of their own assessments. Complementing the education of the team staff is the importance of providing meaningful training for medical students, interns and residents, as well as graduate and undergraduate students. Providing such training in such an academic multidisciplinary and cross-disciplinary site is an unprecedented opportunity, especially given the increasing numbers of individuals identified with ASD. Regardless of what medical or therapeutic field a student eventually selects for his future career path, almost all will become involved with patients on the autism spectrum at some point and they will need to be adequately prepared when that time arises. Experience in a high quality multidisciplinary program should be able to provide a strong background for their future.

In addition to the important clinical opportunities offered by a multidisciplinary approach is the provision of an environment that encourages interdisciplinary research. The ATN has provided a leadership role across its multiple sites focused on a number of important comorbid medical conditions including constipation, sleep disorders as well as dental health and obesity. The opportunity to create and utilize a common registry and database that includes a large number of well-documented patients provides an invaluable resource for present and future research. There is no doubt that a collective and well-designed database will play an important role in pursuing future research including studies that will lead to a better understanding of the underlying neurobiology of the disorder as well as defining potential subgroups, identifying differences between males and females on the spectrum and documenting the life long trajectory of this disorder.

While there are many strong advantages to the availability of multidisciplinary autism centers, there are also challenges. One of the major areas of concern is the financial support needed to sustain these programs. While insurance can cover the cost of some the medical and therapeutic expenses, there continues to be significant gaps in financial resources. The ATN has been supported by Autism Speaks as well as funding from the Health Resources and Services Administration (HRSA) to become the Autism Intervention Research Network on Physical Health (AIR-P). This funding has been critically important for the support of ongoing research efforts and much of the resulting published data. However, despite federal and healthcare insurance support, there is still a need for philanthropic efforts to cover administrative costs and the salary of some

staff who, while being critically essential members of the team, are non-revenue producers.

Conclusion

Autism spectrum disorders are complex, behaviorally defined developmental disorders characterized by impairment of social interactions, delayed and disordered language, repetitive behaviors and restricted areas of interest. Over the past 10 years, there has been a growing awareness that these disorders are often associated with significant medical comorbidities, many of which have been overlooked. When identified and treated, patients show improvement in their development trajectory and quality of life. The availability of multidisciplinary centers providing skilled evaluation and treatment resources can have a critically important impact on the developmental outcomes for those on the autism spectrum. These centers can offer scientifically based health care and therapeutic interventions, provide interdisciplinary treatment approaches, reduce fragmentation of care, provide educational opportunities for staff and students and offer important avenues for clinical research. The LADDERS program provides an example of one such clinical approach but other models may be equally effective depending on the needs and environment of the community in which a specific site may be located. Integrated and collaborative care is an important approach to this complex disorder and can improve short and long term outcomes.

References

1. Autism and Developmental Disabilities Monitoring (ADDM) Network / Centers for Disease Control and Prevention [Web resource]. iSBN 978-0-89042-555-8. URL: http://www.cdc.gov/ncbddd/autism/addm.html (Accessed 31.08.2020).
2. Baio J., Wiggins L., Christensen D.L. et al. Prevalence of autism spectrum disorder among children aged 8 years — Autism and Developmental Disabilities Monitoring Network. 11 sites, United States, 2014. Morbidity and mortality weekly report: Surveillance summaries, 2018, vol. 67, no. 6, pp. 1–23. DOI:10.15585/mmwr.ss6706al
3. Bauman M.L. Medical Comorbidities in Autism: Challenges to Diagnosis and Treatment. Neurotherapeutics, 2010, vol. 7, no. 3, pp. 320–327. DOI: 1016/j.nurt.2010.06.001
4. Coury D.L., Murray D.S., Fedele A. et al. The Autism Treatment Network: Bringing Best Practices to All Children with Autism. Pediatrics, 2020, vol. 145, no. Supplement 1, pp. s13–s19. DOI: 10.1542/2019-1895D.
5. Diagnostic and statistical manual of mental disorder: DSM-5. 5th edition. Arlington: Publ. American Psychiatric Publishing, 2013. ISBN 978-0-89042-555-8.
6. DiBari J.N., Azuine R.E., Linares D.E. et al. Maternal and Child Health Bureau's Autism Research Program. Pediatrics, 2020, vol. 145, no. Supplement 1, pp. s5–s12. DOI: 10.1542/peds.2019-1895C
7. Jones W.E. The American Association of University Affiliated Programs. Developmental Disabilities Research Reviews, 1995, vol. 1, no.4, p ii. DOI: 10.1002/mrdd.1410010414.
8. Kanner L. Autistic disturbances of affective contact. Nervous Child. 1943: 2:217–250.
9. Lord C., Risi S., DiLavore P.S., Shulman C., Thurm A., Pickles A. Autism from 2 to 9 years of age. Archives of General Psychiatry, 2006, vol. 63, no. 6, pp. 694–701. DOI:10.1001/archpsy63.6.694
10. Newschaffer C.J., Croen L.A., Daniels J. et al. The epidemiology of autism spectrum disorders. Annual Review of Public Health, 2007, vol. 28, pp. 235–258. DOI: 10.1146/annurev.pubhealth.28.021406.144007
11. Perrin J.M., Coury D.L., Klatka K. et al. The Autism Intervention Research Network on Physical Health and the Autism Speaks Autism Treatment Network. Pediatrics (suppl). 2016, vol. 137, no. Supplement 2, pp. s67–s71. DOI:10.1542/peds.2015-2851D
12. Warren S.L. Implementation of the President's Program on Mental Retardation. The American Journal of Psychiatry, 1964, no. 121, pp. 549–554. DOI:10.1176/ajp.121.6.549

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Integrating Treatment for Autism: Etiology and Life Cycle

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Autism Spectrum Disorder (ASD) is linked to a multitude of genes, epigenetics, and environmental factors, which contribute to the complexities of treating ASD. A large body of literature suggests benefits from perinatal, early, and later intervention. It is common for physicians to struggle with making a diagnosis of ASD, but once it is made, parents who have been taught effective strategies can be impactful in their child's positive development. Neuroimaging studies of children, adolescents and young adults with ASD suggest that their brain structures change over time and are also capable of being shaped through appropriate interventions. Interventions are also being adapted for adults with ASD to better address their needs, such as employment training programs. We review the wide array of risk factors and interventions to mitigate the challenges individuals with ASD face in their daily lives.

Keywords: autism, risk factors, endophenotypes, intervention, adaptive functioning, primary care.

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Интеграция помощи людям с РАС: этиология и жизненный цикл

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Расстройства аутистического спектра (РАС) связаны с большим количеством генетических, эпигенетических и средовых факторов, что усложняет организацию помощи людям с данным диагнозом. Во множестве опубликованных работ описываются преимущества перинатальных, ранних и более поздних вмешательств. Как правило, врачам бывает непросто диагностировать РАС, однако после постановки диагноза родители, ознакомленные с эффективными стратегиями помощи, могут оказать существенное положительное влияние на развитие своего ребенка. Исследования детей, подростков и молодых людей с РАС, выполненные с применением методов нейровизуализации, показывают, что структуры их мозга меняются с течением времени, и что они также могут меняться под воздействием подходящих вмешательств. Данные вмешательства также адаптируют для взрослых с РАС таким образом, чтобы они лучше соответствовали их потребностям; примером могут служить программы профессиональной подготовки. В статье представлен обзор многих факторов риска и типов вмешательств. Это позволит уменьшить проблемы, с которыми сталкиваются люди с РАС в своей повседневной жизни.

Ключевые слова: аутизм, факторы риска, эндофенотипы, вмешательство, адаптивное функционирование, первичная помощь.

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Integrating Treatment for Autism Spectrum Disorders Through the Life Cycle

According to the Center for Disease Control, Autism Spectrum Disorder (ASD) is currently increasing in prevalence, with 1 in 54 children in the United States receiving the diagnosis. Although reasons for this are inconclusive, factors could include changing diagnostic knowledge and criteria, increased research and monitoring, a change in epigenetic processes, and exposure to environmental toxins and infections. Due to the heterogeneous nature of ASD, individuals with ASD face unique difficulties that may call for flexibility and creativity in multi-level targeted treatments. As the number of people with ASD are being recognized, it is vital to consider the most efficacious implementation of prevention, intervention and treatment for ASD throughout the life cycle.

Genetic and Environmental Etiology

There is a strong link between specific genes and ASD. Multiple genes are associated with ASD, including: CHD8, DYRK1A, FMR1, TSC1, TSC2, CNTNAP2, SMARCC2, CDH8, SHANK3, NRXN1, 15q11.2q13, 15q13.3, 16p11.2, NLGN2, GRIN2B, CDH8, and PTEN [8]. For approximately 25% of people with ASD, there is a clear genetic etiology [32] Many studies have found that there is a 64–88% concordance rate in identical twins with ASD, and between a 9-40% concordance rate in dizygotic twins, where at least one is affected by ASD [32; 39]. De novo ("new") mutations in neurologically expressed genes are associated with ASD that may carry widespread effects. In sibling studies, gene-disrupting mutations (splice site, frame shifts, and copy-number variations) were significantly higher in children with ASD than their unaffected siblings [20]. Researchers in Sweden estimated the genetic heritability influence on ASD to be about 50% [45] So, what comprises the remaining 50%?

ASD does not appear to be solely genetic in origin. Susceptibility to ASD has a larger shared twin environment component than genetic heritability. Polygenic models in which spontaneous coding mutations in a wide number of genes increase risk for ASD by 5–20 times [34]. Recent studies on the genetics suggest that the cause of ASD is also related to gene-by-environment interactions manifested in epigenetic processes [15; 17; 44] Epigenetics is the reversible regulation of mechanisms independent of DNA sequence, mediated largely through DNA methylation, chromatin sequence, and RNA-mediated gene expression [1]. The related endophenotypes connect underlying biologic aspects of a disease to an observable factor [42]. Research hints that epigenetic processes could be reversible by factors such as nutrition, socialization, behavioral interventions, and drugs [43].

Environmental factors are also a related cause of ASD. Evidence has been documented for risk factors including prenatal or early postnatal exposure

to viral infections (such as rubella), valproic acid, and thalidomide [36]. There has also been limited evidence for factors such as maternal metabolic conditions, fever during pregnancy, paternal/maternal age, use selective serotonin reuptake inhibitors (SSRIs), maternal smoking, and environmental pollution [2; 18; 19; 46; 60]. More evidence is needed to determine whether the following environmental factors increase the risk of ASD: mercury, lead, environmental toxins, vaccines, and lack of vitamin D [4; 11; 30; 40; 52; 58].

Parenting from Before Conception

Recent studies reveal that parental experiences also exert effects through epigenetic information. One study found variations in sperm and oocyte cytosine methylation and chromatin patterning, noncoding RNAs, and mitochondria [23]. Transgenerational epigenetic effects often interact with conditions at the time of conception in order to code the trajectory of the developing embryo and fetus, which will affect the health of the child for the rest of their life. For example, Mazina and colleagues [28] linked the presence of copy number variations and maternal infection to social communicative impairments and repetitive/restricted behaviors in study participants. Further investigation of such effects could give insight on how epigenetic variations give rise to ASD itself.

Risks

Various maternal attributes during pregnancy may lead to autism. For example, women aged 35 years or older are less likely to take supplemental iron and five times more likely to give birth to a baby with ASD [48]. Furthermore, prenatal steroid perturbations by the mother may create hormonal changes in a fetus and increase the risk of the child having ASD [13]. During the birth, pre-term babies who are small for their gestational age or delivered via Cesarean section are at a modest increased risk [12; 54; 59]. According to a study by Lyall and colleagues [26], higher maternal intake of certain nutrients and supplements containing folic acid can reduce the risk of ASD. Rodent studies indicate a strong causal relationship between maternal immune activation during pregnancy and ASD symptoms in offspring [49].

Certain obstacles in healthcare prevent important information regarding environmental risk to be passed onto expecting parents. In Stotland's study [51], surveys were sent to fellows from the American Congress of Obstetricians and Gynecologists and three obstetrician focus groups. 78% of obstetricians agreed that environmental health hazards could be reduced through education by counseling patients about them, but 50% reported that they rarely discussed the environmental health history of patients. Furthermore, less than 20% reported routinely asking about environmental hazards in pregnant women in the United States. Only 1 in 15 reported receiving training on the topic. There were several barriers which kept physicians from warning expecting mothers, including lack of education on hazardous environmental evidence, potential lack of capacity in patients to reduce harmful exposures, and concern of causing anxiety in patients. More education on environmental hazards (outlined in the next section) for both providers and expecting parents needs to be disseminated.

Can Autism be Prevented?

As previously mentioned, various factors may impact ASD. These include avoiding environmental toxins, longer duration of breastfeeding, modifying gut flora composition through probiotics, improved nutrition, avoiding acetaminophen use, and limiting the use of antibiotics and/or avoiding infections [33]. Mumper et al.'s study followed 294 general pediatric patients with ASD from 2005 to 2013 and found no new cases of ASD in the families who followed these guidelines. This case series also added vitamin D3, folinic acid, omega-3's and spaced out vaccinations. Given the prevalence of ASD, it is worth researching whether a comprehensive primary care intervention could reduce the risk. Evidence from other studies supports efficacy of folic acid supplements during pregnancy and choline and iron intake during fetal development to reduce ASD rates in children [21; 24; 48]. There are also programs in place to help families understand the factors that impact ASD.

Early Intervention

The majority of research and clinical programs target younger children where neurodevelopment

is more plastic. One such study by Keen et al. [22] found preliminary evidence regarding the impact of family intervention. At or shortly after an ASD diagnosis, parents received training on how to effectively support the communication of their child with ASD. They either learned on a DVD or received support at a parent group workshop and 10 home visits with a facilitator. Those who received the training in person demonstrated a greater improvement over those who watched the training on a DVD about parenting stress and efficacy. There was significantly greater improvement of social communication for the professionally supported group than the self-directed group, and a significant increase in adaptive behavior for participants with a low score at baseline — a promising result.

Many pediatricians struggle with effectively working with patients who have ASD and may not even realize their shortcomings. For instance, practitioners rated themselves higher than parents on ability to address ASD-specific needs and related conditions [5]. In Zuckerman et al.'s study [62], children with ASD were younger when parents first had concerns and first discussed those concerns with a provider than those with ID/DD (intellectual disorder/developmental disorder). However, when compared with parents of children with ID/DD, parents of children with ASD were more likely to be met with passivity or reassurance than with proactive responses when expressing concern. Among children with ASD, those with more proactive provider responses to concerns had shorter delays in being diagnosed compared to those with passive or reassuring provider responses. Furthermore, boys are four times more likely to be diagnosed with ASD than girls, and it is unclear if this is because being male is a risk factor for ASD or because girls show different symptoms that are easily missed by physicians [14]. Despite early parental concern, delays in diagnosis are common, especially when provider's responses are reassuring or passive, demonstrating the need for targeted improvements in primary care.

Later Intervention

Many ask, is late adolescence and young adulthood too late to intervene? Neuroimaging studies suggest that it is not. Structural MRI images have shown an increased brain volume in very early childhood for children with ASD, which typically developing children catch up to between six and eight-years-old. Furthermore, accelerated increase in frontal and temporal lobe volumes is documented in those with ASD [9]. This leads to perturbations in the temporal and regional sequence of typical early brain development. Brain development after early adolescence seems to be dominated by an accelerated age-related decline in total brain volume as well as cortical thickness and surface area.

Associations have been reported between ASD risk genes and neural connectivity. For example, the CNTNAP2-gene, which confers risk for the language phenotype in ASD, is associated with atypical structural and functional connectivity [37]. The thalamus, a key sensorimotor relay area implicated with ASD, appears to develop differently from the non-ASD population. Children with ASD have a distinct thalamic microstructure, but these group differences narrow over the years, suggesting that the thalamus continues to change into adulthood [29]. Another study investigated the dynamic functional connectivity network differences between participants with ASD and without. Compared to controls, the ASD group showed an increase in transient connectivity between the hypothalamus/subthalamus and some sensory networks in specific functional states, and diminished global meta-state dynamics of the whole brain functional network. These unusual dynamic patterns are associated with autistic symptoms using the Autism Diagnostic Observation Schedule [10]. Further investigation of gene-mediated neural differences could allow for more targeted interventions across the lifespan.

Researchers have found promising improvements in socio-emotional functioning of young adults with ASD through the PEERS Social Skills Treatment. Following treatment, participants were noted to exhibit decreased aggression, anxiety, and withdrawal, and improvements in emotional responsiveness, adaptability, leadership, and participation in activities of daily living [25]. This supports that improving social, behavioral, and emotional functioning may help develop and maintain quality peer interactions and remediate social isolation in adolescents with ASD.

Adaptive Functioning in ASD

Adaptive functioning refers to the skills someone needs to succeed in their environment and get along

with others. Many individuals with ASD struggle with this, making transition periods extra difficult. Matthews et al. [27] examined the adaptive functioning of 75 participants with ASD between 16–58 years old using the Vineland Adaptive Behavior Scales. Subscales consist of daily living, communication, and socialization, each with their own subdomains. Daily living skills were relatively stronger than communication and socialization in adults but not adolescents. On average, participants scored highest in writing skills (a subdomain in communication) and lowest in interpersonal skills (a subdomain in socialization). Regardless of participants' cognitive capacity, all standard scores were significantly below average, indicating that lifelong intervention for adaptive functioning is necessary for those with ASD.

Wallace et al. [53] suggest that executive functioning deficits in ASD are associated with internalizing symptoms and adaptive functioning difficulties, regardless of age or IQ. Among children and adolescents with ASD, peak weaknesses were in planning/organization and flexibility, which were robustly associated with adaptive functioning deficits. Appropriate interventions in adaptive functioning for adolescents and adults with ASD can support them at a period of transition as they reach new milestones in their life.

Post-Secondary Employment Experiences Among Young Adults with ASD

Many individuals with ASD face barriers when seeking employment. For young adults with ASD in the workforce, Postsecondary education employment experiences were compared to those of young adults with different disabilities [41]. Approximately one-half (53.4%) of young adults with ASD had ever worked for pay outside the home, the lowest rate among disability groups. Young adults with ASD earned an average of 8.10 USD an hour, significantly lower than average wages in the comparison groups and held jobs that clustered within fewer occupational types. Odds of ever having had a paid job were higher for those who were older, from higher-income households, and with better conversational abilities or functional skills.

Wehman et al. [56] utilized a randomized controlled trial (RCT) design to assess employment outcomes for youth with ASD in their last year of high school. Participants placed in the treatment group moved through three different 10–12 weeklong medical internship rotations, while also receiving instructions on how to reach proficiency in professional skills and adaptive work behavior. They were placed in departments including neonatal and pediatric intensive care units, diabetic wellness units, the hospital pharmacy, the coronary care unit, environmental services, and ambulatory surgery. Historically, youth with ASD have been placed into entry-level service jobs in hospitality or cleaning, so placements of study participants were unusual to them. However, their internships were typically comprised of high-level repetitive tasks that require great attention to detail and focus on order and structure to be successful. Most students in the treatment condition were hired in competitive placements after their internship and received up to 24% higher than the minimum wage. This is one of the first RCTs to demonstrate that young people with ASD can demonstrate success in the workplace as long as they have the proper tools.

Older Adults with ASD

It is estimated that 1 in 75 people of all ages has ASD, however most outcome and prevention studies focus on the experiences of children with ASD [38]. Far less research is being conducted on the health of older adults with ASD. Adults with ASD are more likely than the general population to face a wide array of hardships including mental health difficulties, injurious behavior, chronic health conditions, and nutritional problems [3]

Starkstein et al. [50] discovered preliminary data associating higher rates of parkinsonism in adults with ASD older than 39 years old. A preliminary study included direct examination and diagnosis of 19 adults with ASD over 49 years of age. The method was replicated in an independent sample of 37 adults with ASD over the age of 39 years. Frequency of parkinsonism occurrence rose from 20% in the first study to 25% after the second. While the association between both disorders should be further studied, these findings could lead to further investigation of the neurological underpinnings of ASD and parkinsonism. These findings should also be taken into consideration when delivering care services to older adults with ASD.

Another study measured the quality of life of 52 adults with ASD whose mean age was 49 years. Using the WHO Quality of Life-Brief Questionnaire, informant ratings and self-reports were measured. On self-report ratings, quality of life was significantly negatively correlated with repetitive behaviors and was positively associated with better adult social outcomes (ratings of employment, relationships, and independent living). However, informant ratings indicated few correlations between quality of life and any childhood or adulthood factors. Not all of the participants were able or willing to partake in the self-report [31]. It is possible that the validity of this popular measurement is low, indicating a need for a new tool for assessment of wellness in adults with ASD.

Primary Care for Adults with ASD

Most research on the challenges of ASD focuses on young children and their family. Unfortunately, there is a shortage of research on adults with ASD and effective healthcare practices for this population [6]. Lack of appropriate healthcare for people with ASD can be linked to the biologically based difficulties mentioned in the previous section, as well as social support, employment, level of education, access and delivery of accurate health services, and age of diagnosis [3].

Strengths and weaknesses in adults with ASD can vary. They can develop great abilities in their focused area of interest or utilize their need for consistency to manage their chronic conditions, as well as maintain strong friendships or relationships. With that being said, people with ASD have a wide variety of individual challenges including spoken language, written communication, performance of daily living activities, need for consistency, sensory sensitivity, and emotional regulation [35].Youth aged 11–22 years with ASD and ID (intellectual disability) reported thriving less than peers with ID only. Group differences in socio-communicative ability and school participation mediated the relationship between ASD and less thriving students [57].

Waiting room and wait time are main obstacles adolescents and adults with ASD encounter in receiving care. This was especially pertinent to those who have ID, history of aggressive behavior, or seizures, who found a large benefit in doing the assessment over the phone [47]. Communication barriers with providers is another obstacles people with ASD also face in the primary care office. Potential resolutions are creating tailored communication channels between providers and patients and creating a clinical environment that is more calming (such as having rounded corners and white noise) and allowing for people with ASD to control their stress more easily (such as having distractions, a quiet room, or a clock count down to their appointment time). Future use of input from individuals with ASD in various healthcare settings can be beneficial to accessibility and equity.

Physician Perspectives on Providing Primary Medical Care to Adults with ASD

Physicians experience a vast number of challenges to providing care to adults with ASD. Challenges providing care on a system-level includes: a dearth of services and supports for patients with ASD, a general lack of health-care providers willing to work with individuals with ASD and financial disincentives for potential increased time for providers to include adults with ASD in their practice. On a practice/provision level, challenges include time constraints, the complexity of family involvement, physical inaccessibility, and difficulty communicating with patients during visits. Training and educational challenges include a lack of formal education or training provided from medical school/residency and lack of general knowledge about working with individuals with ASD [55]. In a survey of 922 physicians, 77% rated their knowledge/skills of ASD as fair or poor, and only 13% agreed or strongly agreed that they have the adequate tools/referral resources/practice models to accommodate patients with ASD in their practice [61].

There are solutions and interventions to ameliorate these difficulties. On a systems level, solutions include increasing incentives to enhance provider capacity or decrease financial disincentives related to reimbursement and insurance. On a practice/provision level, it is possible to create a list of local resources and communication techniques, prioritize patients with ASD to lessen their wait time, improve the physical and sensory accessibility of office space, and facilitate communication between pediatricians and general practitioners. On the training and education level, it could be help-

ful to connect physicians to existing programs and services, as well as provide meaningful education about ASD and exposure to practitioners early in their professions as well as training of their office staff [55].

Conclusion

Throughout the life cycle different challenges arise and persist for those with ASD. Early prevention and intervention are commonly touted; our review demonstrates that it is also important to continue treatment and support for adolescents and adults. To get a holistic understanding of this disorder, it is equally important to research the specific genes and mutations linked to ASD as to the environmental risk factors, including birth complications, toxin exposure, and vitamin deficiency.

The promising understanding and interventions covered in this review target ASD from multiple areas, such as: giving expecting mothers specific guidelines to mitigate risk of ASD in their newborn, parental training in juvenile ASD support, social skills and adaptive functioning training for youth with ASD, and employment coaching. Based on our findings, we also suggest adapting the primary care setting to be more accessible to adults with ASD by incentivizing providers to treat more of this population, providing stronger education on how to effectively work with patients who have ASD, and implementing novel practices in the office setting. Asking individuals with ASD for their suggestions on how to implement change in primary care can allow for novel solutions to be executed. It is also crucial to further investigate health and wellbeing in older adults with ASD. Taken together, targeting ASD throughout the lifespan and its associated societal obstacles can be greatly beneficial for individuals with ASD.

References

1. *Allis C.D., Jenuwein T.* The molecular hallmarks of epigenetic control. *Nature Reviews Genetics,* 2016, vol. 17, no. 8, pp. 487—500. DOI: 10.1038/nrg.2016.59
2. *Bölte S., Girdler S., Marschik P.B.* The contribution of environmental exposure to the etiology of autism spectrum disorder. *Cellular and Molecular Life Sciences,* 2018, vol. 76, no. 7, pp. 1275—1297. DOI: s00018-018-2988-4
3. *Calleja S., Islam F., Kingsley J., McDonald R.* The disparities of healthcare access for adults with autism spectrum disorder: Protocol for a systematic review. *Medicine,* 2019, vol. 98, no. 7, p. e14480. DOI: 10.1097/MD.0000000000014480
4. *Cannell J.J.* Vitamin D and Autism, What's New? *Reviews in Endocrine and Metabolic Disorders*, 2017, vol. 18, no. 2, pp. 183—193. DOI: 10.1007/s11154-017-9409-0
5. *Carbone P.S., Murphy N.A., Norlin C., Azor V., Sheng X., Young P.C.* Parent and pediatrician perspectives regarding the primary care of children with autism spectrum disorders. *Journal of Autism and Developmental Disorders*, 2013, vol. 43, no. 4, pp. 964—972. DOI: 10.1007/s10803-012-1640-7
6. *Cashin A., Buckley T., Trollor J.N., Lennox N.* A scoping review of what is known of the physical health of adults with autism spectrum disorder. *Journal of Intellectual Disabilities*, 2018, vol. 22, no. 1, pp. 96—108. DOI: 10.1177/1744629516665242
7. Data & Statistics on Autism Spectrum Disorder / Centers for Disease Control and Prevention [Web resource]. URL: https://www.cdc.gov/ncbddd/autism/data.html (Accessed 20.08.2020).
8. *De la Torre-Ubieta L., Won H., Stein J., Geschwind D.H.* Advancing the understanding of autism disease mechanisms through genetics. *Nature Medicine,* 2016, vol. 22, no. 4, pp. 345—361. DOI: 10.1038/nm.4071
9. *Ecker C., Bookheimer S.Y., Murphy D.G.M.* Neuroimaging in autism spectrum disorder: brain structure and function across the lifespan. *The Lancet Neurology*, 2015, vol. 14, no. 11, pp. 1121—1134. DOI:10.1016/s1474-4422(15)00050-2
10. *Fu Z., Tu Y., Di X., Du Y., Sui J., Biswal B., Zhang Z., Lacy N., Calhoun V.* Transient increased thalamic-sensory connectivity and decreased whole-brain dynamism in autism. *NeuroImage,* 2018, vol. 190, no. 16, pp. 191—204. https://doi.org/10.1016/j.neuroimage.2018.06.003
11. *Gerber J.S., Offit P.A.* Vaccines and Autism: A Tale of Shifting Hypotheses. *Clinical Infectious Diseases*, 2009, vol. 48, no. 4, pp. 456—461. DOI:10.1086/596476
12. *Goldin R.L, Matson J.S.* Premature birth as a risk factor for autism spectrum disorder. *Developmental Neurorehabilitation,* 2016, vol. 19, no. 3, pp. 203—206. DOI: 10.3109/17518423.2015.1044132
13. *Gore A.C., Martien K.M., Gagnidze K., Pfaff D.* Implications of Prenatal Steroid Perturbations for Neurodevelopment, Behavior, and Autism. *Endocrine Reviews*, vol. 35, no. 6, pp. 961—991. DOI:10.1210/er.2013-1122
14. *Halladay A.K., Bishop S., Constantino J.N., Daniels A.M., Koenig K., Palmer K., Messinger D., Pelphrey K., Sanders S.J., Tepper Singer A., Lounds Taylor J., Szatmari P.* Sex and gender differences in autism spectrum disorder: summarizing evidence gaps and identifying emerging areas of priority. *Molecular Autism*, 2015, vol. 6, article no. 36. DOI:10.1186/s13229-015-0019-y
15. *Hallmayer J., Cleveland S., Torres A., Phillips J., Cohen B., Torigoe T., Miller J., Fedele A., Collins J., Smith K., Lotspeich L., Croen L.A., Ozonoff S., Lajonchere C., Grether J.K., Risch N.* Genetic heritability and shared environmental factors

among twin pairs with autism. *Archives of General Psychiatry*, 2011, vol. 68, no. 11, pp. 1095–1102. DOI:10.1001/archgenpsychiatry.2011.76

16. *Hazlett H.C., Poe M., Gerig G., Styner M., Chappell C., Gimpel Smith R. Vachet C., Piven J.* Early Brain Overgrowth in Autism Associated with an Increase in Cortical Surface Area Before Age 2. *Archives of General Psychiatry*, 2011, vol. 68, no. 5, pp. 467–476. DOI:10.1001/archgenpsychiatry.2011.39
17. *Hendren R. L.* Autism: biomedical complementary treatment approaches. *Child and Adolescent Psychiatric Clinics of North America*, 2013, vol. 22, no. 3, pp. 443–456. DOI:10.1016/j.chc.2013.03.002
18. *Herbert M.R.* Contributions of the environment and environmentally vulnerable physiology to autism spectrum disorders. *Current Opinion in Neurology*, 2010, vol. 23, no. 2, pp. 103–110. DOI: 10.1097/WCO.0b013e328336a01f
19. *Krakowiak P., Walker C.K., Bremer A.A., Baker A.S., Ozonoff S., Hansen R.L., Hertz-Picciotto I.* Maternal metabolic conditions and risk for autism and other neurodevelopmental disorders. *Pediatrics*, 2012, vol. 129, no. 5, pp. e1121–e1128. DOI:10.1542/peds.2011-2583
20. *Krumm N., Turner T., Baker C., Vives L., Mohajeri K., Witherspoon K., Raja A., Coe B.P., Stessman H.A., He Z.X., Leal S.M., Bernier R., Eichler E.E.* Excess of rare, inherited truncating mutations in autism. *Nature Genetics*, 2015, vol. 47, no. 6, pp. 582–588. DOI: 10.1038/ng.3303
21. *Blusztajn J.K., Slack B.E., Mellott T.J.* Neuroprotective Actions of Dietary Choline. *Nutrients*, 2017, vol. 9, no. 8, p. 815. DOI:10.3390/nu9080815
22. *Keen D., Couzens D., Muspratt S., Rodger S.* The effects of a parent-focused intervention for children with a recent diagnosis of autism spectrum disorder on parenting stress and competence. *Research in Autism Spectrum Disorders,* 2010, vol. 4, no. 2, pp. 229–241. DOI:10.1016/j.rasd.2009.09.009
23. *Lane M., Robker R.L., Robertson S.A.* Parenting from before conception, *Science*, 2014, vol. 345, no. 6198, pp. 756–760. DOI:10.1126/science.1254400
24. *Levine S.Z., Kodesh A., Viktorin A., Smith L., Uher R., Reichenberg A., Sandin S.* Association of Maternal Use of Folic Acid and Multivitamin Supplements in the Periods Before and During Pregnancy With the Risk of Autism Spectrum Disorder in Offspring. *The Journal of the American Medical Association: Psychiatry*, 2018, vol. 75, no. 2, pp. 176–184. DOI:10.1001/jamapsychiatry.2017.4050
25. *Lordo D.N., Bertolin M., Sudikoff E.L., Keith C., Braddock B., Kaufman D.A.* Parents Perceive Improvements in Socio-emotional Functioning in Adolescents with ASD Following Social Skills Treatment. *Journal of Autism and Developmental Disorders*, 2017, vol. 47, no. 1, pp. 203–214. DOI:10.1007/s10803-016-2969-0
26. *Lyall K., Schmidt R.J., Hertz-Picciotto I.* Maternal lifestyle and environmental risk factors for autism spectrum disorders. *International Journal of Epidemiology*, 2014, vol. 43, no. 2, pp. 443–464. DOI:10.1093/ije/dyt282
27. *Matthews N.L., Smith C.J., Pollard E., Ober-Reynolds S., Kirwan J., Malligo A.* Adaptive Functioning in Autism Spectrum Disorder During the Transition to Adulthood. *Journal of Autism and Developmental Disorders,* 2015, vol. 45, no. 8, pp. 2349–2360. DOI: 10.1007/s10803-015-2400-2
28. *Mazina V., Gerdts J., Trinh S., Ankenman K., Ward T., Dennis M.Y., Girirajan S., Eichler E.E., Bernier R.* Epigenetics of autism-related impairment: copy number variation and maternal infection. *Journal of Developmental and Behavioral Pediatrics*, 2015, vol. 36, no. 2, pp. 61–67. DOI: 10.1097/DBP.0000000000000126
29. *McLaughlin K., Travers B.G., Dadalko O., Dean D.C., Tromp D., Adluru N., Destiche D., Freeman A., Prigge M.D., Froehlich A., Duffield T.C., Zielinski B.A., Bigler E.D., Lange N., Anderson J.S., Alexander A.L., Lainhart J.E.* Longitudinal development of thalamic and internal capsule microstructure in autism spectrum disorder. *Autism Research*, 2018, vol. 11, no. 3, pp. 450–462. DOI: 10.1002/aur.1909
30. *Modabbernia A., Velthorst E., Reichenberg A.* Environmental risk factors for autism: an evidence-based review of systematic reviews and meta-analyses. *Molecular Autism*, 2017, vol. 8, article no. 13. DOI: 10.1186/s13229-017-0121-4
31. *Moss P., Mandy W., Howlin P.* Child and Adult Factors Related to Quality of Life in Adults with Autism. *Journal of Autism and Developmental Disorders*, 2017, vol. 47, no. 6, pp. 2830–1837. DOI: 10.1007/s10803-017-3105-5
32. *Miles J.H.* Autism spectrum disorders — A genetics review. *Genetics in Medicine*, 2011, vol. 13, no. 4, pp. 278–294. DOI:10.1097/GIM.0b013e3181ff67ba
33. *Mumper E.* Can Awareness of Medical Pathophysiology in Autism Lead to Primary Care Autism Prevention Strategies? *North American Journal of Medicine and Science,* 2013, vol. 6, no. 3, pp. 134–144. DOI:10.7156/najms.2013.0603134]
34. *Neale B.M., Kou Y., Liu L., Ma'ayan A., Samocha K.E., Sabo A., Lin C.F., Stevens C., Wang L.S., Makarov V., Polak P., Yoon S., Maguire J., Crawford E.L., Campbell N.G., Geller E.T., Valladares O., Schafer C., Liu H., Daly M.J. et al.* Patterns and rates of exonic de novo mutations in autism spectrum disorders. *Nature*, 2012, vol. 485, no. 7397, pp. 242–345. DOI:10.1038/nature11011
35. *Nicolaidis C., Kripke C.C., Raymaker D.* Primary care for adults on the autism spectrum. *Medical Clinics of North America*, 2014, vol. 98, no. 5, pp. 1169–1191. DOI: 10.1016/j.mcna.2014.06.011
36. *Ornoy A., Weinstein-Fudim L., Ergaz Z.* Prenatal factors associated with autism spectrum disorder (ASD). *Reproductive Toxicology,* 2015, vol. 56, pp. 155–169. DOI: 10.1016/j.reprotox.2015.05.007
37. *Peñagarikano O., Geschwind D.H.* What does CNTNAP2 reveal about Autism Spectrum Disorder? *Trends in Molecular Medicine*, 2012, vol. 18, no. 3, pp. 156–163. DOI: 10.1016/j.molmed.2012.01.003
38. *Robison J.E.* Autism prevalence and outcomes in older adults. *Autism Research*, 2019, vol. 12, no. 3, pp. 370–374. DOI:10.1002/aur.2080
39. *Rosenberg R.E., Law J.K., Yenokyan G., McGready J., Kaufmann W.E., Law P.A.* Characteristics and concordance of autism spectrum disorders among 277 twin pairs. *Archives of Pediatric and Adolescent Medicine*, 2009, vol. 163, no. 10, pp. 907–914. DOI:10.1001/archpediatrics.2009.98

40. *Rossignol D.A., Genuis S.J., Frye R.E.* Environmental toxicants and autism spectrum disorders: a systematic review. *Translational Psychiatry*, 2014, vol. 4, no. 2, article no. e360. DOI:10.1038/tp.2014.4
41. *Roux A.M., Shattuck P.T., Cooper B.P., Anderson K.A., Wagner M., Narendorf S.C.* Postsecondary employment experiences among young adults with an autism spectrum disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, 2013, vol. 52, no. 9, pp. 931—939. DOI: 10.1016/j.jaac.2013.05.019
42. *Rubenstein E., Wiggins L.D., Lee L.* A Review of the Differences in Developmental, Psychiatric, and Medical Endophenotypes Between Males and Females with Autism Spectrum Disorder. *Journal of Developmental and Physical Disabilites,* 2015, vol. 27, no. 1, pp. 119—139. DOI: 10.1007/s10882-014-9397-x
43. *Rutten B.P.F., Mill J.* Epigenetic Mediation of Environmental Influences in Major Psychotic Disorders. *Schizophrenia Bulletin*, 2009, vol. 35, no. 6, pp. 1045—1056. DOI: 10.1093/schbul/sbp104
44. *Sanders S., Murtha M., Gupta A., Murdoch J.D., Raubeson M.J., Willsey J.A.A., Ercan-Sencicek G., DiLullo N.N., Neelroop N.,Parikshak J.L., Stein M.F., Walker G.T., Ober N.A., Teran Y.S., El-Fishawy P., Murtha R.C., Choi M., Overton J.D., Bjornson R.D., State M.W. et al. De novo* mutations revealed by whole-exome sequencing are strongly associated with autism. *Nature*, 2012, vol. 484, no. 13, pp. 237—241. DOI:10.1038/nature10945
45. *Sandin S., Lichtenstein P., Kuja-Halkola R., Larsson H., Hultman C.M., Reichenberg A.* The familial risk of autism. *The Journal of the American Medical Association*, 2014, vol. 311, no. 17, pp. 1770—1777. DOI:10.1001/jama.2014.4144
46. *Sandin S., Schendel D., Magnusson P., Hultman C., Surén P., Susser E., Grønborg T., Gissler M., Gunnes N., Gross R., Henning M., Bresnahan M., Sourander A., Hornig M., Carter K., Francis R., Parner E., Leonard H., Rosanoff M., Stoltenberg C., Reichenberg A.* Autism risk associated with parental age and with increasing difference in age between the parents. *Molecular Psychiatry*, 2016, vol. 21, no. 5, pp. 693—700. DOI:10.1038/mp.2015.70
47. *Saqr Y., Braun E., Porter K., Barnette D., Hanks C.* Addressing medical needs of adolescents and adults with autism spectrum disorders in a primary care setting. *Autism*, 2018, vol. 22, no. 1, pp. 51—61. DOI:10.1177/1362361317709970
48. *Schmidt R.J., Tancredi D.J., Krakowiak P., Hansen R.L., Ozonoff S.* Maternal Intake of Supplemental Iron and Risk of Autism Spectrum Disorder. *American Journal of Epidemiology*, 2014, vol. 180, no. 9, pp. 890—900. DOI:10.1093/aje/kwu208
49. *Solek C.M., Farooqi N., Verly M., Lim T.K., Ruthazer E.S.* Maternal immune activation in neurodevelopmental disorders. *Developmental Dynamics*, 2018, vol. 247, no. 4, pp. 588—619. DOI:10.1002/dvdy.24612
50. *Starkstein S., Gellar S., Parlier M., Payne L., Piven J.* High rates of parkinsonism in adults with autism. *Journal of Neurodevelopmental Disorders*, 2015, vol. 7, article no. 29. DOI:10.1186/s11689-015-9125-6
51. *Stotland N.E., Sutton P.M., Trowbridge J., Atchley D.S., Conry J.A., Trasande L., Gerbert B., Charlesworth A., Woodruff T.J.* Counseling Patients on Preventing Prenatal Environmental Exposures — A Mixed-Methods Study of Obstetricians. *PLoS ONE*, 2014, vol. 9, no. 6, article no. e0098771. DOI:10.1371/journal.pone.0098771
52. *Stubbs G., Henley K., Green J.* Autism: Will vitamin D supplementation during pregnancy and early childhood reduce the recurrence rate of autism in newborn siblings? *Medical Hypotheses,* 2016, vol. 88, no. 17, pp. 74—78. DOI:10.1016/j.mehy.2016.01.015
53. *Wallace G.L., Kenworthy L., Pugliese C.E., Popal H.S., White E., Brodsky E., Martin A.* Real-World Executive Functions in Adults with Autism Spectrum Disorder: Profiles of Impairment and Associations with Adaptive Functioning and Comorbid Anxiety and Depression. *Journal of Autism and Developmental Disorders*, 2016, vol. 46, no. 3, pp. 1071—1083. DOI:10.1007/s10803-015-2655-7
54. *Wang C., Geng H., Liu W., Zhang G.* Prenatal, perinatal, and postnatal factors associated with autism: A meta-analysis. *Medicine (Baltimore),* 2017, vol. 96, no. 18, p. e6696. DOI: 10.1097/MD.0000000000006696
55. *Warfield M.E., Crossman M.K., Delahaye J., Der Weerd E., Kuhlthau K.A.* Physician Perspectives on Providing Primary Medical Care to Adults with Autism Spectrum Disorders (ASD). *Journal of Autism and Developmental Disorders*, 2015, vol. 45, no. 7, pp. 2209—2217. DOI:10.1007/s10803-015-2386-9
56. *Wehman P.H, Schall C.M., McDonough J., Kregel J., Brooke V., Molinelli A., Ham W., Graham C.W., Erin Riehle J., Collins H.T., Thiss W.* Competitive employment for youth with autism spectrum disorders: early results from a randomized clinical trial. *Journal of Autism and Developmental Disorders*, 2014, vol. 44, no. 3, pp. 487—500. DOI:10.1007/s10803-013-1892-x
57. *Weiss J.A., Burnham Riosa P.* Thriving in Youth with Autism Spectrum Disorder and Intellectual Disability. *Journal of Autism and Developmental Disorders*, 2015, vol. 45, no. 8, pp. 2474—2486. DOI:10.1007/s10803-015-2412-y
58. *Yassa H.A.* Autism: A form of lead and mercury toxicity. *Environmental Toxicology and Pharmacology*, 2014, vol. 38, no. 3, pp. 1016—1024. DOI:10.1016/j.etap.2014.10.005
59. *Yip B.H.K., Leonard H., Stock S., Stoltenberg C., Francis R.W., Gissler M., Gross R., Schendel D., Sandin S.* Caesarean section and risk of autism across gestational age: a multi-national cohort study of 5 million births, *International Journal of Epidemiology*, 2017, vol. 46, no. 2, pp. 429—439. DOI:10.1093/ije/dyw336
60. *Zerbo O., Iosif A.M., Walker C., Ozonoff S., Hansen R.L., Hertz-Picciotto I.* Is maternal influenza or fever during pregnancy associated with autism or developmental delays? Results from the CHARGE (Childhood Autism Risks from Genetics and Environment) study. *Journal of Autism and Developmental Disorders*, 2013, vol. 43, no. 1, pp. 25—33. DOI:10.1007/s10803-012-1540-x
61. *Zerbo O., Massolo M.L., Qian Y., Croen L.A.* A Study of Physician Knowledge and Experience with Autism in Adults in a Large Integrated Healthcare System. *Journal of Autism and Developmental Disorders*, 2015, vol. 45, no. 12, pp. 4002—4014. DOI:10.1007/s10803-015-2579-2

62. *Zuckerman K.E., Lindly O.J., Sinche B.K.* Parental concerns, provider response, and timeliness of autism spectrum disorder diagnosis. *The Journal of Pediatrics*, 2015, vol. 166, no. 6, pp. 1431–1439. DOI:10.1016/j.jpeds.2015.03.007

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Overview of Various Treatment Approaches and Their Impact on Several Difficult-to-Treat Conditions

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Several therapeutic approaches including medical, nutritional, sensory, and behavioral are reported to be effective in treating debilitating conditions often associated with autism. An overview of these approaches is discussed within the context of three difficult-to-treat conditions including anxiety, self-harming behavior, and sleep disturbances.

Keywords: autism, treatment, medical approach, sensory approach, nutrition approach, sleep disturbances, anxiety, self-harming behavior.

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Выбор подходящего вмешательства: обзор различных подходов к терапии тревожности, самоповреждающего поведения и нарушений сна при расстройствах аутистического спектра

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Согласно результатам исследований, для эффективной терапии некоторых тяжелых состояний, которые нередко бывают связаны с аутизмом, могут быть использованы несколько терапевтических подходов, включая медицинский, нутритивный, сенсорный и поведенческий. Обзор данных подходов приведен в контексте трех состояний, плохо поддающихся терапии: тревоги, самоповреждающего поведения и нарушений сна.

Ключевые слова: аутизм, терапия, медицинский подход, сенсорный подход, нутритивный подход, нарушения сна, тревога, самоповреждающее поведение

Для цитаты: *Эдельсон С.* Выбор подходящего вмешательства: обзор различных подходов к терапии тревожности, самоповреждающего поведения и нарушений сна при расстройствах аутистического спектра // Аутизм и нарушения развития. 2020. Том 18. № 3. С. 38—45. DOI: https://doi.org/10.17759/autdd.2020180305

During the first two decades after autism was initially recognized as a developmental disability [30], professionals assumed that this condition was untreatable. They often told parents to place their children in government or private residential facilities. In the 1960s, the medical and research communities came to the realization that autism was a biological condition, and that these individuals could benefit from behavioral therapy [19; 34; 50]. Over the past 60 years, there has been a growing consensus that many, if not most, individuals on the spectrum will improve from behavioral, medi-

cal, and other therapeutic interventions. In other words, autism is treatable.

Researchers and experienced clinicians have reported a wide range of effective therapies, and these can be classified into four different treatment categories including behavioral, biomedical, nutritional, and sensory. An overview of these approaches is discussed in relation to three difficult-to-treat challenges including anxiety, self-harming behavior, and sleep problems. It is important to mention that other interventions may also be effective, but a detailed review would involve a lengthy thesis or a comprehensive book on each behavior or condition[1] [15].

Anxiety

Anxiety is estimated to affect as many as 84% of individuals with autism [68]. In his seminal paper on autism, l. Kanner [30] described a child who displayed behaviors consistent with anxiety. He wrote that the child had a "good deal of 'worrying': he frets when the bread is put in the oven to be made into toast, and is afraid it will get burnt and be hurt. He is upset when the sun sets" [30, page 233].

There are several types of anxiety commonly associated with autism including generalized anxiety, obsessive-compulsive disorder, phobias and fears, separation anxiety, and social anxiety [68].

Numerous challenging behaviors are associated with anxiety including aggression, disruptive behavior, irritability, repetitive behaviors, self-harming behavior, severe tantrums, and sleep disturbances [42]. Since anxiety involves an internal physical feeling, it is often difficult to evaluate especially in those individuals with communication challenges. As a result, clinicians often assess anxiety by observing specific characteristic behaviors such as flushed face, heavy breathing, pacing, and sweating [44].

A recent survey of the Autism Research Institute's database of 2,328 cases was analyzed with respect to anxiety. Those who suffer from anxiety are more likely to be female, cover their ears to many sounds, harm themselves, become upset when things are changed, and feel sad or depressed most of the time[2].

Medical

Certain types of medications are sometimes prescribed to reduce anxiety by altering the GABAnergic, noradrenergic, serotonergic, or cannabidiol systems. Beta blockers, such as propranolol, have been shown to reduce anxiety in autism. For reviews, see Hirtoa, Brooks, & Hendren[3] and Vasa, Carroll, Nozzolillo, Mahajan et al. [64].

Nutrition

There is limited empirical support on the impact of nutrition on anxiety. However, some evidence in the scientific literature indicates that healthy nutrition may reduce or eliminate anxiety in the neurotypical population[4]. Several foods have been linked to a reduction in anxiety and include nuts and legumes, fish, fresh fruits, and vegetables [31]. In addition, certain probiotics, such as L rhamnosus, may possibly lower anxiety levels [48]. There it is also research indicating that specific supplements may decrease anxiety including magnesium and omega-3 fatty acids [53; 60].

Sensory

High arousal levels have been associated with anxiety[5] [20] as well as hypersensitivity to certain sensory sensations such as bright lights and strong colors as well as loud, especially unanticipated, sounds[6] [61].

As with nutrition, there is a limited amount of research supporting sensory approaches to treating anxiety. There is some evidence that vestibular stimulation (i.e., slow, rhythmic movement) and

[1] Edelson S.M., Johnson J.B. (eds.). Understanding and treating anxiety in autism. London: Publ. Jessica Kingsley Publishers, 2021.

[2] Edelson S.M., Johnson J.B. (eds.). Understanding and treating anxiety in autism. London: Publ. Jessica Kingsley Publishers, 2021.

[3] Hirtoa T., Brooks J., Hendren R.L. Pharmacotherapy for anxiety in individuals with autism spectrum disorder. In Edelson S.M., Johnson J.B. (eds.) Understanding and treating anxiety in autism. London: Publ. Jessica Kingsley Publishers, 2021. pp. 133–146.

[4] Barnhill K.M. Dietary and nutrition intervention to address issues of anxiety. In Edelson S.M., Johnson J.B. (eds.) Understanding and treating anxiety in autism. London: Publ. Jessica Kingsley Publishers, 2021. pp. 78–90.

[5] Sokhadze E.M., Casanova E., Lamina E.V., Kelly D., Casanova M.F. Psychophysiological markers of arousal and anxiety in children with autism spectrum disorder. In Edelson S.M., Johnson J.B. (eds.) Understanding and treating anxiety in autism. London: Publ. Jessica Kingsley Publishers, 2021. pp. 21–43.

[6] Spielmann V., Miller L.J. Sensory integration and processing — impact on anxiety in autism. In Edelson S.M., Johnson J.B. (eds.) Understanding and treating anxiety in autism. London: Publ. Jessica Kingsley Publishers, 2021. pp. 91–119.

deep pressure may reduce arousal levels and may lead to a calming effect [2; 3; 14].

Irlen (tinted) lenses are popular in the adult autism community [22; 69; 70] and have been reported to lower arousal by reducing brightness and color sensitivity in the non-autism population [29]. Auditory interventions, such as auditory integration training (AIT) and the Tomatis method, are reported by parents to reduce anxiety, but there are no known supportive studies. However, there is evidence that AIT may reduce sound sensitivity [51; 52], and loud sounds may be associated with anxiety[7]. In addition, Sokhadze, Casanova, Tasman, & Brockett [58] documented improved inhibitory neural processing as a direct result of AIT.

Behavior

Numerous researchers have reported benefits soon after providing behavioral therapy [24; 45]. Some of these therapies include modeling (i.e., watching another person confront the situation or interact with the stimulus) and positive reinforcement for "brave" behavior [47]. Two other popular behavior approaches include gradual exposure to the feared object or situation (e.g., systematic desensitization, shaping) and relaxation training (e.g., deep breathing, progressive muscle relaxation)[8] [25].

Self-harming behavior

This is one of the most devastating and difficult-to-treat behaviors exhibited by many individuals on the autism spectrum. Surveys indicate that over 25% of the autism population engage in some form of self-harming behavior [57]. These behaviors vary greatly and range from mild (causing redness or bruising) to moderate (leading to bleeding) to severe (causing bone fractures). Behaviors may involve hitting or banging the head, biting the wrist, hand, or arm, or excessive scratching or pinching of the skin [12].

Medical

Physicians may focus their efforts on alleviating discomfort or pain associated with self-harming behavior. For example, ear hitting may indicate an ear infection, and hitting or banging the head may indicate a headache or migraine [10; 12]. Face-hitting can be a reaction to sinus allergies, dental pain, or even an impacted object in the ear or in the nose [23; 71].

Physicians may also prescribe medications to control the behavior itself including antipsychotics, antidepressants, and opioid agonists [9; 17].

Nutrition

The nutritional approach often takes into account the suspected underlying reason(s) for the self-harming behavior. For example, eye-poking may be a result of a calcium deficiency [8]. In addition, self-harming behavior has been associated with gastrointestinal distress [46; 49]. A popular treatment strategy is to normalize the microbiome using digestive enzymes and/or probiotics (see for a review [55]).

Sensory

Both hypo-reactivity and hyper-reactivity to sensory sensations have been associated with self-harming behavior (see for a review [40]). For example, low tactile sensitivity may lead to excessive rubbing and scratching, which in turn may lead to an increase in the skin's sensitivity to touch [11]. Tactile stimulation, such as rubbing various textures on the skin, is reported to normalize sensitivity and may reduce chronic rubbing and scratching [56]. Conversely, some individuals on the autism spectrum engage in self-harm as a reaction to certain sounds [61]. As mentioned earlier, AIT has been shown to reduce or eliminate sound sensitivity [51; 52].

Behavior

Behavior therapy has a long and controversial history of treating self-harming behavior by either ignoring or punishing the behavior [35]. Today, behaviorists often attribute the cause and/or maintenance of these behaviors to three reasons: obtain attention, avoid or escape attention, and obtain a tangible [5; 16]. Automatic reinforcement has also been recognized as a contributor in which the behavior itself is rewarding [66]. A functional behavioral assessment is often employed to determine the

[7] Spielmann V., Miller L.J. Sensory integration and processing — impact on anxiety in autism. In Edelson S.M., Johnson J.B. (eds.) Understanding and treating anxiety in autism. London: Publ. Jessica Kingsley Publishers, 2021. pp. 91–119.

[8] Groden J., Weidenman L., Woodard, C.R. Stress and autism: Adapted coping interventions for everyone on the spectrum. In Edelson S.M., Johnson J.B. (eds.) Understanding and treating anxiety in autism. London: Publ. Jessica Kingsley Publishers, 2021. pp. 147–196.

physical and social antecedents and consequences of these behaviors [26; 54].

Behavioral programs may include various schedules of reinforcement such as differential reinforcement of other behaviors (DRO), differential reinforcement of incompatible behaviors (DRI), and differential reinforcement of alternative behavior (DRA), see [41]. Relaxation therapy has also been shown to be effective in reducing self-harming behavior [26; 43].

Sleep

Sleep disturbances are relatively common in the autism population [65]. There are numerous suggested causes of sleep problem associated with autism including alterations of circadian rhythms [21], high arousal level [39], sensory sensitivities [63], gastrointestinal disturbances [32; 50], pain [62], and side effects of medications [38].

The American Academy of Neurology recently recommended three approaches for treating sleep problems in autism and suggested an order in which they should be given [4]. These treatments, listed in order, are behavioral approaches, melatonin, and medical interventions.

Medical

In general, there are several types of medications often prescribed to treat sleep disturbances associated with autism including those that increase GABA and decrease histamine release as well as medications that alter acetylcholine, norepinephrine, and serotonin. See [33] for a review.

Over the last two decades, melatonin has been a popular approach for treating sleep problems in autism [36]. Researchers have shown that melatonin can improve sleep onset and duration, has minimal side effects, and improves quality of sleep and life [37].

Nutrition

Nutrition has long been considered helpful in treating sleep problems in the general population [59]. Certain foods are believed to help induce sleep including nuts (e.g., walnuts, almonds), meat (e.g., turkey, fatty fish), fruit (e.g., kiwi, tart cherry juice, bananas), and milk and milk products (e.g., cottage cheese) [18].

Sensory

Sensory approaches are often employed to treat sleep disturbances and usually focus on reducing overall nervous system arousal. This may include setting the room to a comfortable temperature, reducing sounds and lighting, applying deep pressure, and providing slow vestibular stimulation such as rocking (see [67]).

Behavior

A behavioral strategy referred to as "sleep hygiene" is often recommended to help a person fall asleep [1]. This can consist of scheduling appropriate times for going to sleep and awakening, minimizing computer and television watching, and reducing emotional and behavioral stimulation prior to bedtime.

Discussion

Certain difficult-to-treat behaviors, such as those described above, may be caused and/or later maintained by one or more factors associated with the person's biology, sensory system, nutritional status, and/or their surrounding environment. For example, Carr and McDowell [7] reported on an 10-year old boy whose scratching behavior was a result of a skin allergy. Once the allergy was identified and treated, the scratching behavior continued and was maintained by attention contingent on the behavior.

As in the example described above, the treatments outlined in this article are not necessarily independent of one another. In fact, an effective therapeutic plan, especially for difficult-to-treat behaviors, could likely involve a multidisciplinary approach and would include two or more treatments given in a specific order or simultaneously [6]. For example, treating anxiety may involve treating their GI disturbances[9], immune dysregulation[10, 11], and challenging behaviors [42].

[9] Law, Ferguson, Margolis, & Beversdorf. Gastrointestinal symptoms, anxiety, and autism spectrum disorder. In Edelson S.M., Johnson J.B. (eds.) Understanding and treating anxiety in autism. London: Publ. Jessica Kingsley Publishers, 2021. pp. 67–77.

[10] Casanova E.L., Casanova M.F., Sokhadze E.M., Lamina E. Crosstalk between the immune and autonomic nervous systems and their relationship to anxiety in autism. In Edelson S.M., Johnson J.B. (eds.) Understanding and treating anxiety in autism. London: Publ. Jessica Kingsley Publishers, 2021. pp. 45–56.

[11] Edelson S.M., Van de Water J., Edelson M.S.G. The immune system and anxiety: A case for toxic exposure. In Edelson S.M., Johnson J.B. (eds.) Understanding and treating anxiety in autism. London: Publ. Jessica Kingsley Publishers, 2021. pp. 57–66.

Treating a condition or behavior using several approaches simultaneously should not be confused with the research examining intensive behavior analytic intervention (IBT) in relation to an eclectic treatment approach and a general education approach [27; 28]. In these studies, the eclectic approach included the TEACCH program, Picture Exchange Communication System (PECS), sensory integration therapy, and some discrete-trial procedures. Numerous assessments were employed and greater improvement was documented in those who received IBT as compared to the other two groups. In these studies, the eclectic approach consisted of three popular education strategies, whereas three of the four approaches described in this article centered on the individual's physical health (i.e., medical, sensory, and nutrition). Note: sensory integration therapy was included in the eclectic approach; however, Howard et al. [27; 28] did not evaluate changes in sensory sensitivities in their studies. Thus, the effectiveness of sensory integration therapy should not have been part of the conclusions drawn by these researchers.

When treating a condition or behavior, it should not be assumed that all treatments are equally effective; and in many cases the most effective interventions will depend, to a large degree, on the underlying reason for the condition or behavior [13]. Such is the case where eye-poking is a result of a deficiency in calcium [8].

An important scientific question regarding appropriate treatment is: How do we determine objectively the most effective treatments for each individual on the autism spectrum? At first, this may appear to be a daunting and complicated research challenge given the heterogeneity of the autism spectrum as well as chronological age (i.e., toddlers, children, teenagers, adults).

Reliance on traditional experimentation may take decades to determine an optimal treatment plan for each individual on the spectrum. A more efficient scientific approach would involve administering numerous valid and reliable assessments before, during, and after each treatments. This could consist of neurological and laboratory testing (e.g., EEG, evoked-related potentials), direct observation (e.g., functional behavioral analysis, Autism Diagnostic Observation Schedule), and sensory assessments (e.g., the Sensory Profile) in addition to interviews (e.g., Autism Diagnostic Interview) and questionnaires (e.g., Aberrant Behavior Checklist, Pervasive Developmental Disorder — Behavior Inventory). Characteristics of each individual should also be documented (e.g., age, sex, communication and social behavior).

The data from such quantitative assessments could then be analyzed in such a way to create one or more statistical algorithms or formulas. Based on probability, these formulas would be able to predict which treatments would be most effective given the characteristics of each individual [13]. Once this has been accomplished, clinicians could simply rely on a set of assessments, as determined by research, to create an effective treatment plan for each individual. This goal can be a reality given a collaborative and well-coordinated effort by both the research and therapeutic communities.

Conclusion

As evident throughout this article, medical, nutritional, sensory and behavioral approaches have been reported to treat similar conditions and behaviors. More research is needed to understand which treatments are most appropriate given the various underlying reasons and the heterogeneity of the autism population.

References

1. *Abel E., Kim S.Y., Kellerman A.M., Brodhead M.T.* Recommendations for identifying sleep problems and treatment resources for children with autism spectrum disorder. *Behavior Analysis in Practice*, 2017, vol. 10, no. 3, pp. 261—269. DOI:10.1007/s40617-016-0158-4
2. *Aronoff E., Hillyer R., Leon M.* Environmental enrichment therapy for autism: Outcomes with increased access. *Neural Plasticity*, 2016, vol. 2016, article ID 2734915. 23 p. DOI:10.1155/2016/2734915
3. *Bestbier L., Williams T.I.* The immediate effects of deep pressure on young people with autism and severe intellectual difficulties: Demonstrating individual differences. *Occupational Therapy International*, 2017, vol. 2017, article ID 7534972. 7 p. DOI:10.1155/2017/7534972
4. *Buckely A.W., Hirtz D., Oskoui M., Armstrong M.J., Batra A. et al.* Practice guideline: Treatment for insomnia and disrupted sleep behavior in children and adolescents with autism spectrum disorder. *Neurology*, 2020, vol. 94, no.9, pp. 392—404. DOI:10.1212/WNL.0000000000009033

5. *Carr E.G.* The motivation of self-injurious behavior: A review of some hypotheses. *Psychological Bulletin*, 1977, vol. 84, no. 4, pp. 800—816. DOI:10.1037/0033-2909.84.4.800
6. *Carr E.G., Edelson S.M.* Integrating biomedical and behavioral science: The happy future ahead. *The Autism File*, 2009, no. 32, pp. 17—20.
7. *Carr E.G., McDowell J.J.* Social control of self-injurious behavior of organic etiology. *Behavior Therapy*, 1980, vol. 11, no. 3, pp. 402—409. DOI:10.1016/S0005-7894(80)80056-6
8. *Coleman M.* Clinical presentation of patients with autism and hypocalcinuria. *Developmental Brain Dysfunction*, 1994, vol. 7, pp. 63—70.
9. *DeFilippis M., Wagner K.D.* Treatment of autism spectrum disorder in children and adolescents. *Psychopharmacology Bulletin*, 2016, vol. 46, no. 2, pp. 18—41.
10. *De Lissovoy V.* Head banging in early childhood. *Child Development*, 1962, vol. 33, no. 1, pp. 43—56. DOI:10.2307/1126631
11. *Edelson S.M.* Implications of sensory stimulation in self-destructive behavior. *American Journal of Mental Deficiency*, 1984, vol. 89, no. 2, pp. 140—145.
12. *Edelson S.M.* Introduction. In *Edelson S.M., Johnson J.B. (eds.)* Understanding and treating self-injurious behavior in autism. London: Publ. Jessica Kingsley Publishers, 2016. Pp. 11—17. ISBN 978-1-84905741-7.
13. *Edelson S.M.* Optimizing autism treatment [Web resource] / Autism Research Institute. 2019. URL: https://www.autism.org/optimizing-autism-treatment/ (Accessed 07.09.2020).
14. *Edelson S.M., Edelson M.G., Kerr D.C., Grandin T.* Physiological and behavioral changes of deep pressure: A pilot study investigating the efficacy of Temple Grandin's Hug Machine. *American Journal of Occupational Therapy*, 1999, vol. 53, no. 2, pp. 145—152. DOI:10.5014/ajot.53.2.145
15. *Edelson S.M., Johnson J.B. (eds.)* Understanding and treating self-injurious behavior in autism. London: Publ. Jessica Kingsley Publishers, 2016. 302 p., il. ISBN 978-1-84905741-7.
16. *Edelson S.M., Taubman M.T., Lovaas O.I.* Some social contexts to self-destructive behavior. *Journal of Abnormal Child Psychology*, 1983, vol, 11, no. 2, pp. 299—311. DOI:10.1007/BF00912093
17. *Eissa N., Al-Hougani M., Sadeq A., Ojha S.K., Sasse A., Sadek B.* Current enlightenment about etiology and pharmacological treatment of autism spectrum disorder. *Frontiers in Neuroscience*, 2018, vol. 12, p. 304. DOI:10.3389/fnins.2018.00304
18. *Elliott B.* The 9 best foods to eat before bed [Web resource] / Healthline. 2017, October 23. URL: https://www.healthline.com/nutrition/9-foods-to-help-you-sleep (Accessed 07.09.2020).
19. *Ferster C.B., DeMyer M.K.* A method for the experimental analysis of the behavior of autistic children. *American Journal of Orthopsychiatry*, 1962, vol. 32, pp. 89—98. DOI:10.1111/j.1939-0025.1962.tb00267.x
20. *Gillott A., Furniss F., Walter A.* Anxiety in high-functioning children with autism. *Autism*, 2011, vol. 5, no. 3, pp. 277—286. DOI:10.1177/1362361301005003005
21. *Glickman G.* Circadian rhythms and sleep in children with autism. *Neuroscience & Biobehavioral Reviews*, 2010, vol. 34, no. 5, pp. 755—768. DOI:10.1016/j.neubiorev.2009.11.017
22. *Grandin T.* Thinking in pictures: My life with autism. New York: Publ. Doubleday, 1995. 222 p., il. ISBN 978-0-38547792-5.
23. *Green J., O'Hara N.* (2016). Medical and nutritional approaches to treating self-injurious behavior and aggression in autism spectrum disorder: Fifteen case studies. In *Edelson S.M., Johnson J.B. (eds.)* Understanding and treating self-injurious behavior in autism. London: Publ. Jessica Kingsley Publishers, 2016. Pp. 109—127. ISBN 978-1-84905741-7.
24. *Groden J., Cautela J., Prince S., Berryman J.* (1994). The impact of stress and anxiety on individuals with autism and developmental disabilities. In *Schopler E., Mesibov G.E. (eds.)* Behavioral Issues in Autism. New York: Publ. Plenum Press, 1994. Pp. 177—194. ISBN 978-0-30644600-9.
25. *Groden J., Weidenman L., Diller A.* Relaxation: A Comprehensive Manual for Children and Adults with Autism and Other Developmental Disabilities. 2nd edition. Champaign: Publ. Research Press Publishers, 2016. 122 p., il. ISBN 978-0-87822702-0.
26. *Groden J., Weidenman L., Woodard C.R.* A stress-reduction approach to addressing self-injurious behavior in individuals with autism. In *Edelson S.M., Johnson J.B. (eds.)* Understanding and treating self-injurious behavior in autism. London: Publ. Jessica Kingsley Publishers, 2016. Pp. 231—275. ISBN 978-1-84905741-7.
27. *Howard J.S., Sparkman C.R., Cohen H.G., Green G., Stanislaw H.* A comparison of intensive behavior analytic and electric treatments for young children with autism. *Research in Developmental Disabilities*, 2005, vol. 26, no. 4, pp. 359—383. DOI:10.1016/j.ridd.2004.09.005
28. *Howard J.S., Stanislaw H., Green G., Sparkman C.R., Cohen H.G.* Comparison of behavior analytic and eclectic early interventions in young children with autism after three years. *Research in Developmental Disabilities*, 2014, vol. 35, no. 12, pp. 3326—3344. DOI:10.1016/j.ridd.2014.08.021
29. *Irlen H., Lass M.J.* Improving reading problems due to symptoms of Scotopic Sensitivity Syndrome using Irlen lenses and overlays. *Education*, 1989, vol. 109, no. 4, pp. 413—417.
30. *Kanner L.* Autistic disturbances of affective contact. *Nervous Child*, 1943, vol. 2, pp. 217—250.
31. *Khanna P., Chattu V.K., Aeri B.T.* Nutritional aspects of depression in adolescents — a systematic review. *International Journal of Preventive Medicine*, 2019, vol. 10, no. 1, p. 42. DOI:10.4103/ijpvm.IJPVM_400_18
32. *Klukowski M., Wasilewska J., Lebensztejn D.* Sleep and gastrointestinal disturbances in autism spectrum disorder in children. *Developmental Period Medicine*, 2015, vol. 19, no. 2, pp. 157—161.
33. *Lie J.D., Tu K.N., Shen D.D., Wong B.M.* Pharmacological treatment of insomnia. *Pharmacy & Therapeutics*, 2015, vol. 40, no. 11, pp. 759—768.

34. *Lovaas O.I., Freitag G., Kinder M.I., Rubenstein B.D., Schaeffer B., Simmons J.Q.* Establishment of social reinforcers in two schizophrenic children on the basis of food. *Journal of Experimental Child Psychology*, 1966, vol. 4, no. 2, pp. 109—125. DOI:10.1016/0022-0965(66)90011-7
35. *Lovaas O.I., Simmons J.Q.* Manipulation of self-destruction in three retarded children. *Journal of Applied Behavior Analysis*, 1969, vol. 2, no. 3, pp. 143—157. DOI:10.1901/jaba.1969.2-143
36. *Malow B.A., Adkins K.W., McGrew S.G., Wang L., Goldman S.E. et al.* Melatonin for sleep in children with autism: A controlled trial examining dose, tolerability, and outcomes. *Journal of Autism and Developmental Disorders*, 2012, vol. 42, no. 8, pp. 1729—1737. DOI:10.1007/s10803-011-1418-3
37. *Malow B.A., Findling R.L., Schroder C.M., Maras A., Breddy J. et al.* Sleep, growth, and puberty after 2 years of prolonged-release melatonin in children with autism spectrum disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, 2020, article no. S0890-8567(20)30034-4. Online publication ahead of print. DOI:10.1016/j.jaac.2019.12.007
38. *Malow B.A., Katz T., Reynolds A.M., Shui A., Carno M. et al.* Sleep difficulties and medications in children with autism spectrum disorders: A registry study. *Pediatrics*, 2016, vol. 137, no. Supplement 2, pp. S98—S104. DOI:10.1542/peds.2015-2851H
39. *Mazurek M.O., Petroski G.F.* Sleep problems in children with autism spectrum disorder: Examining the contributions of sensory over-responsivity and anxiety. *Sleep Medicine*, 2015, vol. 16, no. 2, pp. 270—279. DOI:10.1016/j.sleep.2014.11.006
40. *Miller L.J., Misher K.* Sensory processing disorder and self-injurious behavior. In *Edelson S.M., Johnson J.B. (eds.)* Understanding and treating self-injurious behavior in autism. London: Publ. Jessica Kingsley Publishers, 2016. Pp. 138—150. ISBN 978-1-84905741-7.
41. *Minshawi N.F., Hurwitz S., Fodstad J.C., Biebl S., Morriss D.H., McDougle C.J.* The association between self-injurious behaviors and autism spectrum disorders. *Psychology Research and Behavior Management*, 2014, vol. 7, pp. 125—136. DOI:10.2147/PRBM.S44635
42. *Moskowitz L.J., Edelson S.M.* Introduction. In *Edelson S.M., Johnson J.B. (eds.)* Understanding and treating self-injurious behavior in autism. London: Publ. Jessica Kingsley Publishers, 2016. Pp. 12—20. ISBN 978-1-84905741-7.
43. *Moskowitz L.J., Ritter A.B.* Assessment and intervention for self-injurious behavior related to anxiety. In *Edelson S.M., Johnson J.B. (eds.)* Understanding and treating self-injurious behavior in autism. London: Publ. Jessica Kingsley Publishers, 2016. Pp. 198—230. ISBN 978-1-84905741-7.
44. *Moskowitz L.J., Rosen T., Lerner M.D., Levine K.* Assessment of anxiety in youth with autism spectrum disorder. In *Kerns C., Storch E., Kendall P., Wood J.J., Renno P. (eds.)* Evidence Based Assessment and Treatment of Anxiety in Children and Adolescents with Autism Spectrum Disorder. London: Publ. Academic Press, 2017. Pp. 79—104. ISBN 978-0-12805122-1.
45. *Moskowitz L.J., Walsh C.E., Mulder E., Magito McLaughlin D., Hajcak G., Carr E.G., Zarcone J.R.* (2017). Intervention for anxiety and problem behavior in children with autism spectrum disorder and intellectual disability. *Journal of Autism and Developmental Disorders*, 2017, vol. 47, no. 12, pp. 3930—3948. DOI:10.1007/s10803-017-3070-z
46. *Neuhaus E., Bernier R.A., Tham S.W., Webb S.J.* Gastrointestinal symptoms among children and adolescents with autism spectrum disorder. *Frontiers in Psychiatry*, 2018, vol. 9, p. 515. DOI:10.3389/fpsyt.2018.00515
47. *Reaven J.* The treatment of anxiety symptoms in youth with high-functioning autism spectrum disorders: Developmental considerations for parents. *Brain Research*, 2011, vol. 1380, pp. 255—263. DOI:10.1016/j.brainres.2010.09.075
48. *Reis D.J., Ilardi S.S., Punt, S.E.W.* The anxiolytic effect of probiotics: A systematic review and meta-analysis of the clinical and preclinical literature. *PLoS ONE*, 2018, vol. 13, no. 6, article no. e0199041. 25 p. DOI:10.1371/journal.pone.0199041
49. Restrepo B., Angkustsiri K., Taylor S.L., Rogers S.J., Cabral J. et al. Developmental-behavioral profiles in children with autism spectrum disorder and co-occurring gastrointestinal symptoms. *Autism Research*. August 6, 2020. Early view before publication. DOI:10.1002/aur.2354
50. *Rimland B. Tukey J.W.* Infantile autism: The syndrome and its implications for a neural theory of behavior. Englewood Cliffs: Publ. Prentice-Hall, 1964. 282 p.
51. *Rimland B., Edelson S.M.* Brief report: a pilot study of auditory integration training in autism. *Journal of Autism and Developmental Disorders*, 1995, vol. 25, no. 1, pp. 61—70. DOI:10.1007/BF02178168
52. *Rimland B., Edelson S.M.* The effects of auditory integration training in autism. *American Journal of Speech-Language Pathology*, 1994, vol. 3, no. 2, pp. 16—24.
53. *Schwalfenberg G.K., Genuis S.J.* The importance of magnesium in clinical healthcare. *Scientifica*, 2017, vol. 2017, pp. 1—14. DOI:10.1155/2017/4179326
54. *Shriver M.D., Anderson C.M., Proctor B.* Evaluating the validity of functional behavior assessment. *School Psychology Review*, 2001, vol. 30, no. 2, pp. 180—192.
55. *Sivamaruthi B.S., Suganthy N., Kesika P., Chaiyasut C.* The role of microbiome, dietary supplements, and probiotics in autism spectrum disorder. *International Journal of Environmental Research and Public Health*, 2020, vol. 17, no. 8, article no. 2647. DOI:10.3390/ijerph17082647
56. *Smith S.A., Press B., Koenig K.P., Kinnealey M.* Effects of sensory integration intervention on self-stimulating and self-injurious behaviors. *American Journal of Occupational Therapy*, 2005, vol. 59, no. 4, pp. 418—425. DOI:10.5014/ajot.59.4.418
57. *Soke G.N., Rosenberg S.A., Hamman R.F., Fingerlin T., Robinson C., Carprenter L. et al.* Brief report: Prevalence of self-injurious behaviors among children with autism spectrum disorders -- A population-based study. *Journal of Autism and Developmental Disorders*, 2016, vol. 46, no. 11, pp. 3607—3614. DOI:10.1007/s10803-016-2879-1

58. *Sokhadze E.M., Casanova M.F., Tasman A., Brockett S.* Electrophysiological and behavioral outcomes of Berard Auditory Integration Training (AIT) in children with autism spectrum disorder. *Applied Psychophysiology and Biofeedback*, 2016, vol. 41, no.4, pp. 405–420. DOI:10.1007/s10484-016-9343-z
59. *St-Onge M.P, Mikic A., Pietrolungo C.E.* Effects of diet on sleep quality. *Advances in Nutrition*, 2016, vol. 7, no. 5, pp. 938–949. DOI:10.3945/an.116.012336
60. *Su K.P., Tseng P.T., Lin P.Y., Okubo R., Chen T.Y., Chen Y.W., Matsuoka Y.J.* Association of use of omega-3 polyunsaturated fatty acids with changes in severity of anxiety symptoms. *JAMA Network Open*, 2018, vol. 1, no. 5, pp. 1–16. DOI:10.1001/jamanetworkopen.2018.2327
61. *Summers J., Shahrami A., Cali S., D'Mello C., Kako M. et al.* Self-injury in autism spectrum disorder and intellectual disability: Exploring the role of reactivity to pain and sensory input. *Brain Sciences*, 2017, vol. 7, no. 11, p. 140. DOI:10.3390/brainsci7110140
62. *Tudor M.E., Walsh C.E., Mulder E.C., Lerner M.D.* Pain as a predictor of sleep problems in youth with autism spectrum disorders. *Autism*, 2014, vol. 19, no. 3, pp. 292–300. DOI:10.1177/1362361313518994
63. *Tzischinsky O., Meiri G., Manelis L., Bar-Sinai A., Flusser H. et al.* Sleep disturbances are associated with specific sensory sensitivities in children with autism. *Molecular Autism*, 2018, vol. 9, p. 22. DOI:10.1186/s13229-018-0206-8
64. *Vasa R.A., Carroll L.M., Nozzolillo A.A., Mahajan R., Mazurek M.O. et al.* A systematic review of treatment for anxiety in youth with autism spectrum disorders. *Journal of Autism and Developmental Disorders*, 2014, vol. 44, no. 12, pp. 3215–3229. DOI:10.1007/s10803-014-2184-9
65. *Veatch O.J., Maxwell-Horn A.C., Malow B.A.* Sleep in autism spectrum disorders. *Current Sleep Medicine Reports*, 2015, vol. 1, no. 2, pp. 131–140. DOI:10.1007/s40675-015-0012-1
66. *Vollmer T.R.* The concept of automatic reinforcement: Implications for behavioral research in developmental disabilities. *Research in Developmental Disabilities*, 1994, vol. 15, no. 3, pp. 187–207. DOI:10.1016/0891-4222(94)90011-6
67. *Wallis C.* How to get children with autism to sleep [Web resource] / Scientific American. 2017, November 18. URL: https://www.scientificamerican.com/article/how-to-get-children-with-autism-to-sleep/ (Accessed 08.09.2020).
68. *White S.W., Oswald D., Ollendick T., Scahill L.* Anxiety in children and adolescents with autism spectrum disorders. *Clinical Psychology Review*, 2009, vol. 29, no. 3, pp. 216–229. DOI:10.1016/j.cpr.2009.01.003
69. *Williams D.* Autism: An inside-out approach: An innovative look at the 'mechanics' of 'autism' and its developmental 'cousins.' London: Publ. Jessica Kingsley Publishers, 1996. 320 p. ISBN 978-1-85302387-3.
70. *Zaks Z.* Life and Love: Positive strategies for autistic adults. Shawnee: Publ. Autism Asperger Publishing Co., 2006. 367 p. ISBN 978-1-93128293-2.
71. *Zeidán-Chuliá F., Gursoy U.K., Könönen E., & Gottfried C.* (2010). A dental look at the autistic patient through orofacial pain. *Acta Odontologica Scandinavica, 69(4),* 193–200. doi:10.3109/00016357.2010.549505

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GABA and Glutamate Imbalance in Autism and Their Reversal as Novel Hypothesis for Effective Treatment Strategy

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Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by reduced social communication and repetitive behaviors. The etiological mechanisms of ASD are still unknown; however, the GABAergic system has received considerable attention due to its potential as a therapeutic target. Based on the fact that individuals with autism demonstrate altered gene expression concomitant with impaired blood brain barrier (BBB), and gut barrier integrities, so increased glutamate levels in the blood and platelets of ASD patients can be related to lower numbers of cerebellar GABAergic neurons, less active GABA-synthesizing enzymes, and decreased brain GABA levels. Excitotoxic levels of released glutamate trigger a cascade of deleterious cellular events leading to delayed neuronal death. According to our understanding of glutamate excitotoxicity, GABA supplementation could theoretically be useful to treat certain autistic phenotypes. While there is still no effective and safe medication for glutamate-related cell damage and death, combined efforts will hopefully develop better treatment options. Here I hypothesize that an integrated treatment strategy with GABA supplements, regulation of chloride (Cl-) and magnesium (Mg2+) levels, vitamin D supplements, probiotics to enhance GABAA receptor and glutamate decarboxylase (GAD) expression, and memantine to activate glutamate transporters and inhibit NMDA receptors, could collectively reduce glutamate levels, maintain functional GABA receptors and thus treat repetitive behavior, impaired social behavior, and seizure activity in individuals with autism.

Keywords: autism; glutamate excitotoxicity; gamma-aminobutyric acid; vitamin D; gut microbiota

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ГАМК, дефициты нейротрансмиттера глутамата при аутизме и их нейтрализация как новая гипотеза эффективной стратегии лечения

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Расстройства аутистического спектра (РАС) — это нарушения психического развития, характеризующиеся снижением социального взаимодействия и повторяющимся поведением. Механизмы этиологии РАС все еще неизвестны; однако ГАМК-эргической системе уделяется большое внимание в связи с тем, что она обладает потенциалом терапевтической мишени. Основываясь на том факте, что у людей с аутизмом отмечена измененная экспрессия генов, сопутствующая нарушению гематоэнцефалического барьера (ГЭБ) и целостности кишечного барьера, повышенный уровень глутамата в крови и тромбоцитах пациентов с РАС может быть связан с меньшим количеством мозжечковых ГАМК-ергических нейронов, менее активными ГАМК-синтезирующими ферментами и сниженным уровнем ГАМК в мозге. Эксайтотоксичные уровни высвобождения глутамата запускают каскад разрушительных клеточных событий, приводящих к отсроченной гибели нейронов. В соответствии с нашим пониманием эксайтотоксичности глутамата добавки ГАМК теоретически могут быть полезны при лечении определенных фенотипов аутизма. Хотя эффективных и безопасных препаратов, предотвращающих вызванные глутаматом повреждение и гибель клеток, до сих пор не существует, мы надеемся, что благодаря совместным усилиям нам удастся разработать лучшие варианты лечения. В данной статье я выдвинула гипотезу о том, что использование интегрированной стратегии лечения с применением добавок ГАМК, регуляцией уровня хлорида (Cl-) и магния (Mg2+), добавками витамина D, пробиотиков для усиления экспрессии рецепторов ГАМК-А и глутаматдекарбоксилазы (GAD), а также мемантина для активации транспортеров глутамата и ингибирования NMDA рецепторов, может привести к снижению уровней глутамата, поддержать функционирование рецепторов ГАМК и тем самым воздействовать на повторяющееся поведение, нарушения социального взаимодействия и судорожные припадки у людей с аутизмом.

Ключевые слова: аутизм; эксайтотоксичность глутамата; гамма-аминомасляная кислота; витамин Д; кишечная микробиота.

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Introduction

Autism spectrum disorder (ASD) is a highly heterogeneous, lifelong neurodevelopmental disorder that clinically presented as social interaction and communication impairments together with restricted interests and stereotyped behaviors [34]. Its prevalence is growing; therefore, there is a need to determine the key etiological mechanisms that would facilitate the identification of predictive and diagnostic markers that might help develop treatments. There are multiple of etiopathological mechanisms attributed to autism; the most known being systemic immune activation and excitotoxicity. It is commonly believed that chronic inflammation is the hallmark of many neurodevelopmental disorders [81; 93] and research on autistic patients has uncovered a number of immune dysfunctions [37; 87]. Neuroinflammation has been described in postmortem brain specimens of both young and old individuals with autism [56; 93; 122].

Progress is being made based on accumulating evidence that genetic and environmental risk factors for autism converge to disturb the balance between glutamate-mediated excitatory and γ-aminobutyric acid (GABA)-mediated inhibitory neurotransmission; and this may help to identify treatment targets for the disorder [18; 89; 104; 107].

The hypothesis that GABA can be targeted as an appropriate means of treating autism is supported by the relatively high incidence of epilepsy in patients suffering from autism, as well as the high frequency of epileptiform activity observed in the electroencephalograms (EEG) of autistic patients [101].

Moreover, electrophysiological and behavioral autism-like features have been observed in mice after blockade of maternal oxytocin signaling, which is important for the early postnatal excitatory-to-inhibitory shift of GABAergic signaling [119; 120].

Based on this information, the model of excitation-inhibition imbalance is one of the leading hypotheses to explain the etiology of autism. There-

fore, a precise and integrated adjustment of brain metabolism through regulation of glutamic acid and GABA could be used as treatment strategy for autism.

We do not yet have a clear mechanism of action regarding GABA supplementation and we have yet to fully understand the role of GABA's behavioral effects, as well as its blood-brain barrier (BBB) permeability in humans. However, evidence from numerous clinical studies strongly supports the therapeutic effects of GABA in the brain [16; 52; 72; 99].

Interlinked Metabolism of Glutamate and GABA

It is well known that glutamate and GABA metabolism is strongly interlinked, so a change in any of the intermediate metabolite can affect both neurotransmitters. Glutaminase as an enzyme catalyzes the conversion of glutamate to glutamine, allowing glutamine to be either stored in astrocytes or converted to glutamate in both glutamatergic and GABAergic neurons [103]. Between synaptic events, normal levels of glutamate and GABA are kept low via permanent transporter-mediated turnover through the plasma membrane [17; 19; 28; 111]. These transporters terminate synaptic neurotransmission, enabling the reuptake of the neurotransmitters. In excitatory neurons, glutamate is transported into vesicles through vesicular glutamate transporters, whereas in inhibitory neurons, glutamate is first transformed to GABA by glutamic acid decarboxylase (GAD), and then transported to vesicles via vesicular GABA transporters. Upon release, both neurotransmitters are taken up by high affinity transporters and returned into neurons and surrounding glia to be reused. Thus, GABA, glutamate, and glutamine are in constant flux. In autism however, the levels of the enzymes controlling glutamine-glutamate-GABA cycles are altered and thus, glutamine-glutamate-GABA metabolism is likely to be unusual in the ASD brain [46; 128].

Among clinical samples, high concentrations of glutamate and glutamine (Glx), and GABA in the temporal lobe, and high levels of glutamate in the auditory cortex have been directly related to the severity of autistic phenotypes [22]. Increased anterior cingulate glutamate/creatine and Glx have been associated with severe social interaction and communication impairments [38; 117]. The hyper-glutamatergic hypothesis of autism reported by Fatemi [47] suggests that lower levels of the GAD enzyme, and increased numbers of astrocytes, which take up synaptic glutamate to resynthesize glutamine and glutamate, leads to excess cortical glutamate in autistic patients. The remarkably lower levels of the 65 and 67 kDa GAD isoforms in individuals with autism may account for the reported increases of glutamate in blood and platelets of autistic subjects [42]. GAD deficiency may be due to, or associated with, abnormalities in levels of glutamate/GABA, or transporter/receptor density in the autistic brain.

Conversion of glutamate to glutamine by glutamine synthetase requires ammonia, which help to clear both molecules. It is well known that patients with liver dysfunction and children with urea cycle disorders cannot efficiently detoxify ammonia, inducing high levels of ammonia and glutamine in the brain [48]. Liu et al. [75] reported that autistic children had high brain ammonia but low levels of glutamine, showing that their serum glutamine levels were low and they had impaired glutamate transporters. This was supported Saleem et al [107] who recorded increased levels of ammonia, a marked reduction in urea concentration, and significant increases in the glutamate/glutamine ratio in the plasma of patients with autism compared with controls, suggesting that the glutamate/glutamine cycle was greatly impaired in these patients. Additionally, Liu [75] identified a panel of 7 urinary amino acid indicators that could discriminate between urine samples from ASD and healthy control children. Collectively, they find a possible imbalance between excitatory and inhibitory amino acid metabolism in ASD children. The significantly altered urinary amino acid indicators could therefore be potential diagnostic biomarkers for ASD.

Noticing high plasma ammonia and high GABA in blood and urine of an autistic boy, Cohen [29] noted plasma GABA levels are positively correlated with those of plasma ammonia. Dhossche et al [33] found high plasma GABA in autistic children aged between 5 and 15 years old. It is also very interesting to note that fever increases CSF taurine but decreases GABA [75].

It has been suggested that ammonia produced by the gut yeast *Candida albicans* forms a metabolite that works like GABA in autistic brains [24] Wakefield et al. [126] suspected that gut bacteria

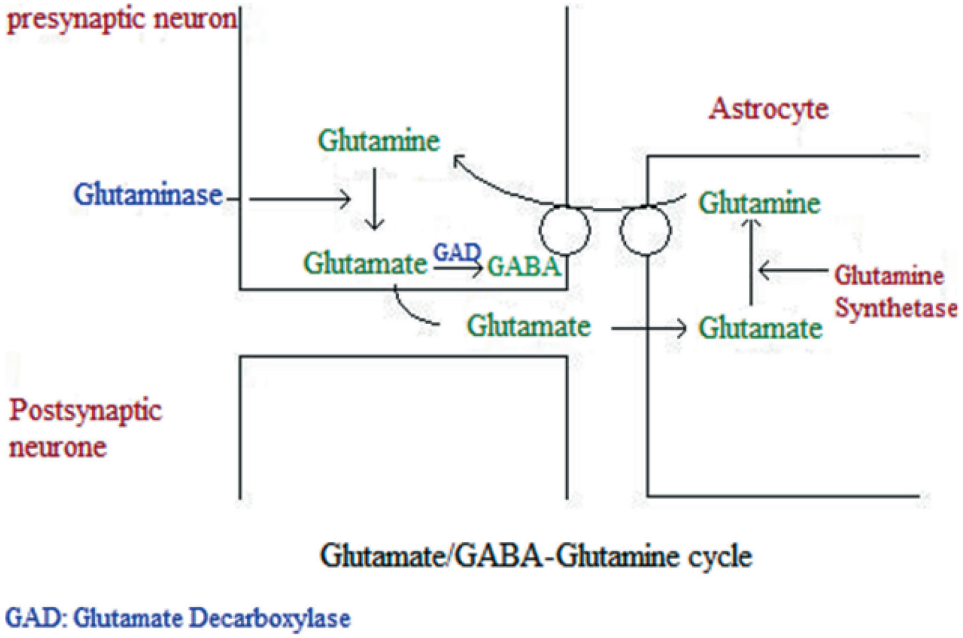

Fig. 1. Glutamate-GABA-Glutamine cycle

in children with autism generate much higher ammonia than their impaired liver can detoxify. This might happen, for example, if an oral antibiotic was given and induces overgrowth of pathogenic bacteria. Another pathogenic consequence is interrelated to glutamate is vaccination. Hoernlein [63] noted that vaccines, specifically those against measles, mumps, rubella (MMR), are usually enclosed in hydrolyzed gelatin, as a rich source of glutamate to reserve the viruses. In the presence of low-affinity glutamate transporter that exchange cystine and glutamate between the interior and exterior of the cell in a 1:1 ratio, extracellular glutamate usually accumulates, obstructs the cystine-glutamate exchange, and resulting in the reduction of cell stores of cystine as a major precursor of sulfur amino acids and glutathione. This may explain the association between glutamate excitotoxicity and oxidative stress as two etiological mechanisms of autism [39].

The GABAergic System in Autism

The role of the GABAergic system in autism has received a large amount of attention due to several factors. Autism studies have reported (1) reduced numbers of cerebellar GABAergic Purkinje cells especially in the posterior lobe [8; 127]; (2) lower activity levels of key synthesizing enzymes (GAD65 and GAD67) in the cerebellum and parietal cortex [46], and decreased levels of GAD67 in Purkinje cells [128]; (3) neuropathology in the deep cerebellar nuclei, a brain region rich with GABAergic neurons, with males more affected than females [23; 65; 88]; (4) reduced density of γ-Aminobutyric acid type A (GABAA) receptors in specific areas of the hippocampus [15; 70; 123]; (5) the most common chromosomal abnormality in autism is an alteration(s) in chromosome 15q11-q13, a region that contains three GABAA receptor subunit candidate genes for autism [108; 110], including the GABAA3 subunit receptor gene [79]; and (6) elevated plasma GABA in autistic children aged between 5 and 15 years [39; 42].

GABAA receptors are heteropentameric ionotropic receptors made of 19 different subunits. The majority contain two α, two β and one γ or δ subunit [91]. GABAA receptors that contain the α5 subunit (α5GABAA α5GABAA) are important because of their limited distribution and distinctive physiological and pharmacological characteristics [28; 74]. Extrasynaptic α5GABAA receptors are highly expressed in the hippocampus and at reduced levels in the cortex, and hypothalamus. Activation of these receptors creates a stimulant inhibitory current that moderates excitability and synaptic plasticity [26; 79]. α5GABAA receptors also play a trophic role that regulates the development of neural circuits [74].

It is very interesting to note that *Gabra5–/–* knocked out mice missing the α5 subunit gene, clinically presents multiple autism-like features, such as impaired social interaction, abnormal cognitive and memory functions, and sleep disturbances [85; 131]. Actually, the most common copy number variant in autism is a duplication of the q11.2–13 region of chromosome 15 [86], which encodes for the α5, β3, and γ3 subunits of the GABAA receptor [86]. Rare variants in the gene that encodes the α5 subunit have also been identified in autistic patients [131]. These findings suggest that dysfunctional α5GABAA receptors could be contributed to glutamate excitotoxicity as etiological mechanism in autism. The role of GABAA receptors in the etiology of autism was confirmed by Han et al. [61] who showed that low doses of benzodiazepines, as a GABAA receptor agonists, increase inhibitory neurotransmission through positive allosteric modulation of postsynaptic GABAA receptors in a rodent model of autism. This was concomitant with improved social interaction, reduced repetitive behavior, much better cognitive ability. In contrast, negative allosteric modulation of GABAA receptors impaired social behavior in C57BL/6J and 129SvJ wild-type mice.

Neuronal chloride control plays a role in the dynamic regulation of GABAergic inhibition both during and after brain development. This regulation is mostly reliant on two cation chloride co-transporters (CCCs), the K^+/Cl– co-transporter KCC2, and the Na^+/K^+/Cl– co-transporter NKCC1, whose activity can decrease or increase neuronal chloride levels respectively. Ben-Ari et al. [10] observed an elevated intracellular chloride (Cl^-) levels and excitatory GABA early during gestation followed by a perinatal excitatory-to-inhibitory shift. This mechanism is found in many brain areas of different animal species which suggest that it happens early in life. It is mediated mostly by the developmentally controlled gene expression of KCC2 and NKCC1, which are exporter and importer of Cl^- respectively. In spite of the straightforward function of GABA receptors in the transmission of information from the presynaptic to the postsynaptic neurons, some other factors are involved. Among these is the difference in membrane potential between the postsynaptic dendrite against the reversal potential for chloride ions. Based on this, GABA can evoke either depolarizing (excitatory) or hyperpolarizing (inhibitory) currents. This can be also affected by the local distribution of large anions, such as glutamate. Three conditions can be observed in which the reversal potential of chloride ions is below, above, or equal to the membrane resting potential. Low intracellular chloride levels can induce the influx of more negatively charged ions is low which can enhance the inhibitory function of GABAA receptors. At higher chloride levels, its reversal potential is above the resting potential of the cell, enhancing the excitatory effects of GABA. When the reversal potential for chloride equals the resting potential of the cell, stimulation of the GABAA receptors will cause no net flux of chloride and no alteration of the membrane potential. As the excitatory potential for GABA and the resting membrane potential are in relatively close proximity, small rises in Cl– can shift the polarity of GABAA currents from inhibitory to excitatory, highlighting the importance of maintaining low Cl^- [66; 76; 98]. Studies are now beginning to examine the connection between NKCC1 and KCC2 and the etiology of autism. Mutations in the C-terminal regulatory domain of KCC2 were found to be related with autistic phenotypes [30; 63; 84]. Several models of genetic disorders strongly associated with autism have been linked to alterations in NKCC1/KCC2 ratios [35]. Exposure of rats to valproate (VPA) during gestational period has shown a significant delay in the shift of GABA from excitatory to inhibitory [62]. Oral treatment with the selective NKCC1 antagonist bumetanide in pregnant VPA- treated rats immediately before delivery has shown a remarkable restoration of the effects of elevated Cl– and excitatory GABA signaling in the new born and can reduce the behavioral problems at childhood [102].

Glutamate Excitotoxicity as an Etiological Mechanism in Autism

Glutamate excitotoxicity arises when glutamate receptors (GluRs) are overstimulated with an excessive amount of the excitatory neurotransmitter, glutamate, followed by the increase of intracellular Ca^{2+} ions, finally lead to neuronal death [90].

Several studies have reported that glutamate excitotoxicity is one of the repeatedly recorded etiological mechanisms in autism. The GluRs are classified as ionotropic receptors, or metabotropic receptors (mGluRs) [43; 44]. Each type is composed of a variable association of subunits,

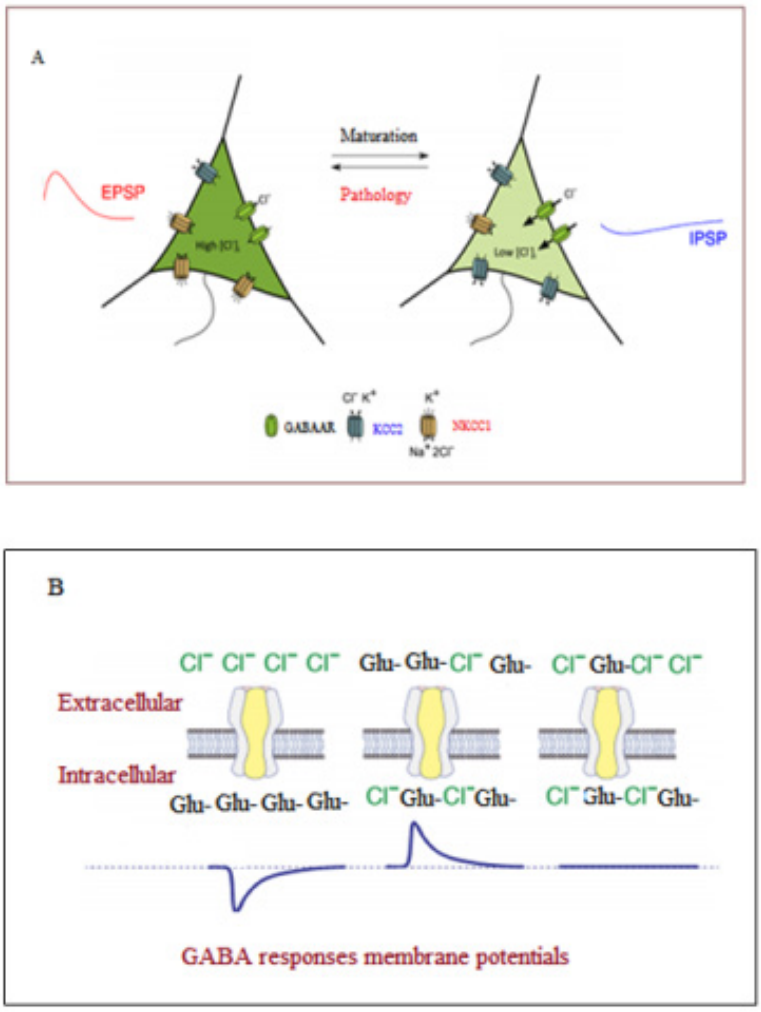

Fig. 2. A: Role of NKCC1/KCC2 ratio in GABA neurotransmission;
B: Different GABA responses membrane potentials

which determines their biophysical and physiological properties. N-methyl-D-aspartate receptor (NMDAR) is an ionotropic GluR that is classically composed of a tetrad arrangement of subtype receptor subunits — GluN1, GluN2A-D, and GluN3A and B. During development, there are significant modifications in the composition of these subunits. In the mammalian brain, functional NMDARs require a GluN1 subunit associated with one or more GluN2 subunits. Magnesium (Mg^{2+}) binding sites inside the NMDAR regulate its function, with Mg^{2+} playing a crucial role as a voltage-dependent channel blocker. Upon depolarization, the Mg^{2+} blockade is released, permitting the action potential to go on. Sensitivity to Mg^{2+} blockade varies with subunit ratio composition. Mg^{2+} ions mainly oppose Ca^{2+} ions, and Mg^{2+} deficiency induced brain seizures can be avoided by treating with NMDA-receptor antagonists [41]. Since Mg^{2+} is required for many brain enzymes, a striking decrease of Mg^{2+} in a propionic acid (PPA)-induced rodent model of autism was recently related to glutamate excitotoxicity as a persistent autistic feature in juvenile rats [41; 50; 78]. When Mg^{2+} deficiency occurs, excessive Ca^{2+} and glutamate can induce synaptic dysfunction in the brain, which can manifest as repetitive behavior, impaired social behavior, seizure activity, and hyperactivity, as previously reported [3; 31; 32].

α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) are ionotropic receptors composed of GluA1-4 subunits (GluR1-4 by older nomenclature). The presence of the GluA2 (GluR2) subunit in the AMPAR blocks Ca^{2+} entry into the neuron [14]. AMPAR sensitivity is regulated by whether they contain or lack a GluA2 (GluR2) subunit when they are transported to the

neuronal membrane. The latter causes the AMPAR to be Ca^{2+} permeable, and trafficking of GluA2-lacking AMPARs to the synaptic unit increases glutamate-induced neuronal activation, which is observed in long-term potentiation (LTP), plasticity, and during neurodevelopment. Under pathological conditions, such as inflammation, the activity of GluA2-lacking AMPARs can trigger excitotoxic damage [50; 71].

Edfawy et al. [36] studied the functional role of *Gprasp2*, a gene linked with neurodevelopmental disorders that encodes a protein that contributes to post-endocytic organization of G-protein-coupled receptors. They observed that *Gprasp2* deletion leads to clinically presented ASD features and changes in synaptic neurotransmission in mice. Manipulating the levels of *Gprasp2* expression reduced the surface availability of mGluR5 and produces alterations in dendritic complexity, spine density and synaptic maturation. These findings demonstrate a role for *Gprasp2* in glutamatergic synapses and suggest a possible mechanism by which this gene is linked to autism.

Astrocyte-mediated clearance of free glutamate from synaptic cleft is mostly accomplished through two astroglia-specific, high-affinity glutamate transporters called excitatory amino acid transporters 1 and 2 (EAAT1 and 2), classified in rodents as glutamate aspartate transporter (GLAST) and glutamate transporter-1 (GLT-1), respectively. These transporters use the electrochemical gradients across the plasma membranes as motivating forces for glutamate transfer into the intracellular compartment [4]. Conventionally it was thought that following uptake into astrocytes, glutamate is converted into non-toxic glutamine by glutamine synthetase, which is then released into the intercellular fluid and taken into neurons to be used for glutamate recycling in order to replenish the neurotransmitter pool [112]. However, more recent data suggest that, on some physiological and pathological circumstances, astrocytes are capable of releasing glutamate via multiple mechanisms [25; 124]. Several mechanisms connecting astrocyte glutamate release with the excitotoxicity present in autism have been described, mainly involving microglia activation [11; 94; 115]. Based on their crucial role in neurological disorders, EAATs are targets for the development of new treatment strategies for brain diseases [59; 115] and a recent study has shown that ß-lactam antibiotics can remarkably increase the gene expression of *EAAT2/GLT-1* in a rodent model of autism [3].

High affinity glutamate (L-Glu) transporters facilitate L-Glu re-uptake into neurons and glial cells [20]. These transporters combine the uptake of L-Glu with the exchange of one H^+ ion, one K^+ ion, and 3 Na^+ ions, [6]. Impaired glutamate and glutamine transporters are repeatedly reported in autism [6]. Cystine is an essential amino acid for the biosynthesis of the reduced glutathione (GSH), and its uptake requires the cystine/glutamate exchanger SLC7A11 [95]. This transporter catalyzes the uptake of one molecule of cystine with the release of one molecule of L-Glu. As it is highly expressed in astrocytes but not in neurons, neurons are dependent on astrocytes for the production of GSH. Once cystine enters astrocytes, it forms the tripeptide GSH. Synthesized GSH can be released into the extracellular space followed by enzymatic catabolism, eventually leading to the formation of cysteine. Cysteine is then taken up by neurons through SLC1A1 transporter to synthesize GSH. GSH depletion as a pathological feature in autism could influence the capacity of cells to scavenge free radicals, making them susceptible to accumulate reactive oxygen species (ROS), possibly injuring of the L-Glu transporter SLC1A2, especially in motor neurons. Together with additional alterations, including activation of caspases as pro-apoptotic markers, this will finally lead to neuronal death.

Ford et al. [53] revealed that strong autistic tendencies are associated with the GABA+ concentration and an increased glutamate/GABA+ ratio in the lower right hemisphere of the brain. Previous reports also show that increased excitatory and reduced inhibitory neurotransmission is implicated across the autism spectrum, particularly in the social domain [54; 55; 68; 129]. These findings are consistent with evidence from animal studies showing that social deficits caused by increased glutamate/GABA+ ratio can be reduced by increasing in the inhibitory neurotransmission of GABAergic neurons [27; 109; 129].

To understand the role of microglia activation in excitatory/inhibitory imbalance in autism, Lieberman et al [73] proposed two different hypotheses. It is well known that the healthy developing brain initially form additional, inappropriate excitatory synapses. These unnecessary or less active synapses are pruned by microglia, and only functionally mature synapses are conserved [12]. Their first hypothesis

stated that in autism, microglia may fail to detect and prune immature synapses, which would result in the conservation of an excess number of glutamate excitatory synapses. Their second hypothesis stated that over-activated microglia may selectively prune GABAergic inhibitory synapses.

These hypotheses are consistent with the idea that disturbance of microglial activation by immune stimulation such as maternal infection during a critical period can deleteriously affect synaptogenesis [13]. Pruning by microglia is activity dependent, which suggests that excitotoxic stimulation during prenatal or early post-natal periods could also adversely affect brain architecture. Bilbo et al. have shown that activation of brain microglia early in life can have long-term consequences on brain function, even into adulthood [12; 13].

Vitamin D Deficiency and Imbalanced Excitatory/Inhibitory Neurotransmission in Autism

It is well known that autism is more prevalent in areas of relatively poor ultraviolet light exposure, such as urban areas, areas with high air pollution, and areas of high precipitation [45]. Animal studies have confirmed that severe vitamin D deficiency during pregnancy negatively affects numerous proteins which contribute to brain development, resulting in pathological alterations in neonatal animals similar to those seen in autistic patients [60; 125]. Meguid et al. [82] measured serum levels of vitamin D in Egyptian children with autism compared to healthy controls, and reported that the level of vitamin D3 was remarkably lower in autistic patients. Multiple studies have confirmed vitamin D deficiency as an etiological mechanism in autism [1; 40; 51; 57; 87; 125], whereas only two studies have shown no difference between children with autism and controls [121].

Based on this, vitamin D supplementation for autistic children with insufficient vitamin D is necessary. Saad et al. [105] reported that vitamin D supplementation can help as a treatment strategy in autism. Their cohort study of autism spectrum disorder children receiving vitamin D supplementation at a dose of 300 IU/kg/day showed that children with a final vitamin D3 serum level below 30 ng/ml demonstrated no improvements in clinical presentation, 31/102 children with final vitamin D3 serum levels between 30–39 ng/ml had decreased childhood autism rating scale scores (CARS) by 1.5–4.5 points, while those with a final serum vitamin D3 levels above 40 ng/ml had decreased CARS by 3.5 to 6.5 points. This seems to suggest that the lower limit for vitamin D levels in autism treatment is 40 ng/ml, or at least above 30 ng/ml. Feng et al [49] showed that autistic phenotypes were greatly improved after 3 months of vitamin D being either intramuscularly injected or orally supplemented, with younger patients being more responsive. Moreover, animal studies have shown that vitamin D demonstrates a protective rather than therapeutic effect on PPA-induced neurotoxicity in rats, as there was a remarkable amelioration of the impaired interferon-gamma IFN-γ, serotonin, Glutathione-s-transferase, and DNA damage [2]. Of course, additional large scale, international multi-center studies are essential to explore the relationships between the clinical response to vitamin D supplementation, long-term effect of vitamin D supplementation, and the biochemical changes in autistic patients.

Epidemiological studies have revealed that vitamin D deficiency is associated with a wide range of neuropsychiatric disorders, including autism [58; 60; 67; 69]. It is known that vitamin D deficiency significantly reduces the levels of glutamic acid decarboxylase, the key enzyme in GABAergic interneurons, and glutamate and glutamine in mouse brain tissue [60]. This suggests that glutamate excitotoxicity, and impaired glutamate-glutamine-GABA cycle in autism can be corrected through the treatment of vitamin D insufficiency or deficiency [125].

To validate this suggestion, we can consider the recent study by Krisanova et al. [69] who showed that vitamin D3 deficiency disturbs synaptic neurotransmission by affecting both Ca^{2+}-dependent and Ca^{2+}-independent processes. The Ca^{2+}-dependent action of vitamin D3 deficiency was associated with a decrease in exocytotic release of glutamate and GABA, presumably caused by malfunctioning voltage-gated Ca^{2+} channels. The Ca^{2+}-independent action of vitamin D3 deficiency was associated with a decrease in the expression of glutamate and GABA transporters that in turn result in the decrease of glutamate and GABA reuptake. Their main finding demonstrates that vitamin D3 deficiency could be and etiological mechanism in autism by contributing to an impaired glutamate/GABA transporter expressions and excitation/inhibition imbalance.

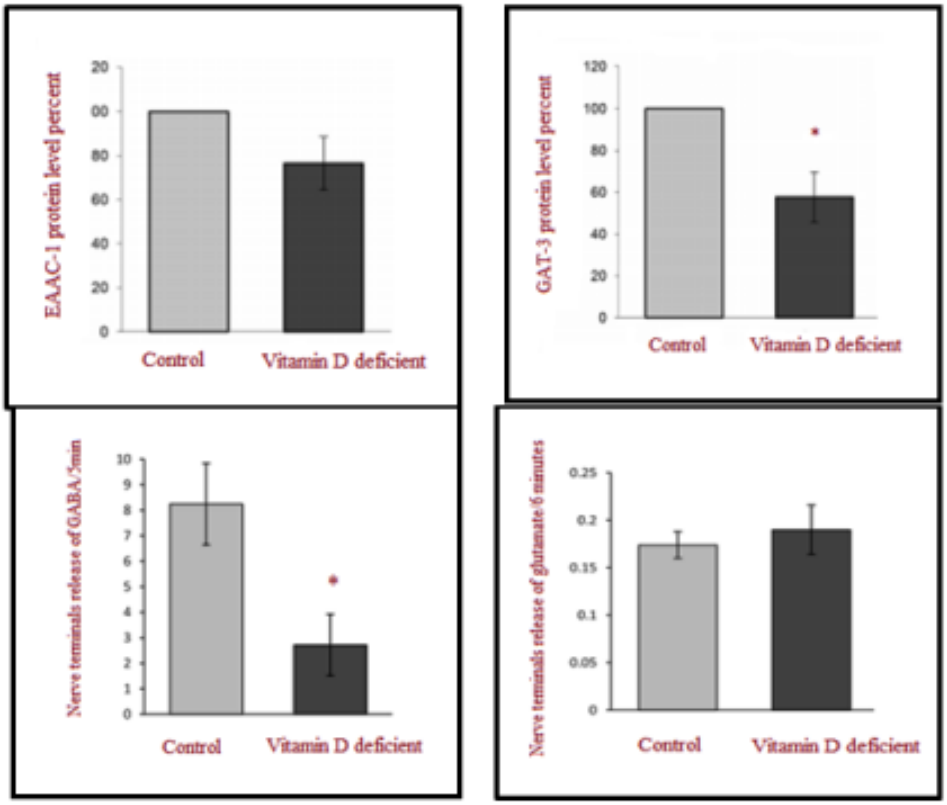

Fig. 3. Protein expression of EAAC-1 and GAT-3 transporters (UP) and release of GABA and glutamate from nerve terminals (Down) in control and vitamin D3-deficient rats (Modified from Krisanova et al., [70])

Role of Microbial Glutamate and Gaba sSignaling in Autism

Microbial endocrinology concerns the role of microorganism-produced neurochemicals such as GABA, glutamate, and serotonin, as a common language that allows crosstalk between microbe and host. Understanding the gut microbiota—brain axis in humans as a bidirectional cross talk system that links the gut with the brain through several pathways including endocrine, immune, and neural, might open the road toward the use of neurochemical-producing probiotics as a therapeutic strategy to treat autism.

The impaired methylation capacity reported in autism may be related to the imbalanced GABA/Glu ratio in autism. Impairment of the methylation pathway prevents the use of folate, which is broken down into glutamate. The Krebs cycle is critical for methylation, and can become impaired in a variety of ways, such as vitamin B deficiency, the presence of heavy metals, and toxins from bacteria or *Candida* [7]. *Candida* overgrowth is known to occur in autistic patients [64; 65]. If methylation is impaired, then it is even more important to manage glutamate levels.

Lactobacillus plantarum, *L. paracasei*, *L. lactis*, *Corynebacterium glutamicum*, *Brevibacterium lactofermentum*, and *B. flavum* are among the bacterial strains which are capable of producing glutamate [116; 130]. A study has revealed that about 15% of lactic acid bacteria strains isolated from Asian fermented foods are glutamate producers [96]. Both Gram-positive and Gram-negative bacteria such as *E. coli* and *Pseudomonas* can produce GABA via the decarboxylation of glutamate catalyzed by GAD. This enzyme has been found to be associated with pH homeostasis and the generation of metabolic energy [9].

Amongst the microorganisms that are commonly identified as health-promoting probiotics, one *Lactobacillus* strain and four strains of *Bifidobacterium* isolated from the human intestine have been reported to be able to produce GABA [97]. Furthermore, an analysis on metagenomic data from the human microbiome project suggests that genes encoding GAD could be present in a significant proportion of human gut microbiota [21]. Real time PCR revealed decreases in both the *Lactobacillus* and *Prevotella* in both male and female *Shank3* knockout mice, a genetic model of

autism, compared to wild type mice. Moreover, examination of stool and colon microbiota of normal healthy female mice revealed a significant increase in genera and species of *Lactobacillus* compared to males. This suggests that higher levels of *Lactobacillus* in female mice could act as a protective factor and may explain the sex bias of autism towards males. Previous studies have suggested a possible connection between *Lactobacillus*, autism-related behaviors, and GABAergic function. In particular, Bravo et al. [21] determined that *Lactobacillus* may regulate GABA receptor expression in the brain through secretion of GABA. In *Shank3* knockout mice, GABA receptor expression is particularly affected in multiple brain regions, including the hippocampus, which is also one of the regions that have been shown to be affected in ASD patients. Pearson correlation analysis between levels of *L. reuteri*, *L. brevis*, *L. ruminis* and GABA receptor levels revealed specifically that the abundance of *L. reuteri* correlated significantly with expression of each of the three GABA receptor sub-units (GABARA1, GABARA2, and GABARA3).

Therapeutic Targets of Glutamate Excitotoxicity as Rational Treatment Strategy

1. Glutamate transporters GLAST/GLT-1

Recently Pajarillo et al. [92] reported that GLAST/GLT-1 may be dysregulated at the genetic, epigenetic, transcriptional or translational levels, leading to high levels of extracellular glutamate and excitotoxicity. Accordingly, understanding the regulatory mechanisms of GLAST/GLT-1 has been highlighted as a means to develop therapeutic targets for the treatment of autism [3; 92]. Pharmacological agents such as β-lactam antibiotics, estrogen/selective estrogen receptor modulators (SERMs), growth factors, histone deacetylase inhibitors (HDACi), and translational activators have presented noteworthy effectiveness in increasing the expression and function of GLAST/GLT-1 and glutamate uptake both *in vitro* and *in vivo* [92]. Torrez et al. [118] reported neuroprotective effects of memantine (MN), a glutamatergic NMDAR channel blocker. The drug could prevent the increase in cerebrospinal fluid (CSF) glutamate levels and cognitive decline in treated rats. It decreased glutamate uptake in the hippocampus and increased the release of S100B protein in the CSF in response to okadaic acid (OKA)-induced neurotoxicity. This identifies a promising neuron-astrocyte coupling protective mechanism, and sheds light on astrocytes as potential targets for treating glutamate excitotoxicity.

2. Oxidative stress:

Oxidative stress and related mitochondrial dysfunction are directly related to glutamate excitotoxicity in autism. Through the use of multiple regression analysis, El-Ansary [39] showed that high levels of lipid peroxidation (LPO), a marker of oxidative stress, together with lower enzymatic and non-enzymatic antioxidants (GSH, GSH/GSSG, thioredoxin, peroxiredoxins), were related to glutamate excitotoxicity, presented as glutamate, glutamine, glutamate/glutamine ratio, and glutamate dehydrogenase. This suggests that oxidative stress could be a target to treat glutamate excitotoxicity related phenotypes in autistic patients [5; 113].

LPO products affect the electron transport chain in the inner membrane of the mitochondria, leading to the loss of the membrane potential (ΔΨm) and boosting the generation of ROS, such as superoxide anion and hydrogen peroxide [83]. Although, neurons have strong antioxidant defenses, such as peroxiredoxins, superoxide dismutase enzymes (SODs) such as Cu^{2+}/ $Zn2^{+}$-SOD (SOD1), Mn^{2+}-SOD (SOD2), glutathione peroxidase, and catalase (in low amounts), their function is greatly compromised in autism [100]. Recently, Rivero-Segura et al [100] assessed the probable antioxidant effect of prolactin (PRL), a hormone secreted by numerous cells and tissues including the mammary glands, T-lymphocytes, and hypothalamus. They proved that PRL augments the activity and amount of the antioxidant SODs and lowers LPO as marker of oxidative stress, which is repeatedly reported to be significantly higher in autistic patients. Moreover, they demonstrate that PRL prevents mitochondrial dysfunction induced by glutamate and significantly ameliorates membrane potential (ΔΨm) of dysfunctional mitochondria which help to suggest its effectiveness as treatment option. Their related findings are presented collectively in *Fig. 4*.

3. Inactivation of NMDAR and activation of mGlu receptors:

Excessive activation of NMDARs leads to the accumulation of intracellular Ca^{2+} and consequent neuronal death [131]. Many compounds, includ-

ing memantine and neurosteroids, are able to target glutamate toxicity through the modulation of NMDARs. 20-oxo-5β-pregnan-3α-yl sulfate (pregnanolone sulfate, PAS) is an endogenous neurosteroid that inhibits NMDAR currents. Glutamatergic NMDAR has also been targeted with multiple synthetic neurosteroids [80; 114]. Among the studied compounds, the 3α, 5β-pregnanolone glutamate (PAG) -like steroid compound (*Fig. 5*) demonstrated the most promising NMDAR-mediated neuroprotective effect. This suggests it could act as a therapeutic agent for improving glutamate-related autistic phenotypes by decreasing Ca^{2+} level, scavenging ROS, and preventing glutamate-induced caspase-3 activation.

It is very interesting to note that functional GABAA receptors tend to cluster; overstimulation of glutamate NMDA receptors by high glutamate concentrations leads to calcium influx and the loss of GABAA receptor-clustering, which negatively affects the inhibitory effect of GABA. Glutamate can also bind to the mGluR receptor to induce the release of internally-stored calcium into the cytosol of the neuron. This calcium can, in turn, restore the clustering of postsynaptic GABAA receptors by interacting with protein kinase C. These findings demonstrate that glutamate signaling is activated by distinct receptors and calcium signaling patterns, which oppose the control of inhibitory GABA synapses (*Fig. 6*).

4. Activation of GABAergic receptor:

The release of excitotoxic levels of glutamate triggers a cascade of events leading to neuronal death. This phenomenon involves imbalance between excitation and inhibition. Mazzone and Nistri [80] hypothesized that augmenting the inhibitory network should prevent excitotoxicity and provide

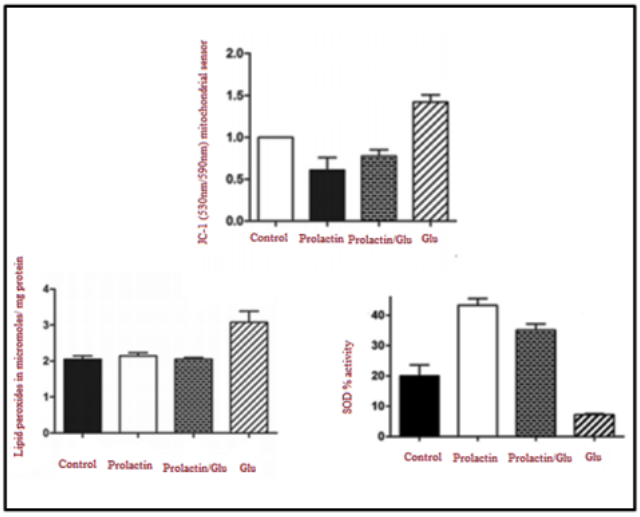

Fig. 4. Therapeutic effects of prolactin through amelioration of glutamate induced mitochondrial dysfunction, lipid peroxidation, and SOD antioxidant enzyme. JC-1 is a mitochondrial membrane potential (ΔΨm) sensor, which emits fluorescence at 590 nm when the mitochondrion is polarized (functional) and at 530 nm when mitochondrion is depolarized (dysfunctional).
(Modified from Rivero-Segura et al., 2019 [101])

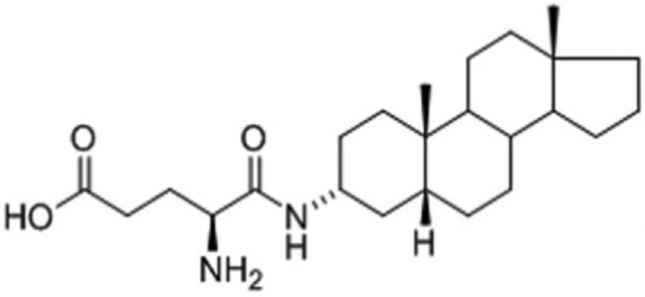

Fig. 5. Chemical structure of 3α, 5β-pregnanolone glutamate (PAG)-like steroid compound tested for a neuroprotective effect against glutamate-induced excitotoxicity

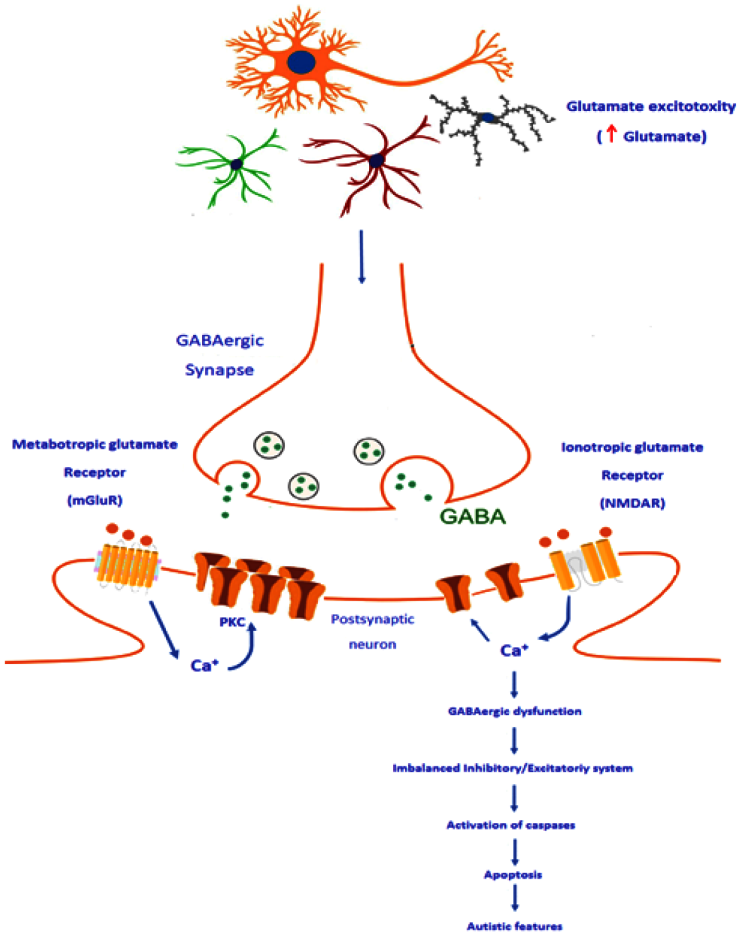

Fig. 6. A suggested mechanism of inhibitory connections dysfunction as an etiological mechanism in autism spectrum disorder through the loss of GABA receptors clustering caused by glutamate as an excitatory neurotransmitter. In the left part binding of glutamate to the mGluR receptor induces the release of internally stored calcium into the neuron's internal environment, activates protein kinase C to maintain clustering and functional GABAA receptors at the postsynaptic membrane. Under the effect of glutamate excitotoxicity, and down-regulation of mGluR receptors in ASD patients, NMDA receptor overstimulation with glutamate leads to an excess of incoming calcium, which causes the receptors to become more spread out, reducing how much GABA can inhibit the neuron. This can lead to an imbalance of the inhibitory/excitatory system, followed by activation of caspases as pro-apoptotic proteins, and finally leading to autistic features

neuroprotection. They proved that glutamate release induced by kainate was intensely decreased by the allosteric GABAA modulator midazolam (10 nM) or the GABA agonist 4,5,6,7 — tetrahydroisoxazolo [5,4-c]-pyridin-3-ol (THIP; 10 μM), leading to neuroprotection.

Conclusion

This work presents evidence of glutamate excitotoxicity's involvement in autism, making it a potentially viable treatment strategy in ASD. Correction of imbalanced Glut/ GABA ratio in individuals with autism may be tried at different levels through the use of multiple targets such as: 1) activation of GLAST/GLT-1 to increase glutamate reuptake; 2) amelioration of oxidative stress; 3) inactivation of NMDAR and activation of mGlu receptors to induce the proper function of GABA receptors; 4) supplementation of GABA; 5) use of GABA and GAD producing probiotics such as lactobacillus and bifidobacterial; and 6) activation of GABAergic receptors. Collectively, these targets can help to lower glutamate levels and thus induce the proper function of GABA receptors, which make GABA supplementation a successful and promising treatment strategy.

Future research in this direction will help to design specific drugs targeting these signaling proteins and possibly modulate the expression dynamics of glutamate NMDAR and mGlu receptors,

transporters, and GABA receptors for therapeutic application in autism.

Further studies using the optimal animal model followed by clinical trials are recommended to prove the safety and efficacy of the suggested strategy in order to improve the success of translational research and future clinical applications.

List of abbreviations:

α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs); Childhood autism rating scale scores (CARS); Cation chloride co-transporters (CCCs); Cerebrospinal fluid (CSF); Electroencephalogram (EEG); Excitatory amino acid transporters 1 (EAAT1); Glutamate receptors (GluRs); Glutamate aspartate transporter (GLAST); γ-aminobutyric acid (GABA); Glutamate (Glu); Glutamic acid decarboxylase (GAD); Glutamate transporter-1 (GLT-1); Glutamine (Glx); γ-Aminobutyric acid type A (GABAA); Glutathione (GSH); Histone deacetylase inhibitors (HDACi); Interferon-gamma IFN-$^{\gamma}$; K^+/Cl^- Co-transporter (KCC2); Long-term potentiation (LTP); $Na^+/K^+/Cl^-$ co-transporter (NKCC1); N-methyl-D-aspartate receptor (NMDAR); Reactive oxygen species (ROS); Superoxide dismutase enzymes (SODs); Prolactin (PRL); Propionic acid (PPA); Valproate (VPA).

Compliance with Ethical Standards.

Competing interests:

No conflict of interests.

References

1. *Adams J.B. et al.* Nutritional and metabolic status of children with autism vs. neurotypical children, and the association with autism severity. *Nutrition & metabolism*, 2011, vol. 8, no. 1, p. 34. DOI: 10.1186/1743-7075-8-34
2. *Alfawaz H., Tamim H., Alharbi S., Aljaser S., Tamimi W.* Vitamin D status among patients visiting a tertiary care center in Riyadh, Saudi Arabia: a retrospective review of 3475 cases. *BMC public health*, 2014, vol. 14, no. 1, p. 159. DOI: 10.1186/1471-2458-14-159
3. *Al-Suwailem E., Abdi S., Bhat R.S., El-Ansary A.* Glutamate Signaling Defects in Propionic Acid Orally Administered to Juvenile Rats as an Experimental Animal Model of Autism. *Neurochemical Journal*, 2019, vol. 13, no. 1, pp. 90—98. DOI: 10.1134/S1819712419010021
4. *Anderson C.M., Swanson R.A.* Astrocyte glutamate transport: review of properties, regulation, and physiological functions. *Glia*, 2000, vol. 32, no. 1, pp. 1—14.
5. *Angelova P.R., Abramov A.Y.* Role of mitochondrial ROS in the brain: from physiology to neurodegeneration. *FEBS letters*, 2018, vol. 592, no. 5, pp. 692—702. DOI: 10.1002/1873-3468.12964
6. *Aoki Y., Cortese S.* Mitochondrial aspartate/glutamate carrier SLC25A12 and autism spectrum disorder: a meta-analysis. *Molecular neurobiology*, 2016, vol. 53, no. 3, pp. 1579—1588. DOI: 10.1007/s12035-015-9116-3
7. *Ashwood P., Hughes H.K.* Brief Report: Anti-Candida albicans IgG antibodies in children with autism spectrum disorders. *Frontiers in psychiatry*, 2018, vol. 9, p. 627. DOI: 10.3389/fpsyt.2018.00627
8. *Bailey A. et al.* A clinicopathological study of autism. *Brain: a journal of neurology*, 1998, vol. 121, no. 5, pp. 889—905. DOI: 10.1093/brain/121.5.889
9. *Barrett E., Ross R.P., O'Toole P.W., Fitzgerald G.F., Stanton C.* γ-Aminobutyric acid production by culturable bacteria from the human intestine [correction published in: *Journal of applied microbiology*, 2014, vol. 116, no. 5, pp. 1384—1386]. *Journal of applied microbiology*, 2012, vol. 113, no. 2, pp. 411—417. DOI: 10.1111/j.1365-2672.2012.05344.x
10. *Ben-Ari Y.* The GABA excitatory/inhibitory developmental sequence: a personal journey. *Neuroscience*, 2014, vol. 279, pp. 187—219. DOI: 10.1016/j.neuroscience.2014.08.001
11. *Bezzi P. et al.* CXCR4-activated astrocyte glutamate release via TNFα: amplification by microglia triggers neurotoxicity. *Nature neuroscience*, 2001, vol. 4, no. 7, pp. 702—710. DOI: 10.1038/89490
12. *Bilbo S.D., Schwarz J.M.* Early-life programming of later-life brain and behavior: a critical role for the immune system. *Frontiers in behavioral neuroscience*, 2009, vol. 3, p. 14. DOI: 10.3389/neuro.08.014.2009
13. *Bilbo S.D., Smith S.H., Schwarz J.M.* A lifespan approach to neuroinflammatory and cognitive disorders: a critical role for glia. *Journal of Neuroimmune Pharmacology*, 2012, vol. 7, no. 1, pp. 24—41. DOI: 10.1007/s11481-011-9299-y
14. *Biou V., Bhattacharyya S., Malenka R.C.* Endocytosis and recycling of AMPA receptors lacking GluR2/3. *Proceedings of the National Academy of Sciences of the United States of America*, 2008, vol. 105, no. 3, pp. 1038—1043. DOI: 10.1073/pnas.0711412105
15. *Blatt G.J. et al.* Density and distribution of hippocampal neurotransmitter receptors in autism: an autoradiographic study. *Journal of autism and developmental disorders*, 2001, vol. 31, no. 6, pp. 537—543. DOI: 10.1023/a:1013238809666
16. *Boonstra E., de Kleijn R., Colzato L.S., Alkemade A., Forstmann B.U., Nieuwenhuis S.* Neurotransmitters as food supplements: the effects of GABA on brain and behavior. *Frontiers in Psychology*, 2015, vol. 6, p. 1520. DOI: 10.3389/fpsyg.2015.01520
17. *Borisova T. et al.* Effects of new fluorinated analogues of GABA, pregabalin bioisosters, on the ambient level and exocytotic release of [(3)H]GABA from rat brain nerve terminals. *Bioorganic & Medicinal Chemistry*, 2017, vol. 25, no. 2, pp. 759—764. DOI: 10.1016/j.bmc.2016.11.052
18. *Borisova T.* Nervous System Injury in Response to Contact With Environmental, Engineered and Planetary Micro- and Nano-Sized Particles. *Frontiers in Physiology*, 2018, vol. 9, p. 728. DOI: 10.3389/fphys.2018.00728

19. *Borisova T.* Permanent dynamic transporter-mediated turnover of glutamate across the plasma membrane of presynaptic nerve terminals: arguments in favor and against. *Reviews in the Neurosciences*, 2016, vol. 27, no. 1, pp. 71—81. DOI: 10.1515/revneuro-2015-0023
20. *Borisova T., Borysov A.* Putative duality of presynaptic events. *Reiews in the Neurosciences*, 2016, vol. 27, no. 4, pp. 377—383. DOI: 10.1515/revneuro-2015-0044
21. *Bravo J.A. et al.* Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. *Proceedings of the National Academy of Sciences of the United States of America*, 2011, vol. 108, no. 38, pp. 16050—16055. DOI: 10.1073/pnas.1102999108
22. *Brown M.S., Singel D., Hepburn S., Rojas D.C.* Increased glutamate concentration in the auditory cortex of persons with autism and first-degree relatives: a (1)H-MRS study. *Autism Research*, 2013, vol. 6, no. 1, pp. 1—10. DOI: 10.1002/aur.1260
23. *Bruchhage M.K., Bucci M.-P., Becker E.B.E.* Cerebellar involvement in autism and ADHD. *Handbook of clinical neurology*, 2018, vol. 155, pp. 61—72. DOI: 10.1016/B978-0-444-64189-2.00004-4
24. *Burrus C J.* A biochemical rationale for the interaction between gastrointestinal yeast and autism. *Medical Hypotheses*, 2012, vol. 79, no. 6, pp. 784—785. DOI: 10.1016/j.mehy.2012.08.029
25. *Canitano R., Pallagrosi M.* Autism spectrum disorders and schizophrenia spectrum disorders: excitation/inhibition imbalance and developmental trajectories. *Frontiers in psychiatry*, 2017, vol. 8, p. 69. DOI: 10.3389/fpsyt.2017.00069
26. *Caraiscos V.B. et al.* Tonic inhibition in mouse hippocampal CA1 pyramidal neurons is mediated by α5 subunit-containing γ-aminobutyric acid type A receptors. *Proceedings of the National Academy of Sciences of the United States of America*, 2004, vol. 101, no. 10, pp. 3662—3667. DOI: 10.1073/pnas.0307231101
27. *Cellot G., Cherubini E.* GABAergic signaling as therapeutic target for autism spectrum disorders. *Frontiers in pediatrics*, 2014, vol. 2, p. 70. DOI: 10.3389/fped.2014.00070
28. *Chebib M., Johnston G.A.* The 'ABC' of GABA receptors: a brief review. *Clinical and experimental pharmacology and physiology*, 1999, vol. 26, no. 11, pp. 937—940. DOI: 10.1046/j.1440-1681.1999.03151.x
29. *Cohen B.I.* GABA-transaminase, the liver and infantile autism. *Medical Hypotheses*, 2001, vol. 57, no. 6, pp. 673—674. DOI: 10.1054/mehy.2001.1350
30. *Côme E., Marques X., Poncer J.C., Lévi S.* Neuronal protein mobility KCC2 membrane diffusion tunes neuronal chloride homeostasis. *Neuropharmacology*, 2020, vol. 169. DOI: 10.1016/j.neuropharm.2019.03.014
31. *Cull-Candy S., Kelly L., Farrant M.* Regulation of Ca2+-permeable AMPA receptors: synaptic plasticity and beyond. *Current opinion in neurobiology*, 2006, vol. 16, no. 3, pp. 288—297. DOI: 10.1016/j.conb.2006.05.012
32. *Daghestani M.H. et al.* The role of apitoxin in alleviating propionic acid-induced neurobehavioral impairments in rat pups: the expression pattern of Reelin gene. *Biomedicine & Pharmacotherapy*, 2017, vol. 93, pp. 48—56.
33. *Dhossche D. et al.* Elevated plasma gamma-aminobutyric acid (GABA) levels in autistic youngsters: stimulus for a GABA hypothesis of autism. *Medical Science Monitor*, 2002, vol. 8, no. 8, pp. PR1—PR6.
34. Diagnostic and statistical manual of mental disorders: DSM-5. 5th edition. Arlington: Publ. American Psychiatric Publishing, 2013. ISBN 978-0-89042-555-8.
35. *Duarte S.T. et al.* Abnormal expression of cerebrospinal fluid cation chloride cotransporters in patients with Rett syndrome. *PLoS One*, 2013, vol. 8, no. 7, article no. e68851. DOI: 10.1371/journal.pone.0068851
36. *Edfawy M. et al.* Abnormal mGluR-mediated synaptic plasticity and autism-like behaviours in Gprasp2 mutant mice. *Nature Communications*, 2019, vol. 10, no. 1, p. 1431. DOI: 10.1038/s41467-019-09382-9
37. *Edmiston E., Ashwood P., Van de Water J.* Autoimmunity, autoantibodies, and autism spectrum disorder. *Biological psychiatry*, 2017, vol. 81, no. 5, pp. 383—390. DOI: 10.1016/j.biopsych.2016.08.031
38. *Egerton A. et al.* Anterior cingulate glutamate levels related to clinical status following treatment in first-episode schizophrenia. *Neuropsychopharmacology, 2012, vol. 37*, no. 11, pp. 2515—2521. DOI: 10.1038/npp.2012.113
39. *El-Ansary A.* Data of multiple regressions analysis between selected biomarkers related to glutamate excitotoxicity and oxidative stress in Saudi autistic patients. *Data in brief*, 2016, vol. 7, pp. 111—116. DOI: 10.1016/j.dib.2016.02.025
40. *El-Ansary A. et al.* In the search for reliable biomarkers for the early diagnosis of autism spectrum disorder: the role of vitamin D. *Metabolic brain disease*, 2018, vol. 33, no. 3, pp. 917—931. DOI: 10.1007/s11011-018-0199-1
41. *El-Ansary A. et al.* Probiotic treatment reduces the autistic-like excitation/inhibition imbalance in juvenile hamsters induced by orally administered propionic acid and clindamycin. *Metabolic brain disease*, 2018, vol. 33, no. 4, pp. 1155—1164. DOI: 10.1007/s11011-018-0212-8
42. *El-Ansary A., Al-Ayadhi L.* GABAergic/glutamatergic imbalance relative to excessive neuroinflammation in autism spectrum disorders. *Journal of Neuroinflammation*, 2014, vol. 11, p. 189. DOI: 10.1186/s12974-014-0189-0
43. *El-Ansary A., Al-Salem H.S., Asma A., Al-Dbass A.* Glutamate excitotoxicity induced by orally administered propionic acid, a short chain fatty acid can be ameliorated by bee pollen. *Lipids in health and disease*, 2017, vol. 16, no. 1, p. 96. DOI: 10.1186/s12944-017-0485-7
44. *Essa M.M., Braidy N., Subash S., Vijayan R.K., Guillemin G.J.* Excitotoxicity in the Pathogenesis of Autism. In *Kostrzewa R.M.* (ed.) Handbook of Neurotoxicity. Springer, New York: Publ. Springer, 2014. 636 p. ISBN 978-1-46145835-7.
45. *Eyles D.W.* Vitamin D and autism: does skin colour modify risk? *Acta paediatrica*, 2010, vol. 99, no. 5, pp. 645—647. DOI: 10.1111/j.1651-2227.2010.01797.x
46. *Fatemi S.H. et al.* Glutamic acid decarboxylase 65 and 67 kDa proteins are reduced in autistic parietal and cerebellar cortices. *Biological Psychiatry*, 2002, vol. 52, no. 8, pp. 805—810. DOI: 10.1016/s0006-3223(02)01430-0

47. *Fatemi S.H.* The hyperglutamatergic hypothesis of autism. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 2008, vol. 32, no. 3, p. 911 [author reply 912—913]. DOI: 10.1016/j.pnpbp.2007.11.004
48. *Felipo V., Butterworth R.F.* Neurobiology of ammonia. *Progress in Neurobiology*, 2002, vol. 67, no. 4, pp. 259—279. DOI: 10.1016/s0301-0082(02)00019-9
49. *Feng J. et al.* Clinical improvement following vitamin D3 supplementation in autism spectrum disorder. *Nutritional neuroscience*, 2017, vol. 20, no. 5, pp. 284—290. DOI: 10.1080/1028415X.2015.1123847
50. *Ferguson A.R. et al.* Group I metabotropic glutamate receptors control metaplasticity of spinal cord learning through a protein kinase C-dependent mechanism. *Journal of Neuroscience*, 2008, vol. 28, no. 46, pp. 11939—11949. DOI: 10.1523/JNEUROSCI.3098-08.2008
51. *Fernell E. et al.* Autism spectrum disorder and low vitamin D at birth: a sibling control study. *Molecular autism*, 2015, vol. 6, no. 1, p. 3. DOI: 10.1186/2040-2392-6-3
52. *Fiorentino M., Sapone A., Senger S. et al.* Blood-brain barrier and intestinal epithelial barrier alterations in autism spectrum disorders. *Molecular Autism*, 2016, vol. 7, p. 49. DOI:10.1186/s13229-016-0110-z
53. *Ford T.C., Abu-Akel A., Crewther D.P.* The association of excitation and inhibition signaling with the relative symptom expression of autism and psychosis-proneness: Implications for psychopharmacology. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 2019, vol. 88, pp. 235—242. DOI: 10.1016/j.pnpbp.2018.07.024
54. *Ford T.C., Nibbs R., Crewther D.P.* Glutamate/GABA+ ratio is associated with the psychosocial domain of autistic and schizotypal traits. *PloS one*, 2017, vol. 12, no. 7, article no. e0181961. DOI: 10.1371/journal.pone.0181961
55. *Ford T.C., Nibbs R., Crewther D.P.* Increased glutamate/GABA+ ratio in a shared autistic and schizotypal trait phenotype termed Social Disorganisation. *NeuroImage: Clinical*, 2017, vol. 16, pp. 125—131. DOI: 10.1016/j.nicl.2017.07.009
56. *Gegelashvili G., Bjerrum O.J.* High-affinity glutamate transporters in chronic pain: an emerging therapeutic target. *Journal of neurochemistry*, 2014, vol. 131, no.6, pp. 712—730. DOI: 10.1111/jnc.12957
57. *Gong Z.-L. et al.* Serum 25-hydroxyvitamin D levels in Chinese children with autism spectrum disorders. *Neuroreport*, 2014, vol. 25, no. 1, pp. 23—27. DOI: 10.1097/WNR.0000000000000034
58. *Grant W.B., Cannell J.J.* Autism prevalence in the United States with respect to solar UV-B doses: an ecological study. *Dermato-endocrinology*, 2013, vol. 5, no. 1, pp. 159—164. DOI: 10.4161/derm.22942
59. *Grewer C. et al.* Individual subunits of the glutamate transporter EAAC1 homotrimer function independently of each other. *Biochemistry*, 2005, vol. 44, no. 35, pp. 11913—11923. DOI: 10.1021/bi050987n
60. *Groves N.J. et al.* Adult vitamin D deficiency leads to behavioural and brain neurochemical alterations in C57BL/6J and BALB/c mice. *Behavioural brain research*, 2013, vol. 241, pp. 120—131. DOI: 10.1016/j.bbr.2012.12.001
61. *Han S., Tai C., Jones C.J., Scheuer T., Catterall W.A.* Enhancement of inhibitory neurotransmission by $GABA_A$ receptors having $\alpha_{2,3}$-subunits ameliorates behavioral deficits in a mouse model of autism. *Neuron*, 2014, vol. 81, no. 6, pp. 1282—1289. DOI: 10.1016/j.neuron.2014.01.016
62. *He Q., Nomura T., Xu J., Contractor A.* The developmental switch in GABA polarity is delayed in fragile X mice. *Journal of Neuroscience*, 2014, vol. 34, no. 2, pp. 446—450. DOI: 10.1523/JNEUROSCI.4447-13.2014
63. *Hoernlein C.* MSG and autism [Web resource]. 2019. URL: https://www.msgtruth.org/msg-autism (Accessed 03.09.2020).
64. *Iovene M.R. et al.* Intestinal dysbiosis and yeast isolation in stool of subjects with autism spectrum disorders. *Mycopathologia*, 2017, vol. 182, no. 3-4, pp. 349—363. DOI: 10.1007/s11046-016-0068-6
65. *Kemper T.L., Bauman M.* Neuropathology of infantile autism. *Journal of neuropathology and experimental neurology*, 1998, vol. 57, no. 7, pp. 645—652. DOI: 10.1097/00005072-199807000-00001
66. *Knoflach F., Hernandez M.-C., Bertrand D.* $GABA_A$ receptor-mediated neurotransmission: Not so simple after all. *Biochemical pharmacology*, 2016, vol. 115, pp. 10—17. DOI: 10.1016/j.bcp.2016.03.014
67. *Kočovská E., Gaughran F., Krivoy A., Meier U.C.* Vitamin-D deficiency as a potential environmental risk factor in multiple sclerosis, schizophrenia, and autism. *Frontiers in psychiatry*, 2017, vol. 8, no. 47. DOI: 10.3389/fpsyt.2017.00047
68. *Koyama R., Ikegaya Y.* Microglia in the pathogenesis of autism spectrum disorders. *Neuroscience research, 2015, vol. 100*, pp. 1—5. DOI: 10.1016/j.neures.2015.06.005
69. *Krisanova N. et al.* Vitamin D3 deficiency in puberty rats causes presynaptic malfunctioning through alterations in exocytotic release and uptake of glutamate/GABA and expression of EAAC-1/GAT-3 transporters. *Food and Chemical Toxicology*, 2019, vol. 123, pp. 142—150. DOI: 10.1016/j.fct.2018.10.054
70. *Lee V., Maguire J.* The impact of tonic $GABA_A$ receptor-mediated inhibition on neuronal excitability varies across brain region and cell type. *Frontiers in neural circuits*, 2014, vol. 8, p. 3. DOI: 10.3389/fncir.2014.00003
71. *Leonoudakis D., Zhao P., Beattie E.C.* Rapid tumor necrosis factor α-induced exocytosis of glutamate receptor 2-lacking AMPA receptors to extrasynaptic plasma membrane potentiates excitotoxicity. *Journal of Neuroscience*, 2008, vol. 28, no. 9, pp. 2119—2130. DOI: 10.1523/JNEUROSCI.5159-07.2008
72. *Leonte A., Colzato L.S., Steenbergen L., Hommel B., Akyürek E.G.* Supplementation of gamma-aminobutyric acid (GABA) affects temporal, but not spatial visual attention. *Brain and Cognition,* 2018, vol. 120, pp. 8—16. DOI: 10.1016/j.bandc.2017.11.004
73. *Lieberman O., McGuirt A.F., Tang G., Sulzer D.* Roles for neuronal and microglial autophagy in synaptic pruning during development. *Neurobiology of Disease*, 2019, vol. 122, pp. 49—63. DOI: 10.1016/j.nbd.2018.04.017
74. *Lingford-Hughes A. et al.* Imaging the GABA-benzodiazepine receptor subtype containing the α5-subunit in vivo with [11C] Ro15 4513 positron emission tomography. *Journal of Cerebral Blood Flow & Metabolism*, 2002, vol. 22, no. 7, pp. 878—889. DOI: 10.1097/00004647-200207000-00013

75. *Liu A., Zhou W., Qu L., He F., Wang H., Wang Y., Cai C., Li X., Zhou W., Wang M.* Altered Urinary Amino Acids in Children With Autism Spectrum Disorders. *Frontiers in Cellular Neuroscience*, 2019, vol. 13, p. 7. DOI: 10.3389/fncel.2019.00007
76. *Lu J.-C. et al.* $GABA_A$ Receptor-Mediated Tonic Depolarization in Developing Neural Circuits. *Molecular neurobiology*, 2014, vol. 49, no. 2, pp. 702–723. DOI: 10.1007/s12035-013-8548-x
77. *MacDermott A.B., Mayer M.L., Westbrook G.L., Smith S.J., Barker J.L.* NMDA-receptor activation increases cytoplasmic calcium concentration in cultured spinal cord neurones. *Nature*, 1986, vol. 321, no. 6069, pp. 519–522. DOI: 10.1038/321519a0
78. *MacFabe D.F. et al.* Neurobiological effects of intraventricular propionic acid in rats: possible role of short chain fatty acids on the pathogenesis and characteristics of autism spectrum disorders. *Behavioural brain research*, 2007, vol. 176, no. 1, pp. 149–169. DOI: 10.1016/j.bbr.2006.07.025
79. *Martin L.J. et al.* α5$GABA_A$ receptor activity sets the threshold for long-term potentiation and constrains hippocampus-dependent memory. *Journal of Neuroscience*, 2010, vol. 30, no. 15, pp. 5269–5282. DOI: 10.1523/JNEUROSCI.4209-09.2010
80. *Mazzone G.L., Nistri A.* Modulation of extrasynaptic GABAergic receptor activity influences glutamate release and neuronal survival following excitotoxic damage to mouse spinal cord neurons. *Neurochemistry International*, 2019, vol. 128, pp. 175–185. DOI: 10.1016/j.neuint.2019.04.018
81. *Mead J., Ashwood P.* Evidence supporting an altered immune response in ASD. *Immunology Letters*, 2015, vol. 163, no. 1, pp. 49–55. DOI: 10.1016/j.imlet.2014.11.006
82. *Meguid N.A., Hashish A.F., Anwar M., Sidhom G.* Reduced serum levels of 25-hydroxy and 1, 25-dihydroxy vitamin D in Egyptian children with autism. *The Journal of Alternative and Complementary Medicine*, 2010, vol. 16, no. 6, pp. 641–645. DOI: 10.1089/acm.2009.0349
83. *Mehta A., Prabhakar M., Kumar P., Deshmukh R., Sharma P.L.* Excitotoxicity: bridge to various triggers in neurodegenerative disorders. *European journal of pharmacology*, 2013, vol. 698, no. 1-3, pp. 6–18. DOI: 10.1016/j.ejphar.2012.10.032
84. *Merner N.D. et al.* Regulatory domain or CpG site variation in SLC12A5, encoding the chloride transporter KCC2, in human autism and schizophrenia. *Frontiers in cellular neuroscience*, 2015, vol. 9, p. 386. DOI: 10.3389/fncel.2015.00386
85. *Mesbah-Oskui L. et al.* Reduced expression of α5$GABA_A$ receptors elicits autism-like alterations in EEG patterns and sleep-wake behavior. *Neurotoxicology and teratology*, 2017, vol. 61, pp. 115–122. DOI: 10.1016/j.ntt.2016.10.009
86. *Moreno-De-Luca D. et al.* Using large clinical data sets to infer pathogenicity for rare copy number variants in autism cohorts. *Molecular psychiatry*, 2013, vol. 18, no. 10, pp. 1090–1095. DOI: 10.1038/mp.2012.138
87. *Mostafa G.A., Al-Ayadhi L.Y.* Reduced serum concentrations of 25-hydroxy vitamin D in children with autism: relation to autoimmunity. *Journal of neuroinflammation*, 2012, vol. 9, no. 1, p. 201. DOI: 10.1186/1742-2094-9-201
88. *Mowery T.M. et al.* Embryological exposure to valproic acid disrupts morphology of the deep cerebellar nuclei in a sexually dimorphic way. *International Journal of Developmental Neuroscience*, 2015, vol. 40, no. 1, pp. 15–23. DOI: 10.1016/j.ijdevneu.2014.10.003
89. *Nelson S.B., Valakh V.* Excitatory/Inhibitory Balance and Circuit Homeostasis in Autism Spectrum Disorders. *Neuron*, 2015, vol. 87, no. 4, pp. 684–698. DOI: 10.1016/j.neuron.2015.07.033
90. *Olloquequi J. et al.* Excitotoxicity in the pathogenesis of neurological and psychiatric disorders: Therapeutic implications. *Journal of Psychopharmacology*, 2018, vol. 32, no. 3, pp. 265–275. DOI: 10.1177/0269881118754680
91. *Olsen R.W., Sieghart W.* $GABA_A$ receptors: subtypes provide diversity of function and pharmacology. *Neuropharmacology*, 2009, vol. 56, no. 1, pp. 141–148. DOI: 10.1016/j.neuropharm.2008.07.045
92. *Pajarillo E., Rizor A., Lee J., Aschner M., Lee E.* The role of astrocytic glutamate transporters GLT-1 and GLAST in neurological disorders: potential targets for neurotherapeutics. *Neuropharmacology*, 2019, vol. 161, article no. 107559. DOI: 10.1016/j.neuropharm.2019.03.002
93. *Pardo C.A., Vargas D.L., Zimmerman A.W.* Immunity, neuroglia and neuroinflammation in autism. *International review of psychiatry*, 2005, vol. 17, no. 6, pp. 485–495. DOI: 10.1080/02646830500381930
94. *Pascual O., Ben Achour S., Rostaing P., Triller A., Bessis A.* Microglia activation triggers astrocyte-mediated modulation of excitatory neurotransmission. *Proceedings the National Academy of Sciences of the United States of America*, 2012, vol. 109, no. 4, pp. E197–E205. DOI: 10.1073/pnas.1111098109
95. *Patel D., Kharkar P.S., Nandave M.* Emerging roles of system x_c^- anti-porter and its inhibition in CNS disorders. *Molecular membrane biology*, 2015, vol. 32, no. 4, pp. 89–116. DOI: 10.3109/09687688.2015.1096972
96. *Pessione E.* Lactic acid bacteria contribution to gut microbiota complexity: lights and shadows. *Frontiers in cellular and infection microbiology, 2012, vol. 2*, p. 86. DOI: 10.3389/fcimb.2012.00086
97. *Pokusaeva K. et al.* GABA-producing Bifidobacterium dentium modulates visceral sensitivity in the intestine. *Neurogastroenterology & Motility*, 2017, vol. 29, no. 1, article no. e12904. DOI: 10.1111/nmo.12904
98. *Raimondo J.V., Richards B.A., Woodin M.A.* Neuronal chloride and excitability — the big impact of small changes. *Current opinion in neurobiology*, 2017, vol. 43, pp. 35–42. DOI: 10.1016/j.conb.2016.11.012
99. *Reuter E., Tafelski S., Thieme K. et al.* Die Behandlung des Fibromyalgiesyndroms mit Gamma-Hydroxybuttersäure: Eine randomisierte, kontrollierte Studie [Treatment of fibromyalgia syndrome with gamma-hydroxybutyrate: A randomized controlled study] [published correction appears in: *Der Schmerz*, 2017, vol. 31, no. 4, pp. 407–412]. *Der Schmerz* [*The pain*], 2017, vol. 31, no. 2, 149–158. DOI: 10.1007/s00482-016-0166-x
100. *Rivero-Segura N. et al.* Prolactin prevents mitochondrial dysfunction induced by glutamate excitotoxicity in hippocampal neurons. *Neuroscience letters*, 2019, vol. 701, pp. 58–64. DOI: 10.1016/j.neulet.2019.02.027
101. *Robertson A.E., David R.S.R.* The sensory experiences of adults with autism spectrum disorder: A qualitative analysis. *Perception*, 2015, vol. 44, no. 5, pp. 569–586. DOI: 10.1068/p7833

102. *Rojas D.C.* The role of glutamate and its receptors in autism and the use of glutamate receptor antagonists in treatment. *Journal of Neural Transmission*, 2014, vol. 121, no. 8, pp. 891—905. DOI: 10.1007/s00702-014-1216-0
103. *Rowley N.M., Madsen K.K., Schousboe A., Steve White H.* Glutamate and GABA synthesis, release, transport and metabolism as targets for seizure control. *Neurochemistry International*, 2012, vol. 61, no. 4, pp. 546—558. DOI: 10.1016/j.neuint.2012.02.013
104. *Rubenstein J.L., Merzenich M.M.* Model of autism: increased ratio of excitation/inhibition in key neural systems. *Genes, Brain and Behavior*, 2003, vol. 2, no. 5, pp. 255—267. DOI: 10.1034/j.1601-183x.2003.00037.x
105. *Saad K. et al.* Vitamin D status in autism spectrum disorders and the efficacy of vitamin D supplementation in autistic children. *Nutritional neuroscience*, 2016, vol. 19, no. 8, pp. 346—351. DOI: 10.1179/1476830515Y.0000000019
106. *Saleem T.H., Shehata G.A., Toghan R. et al.* Assessments of Amino Acids, Ammonia and Oxidative Stress Among Cohort of Egyptian Autistic Children: Correlations with Electroencephalogram and Disease Severity [correction published in: *Neuropsychiatric Disease and Treatment*, 2020, vol. 16, p. 325]. *Neuropsychiatric Disease and Treatment*, 2020, vol. 16, pp. 11—24. DOI: 10.2147/NDT.S233105
107. *Sano C.* History of glutamate production. *The American journal of clinical nutrition*, 2009, vol. 90, no. 3, pp. 728S—732S. DOI: 10.3945/ajcn.2009.27462F
108. *Schroer R.J. et al.* Autism and maternally derived aberrations of chromosome 15q. *American journal of medical genetics*, 1998, vol. 76, no. 4, pp. 327—336. DOI: 10.1002/(SICI)1096-8628(19980401)76:4<327::AID-AJMG8>3.0.CO;2-M
109. *Sgadò P. et al.* Loss of GABAergic neurons in the hippocampus and cerebral cortex of Engrailed-2 null mutant mice: implications for autism spectrum disorders. *Experimental neurology*, 2013, vol. 247, pp. 496—505. DOI: 10.1016/j.expneurol.2013.01.021
110. *Shao Y. et al.* Fine mapping of autistic disorder to chromosome 15q11-q13 by use of phenotypic subtypes. *The American Journal of Human Genetics*, 2003, vol. 72, no. 3, pp. 539—548. DOI: 10.1086/367846
111. *Shimmura C. et al.* Enzymes in the glutamate-glutamine cycle in the anterior cingulate cortex in postmortem brain of subjects with autism. *Molecular Autism*, 2013, vol. 4, no. 1, p. 6. DOI: 10.1186/2040-2392-4-6
112. *Sibson N.R. et al.* In vivo 13C NMR measurements of cerebral glutamine synthesis as evidence for glutamate—glutamine cycling. *Proceedings of the National Academy of Sciences of the United States of America*, 1997, vol. 94, no. 6, pp. 2699—2704. DOI: 10.1073/pnas.94.6.2699
113. *Smaga I. et al.* Oxidative stress as an etiological factor and a potential treatment target of psychiatric disorders. Part 2. Depression, anxiety, schizophrenia and autism. *Pharmacological Reports*, 2015, vol. 67, no. 3, pp. 569—580. DOI: 10.1016/j.pharep.2014.12.015
114. *Smidkova M. et al.* Screening of Novel 3α5β-Neurosteroids for Neuroprotective Activity against Glutamate-or NMDA-Induced Excitotoxicity. *The Journal of steroid biochemistry and molecular biology*, 2019, vol. 189, pp. 195—203. DOI: 10.1016/j.jsbmb.2019.03.007
115. *Soni N., Reddy B.V.K., Kumar P.* GLT-1 transporter: an effective pharmacological target for various neurological disorders. *Pharmacology, Biochemistry and Behavior*, 2014, vol. 127, pp. 70—81. DOI: 10.1016/j.pbb.2014.10.001
116. *Tanous C., Gori A., Rijnen L., Chambellon E., Yvon M.* Pathways for α-ketoglutarate formation by Lactococcus lactis and their role in amino acid catabolism. *International Dairy Journal*, 2005, vol. 15, no. 6-9, pp. 759—770. DOI: 10.1016/j.idairyj.2004.09.011
117. *Tebartz van Elst L. et al.* Disturbed cingulate glutamate metabolism in adults with high-functioning autism spectrum disorder: evidence in support of the excitatory/inhibitory imbalance hypothesis. *Molecular Psychiatry*, 2014, vol. 19, no. 12, pp. 1314—1325. DOI: 10.1038/mp.2014.62
118. *Torrez V.R. et al.* Memantine mediates astrocytic activity in response to excitotoxicity induced by PP2A inhibition. *Neuroscience letters*, 2019, vol. 696, pp. 179—183. DOI: 10.1016/j.neulet.2018.12.034
119. *Tyzio R. et al.* Maternal oxytocin triggers a transient inhibitory switch in GABA signaling in the fetal brain during delivery. *Science*, 2016, vol. 314, no. 5806, pp. 1788—1792. DOI: 10.1126/science.1133212
120. *Tyzio R. et al.* Oxytocin-mediated GABA inhibition during delivery attenuates autism pathogenesis in rodent offspring. *Science*, 2014, vol. 343, no. 6171, pp. 675—679. DOI: 10.1126/science.1247190
121. *Uğur Ç., Gürkan C.K.* Serum vitamin D and folate levels in children with autism spectrum disorders. *Research in Autism Spectrum Disorders*, 2014, vol. 8, no. 12, pp. 1641—1647. DOI: 10.1016/j.rasd.2014.09.002
122. *Vargas D.L., Nascimbene C., Krishnan C., Zimmerman A.W., Pardo C.A.* Neuroglial activation and neuroinflammation in the brain of patients with autism. *Annals of Neurology*, 2005, vol. 57, no. 1, pp. 67—81. DOI: 10.1002/ana.20315
123. *Varman D., Soria-Ortíz M.B., Martínez-Torres A., Reyes-Haro D.* GABAρ3 expression in lobule X of the cerebellum is reduced in the valproate model of autism. *Neuroscience letters*, 2018, vol. 687, pp. 158—163. DOI: 10.1016/j.neulet.2018.09.042
124. *Vesce S., Rossi D., Brambilla L., Volterra A.* Glutamate release from astrocytes in physiological conditions and in neurodegenerative disorders characterized by neuroinflammation. *International review of neurobiology*, 2007, vol. 82, pp. 57—71. DOI: 10.1016/S0074-7742(07)82003-4
125. *Vinkhuyzen A.A. et al.* Gestational vitamin D deficiency and autism-related traits: the Generation R Study. *Molecular psychiatry*, 2018, vol. 23, no. 2, pp. 240—246. DOI: 10.1038/mp.2016.213
126. *Wakefield A.J. et al.* Review article: the concept of entero-colonic encephalopathy, autism and opioid receptor ligands. *Alimentary Pharmacology & Therapeutics*, 2002, vol. 16, no. 4, pp. 663—674. DOI: 10.1046/j.1365-2036.2002.01206.x
127. *Whitney E., et al.* Cerebellar Purkinje cells are reduced in a subpopulation of autistic brains: a stereological experiment using calbindin-D28k. *Cerebellum.* 2008;7(3):406-416. doi:10.1007/s12311-008-0043-y
128. *Yip J., Soghomonian J.J., Blatt G.J.* Decreased GAD67 mRNA levels in cerebellar Purkinje cells in autism: pathophysiological implications. *Acta neuropathologica*, 2007, vol. 113, no. 5, pp. 559—568. DOI: 10.1007/s00401-006-0176-3

129. *Yizhar O. et al.* Neocortical excitation/inhibition balance in information processing and social dysfunction. *Nature*, 2011, vol. 477, no. 7363, pp. 171–178. DOI: 10.1038/nature10360
130. *Zareian M., Ebrahimpour A., Mohammed A.K.S., Saari N.* Modeling of glutamic acid production by Lactobacillus plantarum MNZ. *Electronic Journal of Biotechnology*, 2013, vol. 16, no. 4, p. 1–16. DOI: 10.2225/vol16-issue4-fulltext-10
131. *Zurek A.A. et al.* α5GABA$_A$ receptor deficiency causes autism-like behaviors. *Annals of clinical and translational neurology*, 2016, vol. 3, no. 5, pp. 392–398. DOI: 10.1002/acn3.303

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EXPERT OPINION

МНЕНИЕ ЭКСПЕРТА

«If you don't Expose Children, they are not Going to get Interested»

Temple Grandin interview

Temple Grandin
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Present interview of Temple Grandin, PhD in animal science, professor of Colorado State University, given to guest editor of the Journal Stephen Edelson discusses person's with autism perception of changes in lifestyle associated with the onset of the COVID-19 pandemic. During the interview, Professor Grandin gives advice on the schooling of children with ASD during the transition to distance learning. The questions of employment of people with autism are also proposed — what positions are best for people with ASD, how to get the employer interested in hiring a person with autism.

Keywords: autism, COVID-19, perception, employment, distant learning.

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«Если вы не откроете детям мир, они ничем не заинтересуются»

Интервью с Темпл Грандин

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В интервью тематическому редактору номера Стивену Эдельсону профессор Университета Колорадо, доктор сельскохозяйственных наук Тэмпл Грандин рассказывает о восприятии человеком с аутизмом изменений в жизненном укладе, связанных с наступлением пандемии COVID-19. В ходе интервью профессор Грандин дает советы по образованию детей с расстройствами аутистического спектра (РАС) в период перехода на дистанционную форму обучения. Были затронуты и вопросы трудоустройства людей с аутизмом: какие позиции лучше всего подходят для людей с РАС, как заинтересовать работодателя в найме человека с аутизмом.

Ключевые слова: аутизм, COVID-19, восприятие, трудоустройство, дистанционное обучение.

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Stephen Edelson:

— What things are the most difficult for you?

Temple Grandin:

— For me and many others, I have had great difficulty multitasking and remembering long verbal sequential information, especially with projects involving a series of tasks. I remember when I was in graduate school, and I had to work on a milking machine. It involved many steps to start up the machine and then clean it afterward. Fortunately, there was a checklist on the wall with all of the tasks listed in order. Basically, I need a checklist of keywords to describe each step. These keywords trigger my memory. Learning a sequence does not happen to me instantly.

Edelson:

— What happens after you perform the same tasks over and over again? Do the tasks become easier to remember?

Grandin:

— Eventually, I create a videotape in my head. This would take a few weeks or possibly longer. I would then no longer need a written checklist to look at.

Edelson:

— I know that you think in pictures. Do you also think in videos?

Grandin:

— Yes, but I have to do the tasks many times before I can remember the entire sequence in my mind's video. I remember when I first went into a large meat plant. I thought this place was very complicated, and I wondered how does the manager understand everything. So I started focusing on the most interesting details in each task. After visiting the plant for an hour every Tuesday afternoon for several weeks, I was able to create a videotape in my mind of the entire plant. It was then easy for me to start at the beginning and walked through the entire video.

Edelson:

— Can you start in the middle of your mind's video?

Grandin:

— Yes, I can start anywhere I want to. Again, this does not happen overnight. I have to literally videotape a lot of small details in my head.

Edelson:

— How has your life changed during the COVID-19 pandemic?

Grandin:

— Since early March, my travels have stopped. When I had an opportunity to do a Zoom meeting with someone, I jumped on it. I wanted to learn so I could both see and hear other people. As a visual thinker, it is better for me to see someone when I talk to them; the telephone is only audio and not visual.

Now when I do a Zoom meeting, I give a 20-minute presentation and then allow lots of questions. I find that this works well because people will type in many questions.

The other thing that I have learned during this pandemic is to get on a schedule. I get up in the morning, shower, and dress for work by 8 every morning.

I also looked up the lifestyle on the international space station because they are living in very tight quarters. Through the years, they have learned that they need to be on a schedule. They get up in the morning, get dressed, do their chores and experiments, exercise, and have a midday meal, all scheduled at specific times throughout the day. They also schedule free time.

I found a copy of a space station schedule. If you examine the schedule over an entire week, the midday meal is always at the same time throughout the week, and everyone must be together for the midday meal.

Edelson:

— Do you have advice on schooling?

Grandin:

— Given the pandemic crisis, families, especially those with young children on the autism spectrum, will likely have a difficult time having their young children do their school work while on the computer. Teachers need to watch and coach parents on how to work with the children.

With regard to mask wearing to protect them from the COVID virus, give them some choices. Let them try some different ones.

Autism is such a big spectrum, and these children need very different services. For early intervention,

everything is pretty much the same for most or all of them. But once the kids get a little older, it's not all the same because autism is a spectrum. A smart Asperger kid should probably learn computer programming, and someone like me, a visual thinker, should go into art or some high-end skilled trades. And for those with more severe challenges, such as those who cannot dress themselves, they need totally different services.

Edelson:

— Do you have any advice for some of the challenges faced by individuals on the autism spectrum?

Grandin:

— I have an important suggestion on how to deal with sound sensitivity. For those sounds that the child hates and runs away from, such as a vacuum cleaner or a hairdryer, give them some control over them. Let them turn the machine on and off. Let them play with it. Many of them can better tolerate the sounds after they have control over the source. Sometimes these hated things can actually become one of their favorite things.

Edelson:

— Employment for people with autism is a topic which excites parent community as well as professionals and employers. In which professions can people with autism be most successful?

Grandin:

— First, one should learn how to work before graduating from high school because academic skills and work skills are very different. Little kids should start out with chores, 10- and 11-year-old kids should have a volunteer job in their community, and teenagers should find a part-time job, also in their community. Basically, they have got to learn how to work.

Multitasking is difficult for most on the autism spectrum. Working at a busy McDonald's would not be the best choice.

Another important issue is driving. If I did not learn to drive, I would not have had a career in the livestock industry. Let me tell you one thing that helped me. I did 200 miles of driving on dirt roads before I drove in traffic. Driving involves multitasking, and this can be a problem. Those on the autism spectrum need a lot more practice in a safe area to get driving skills into their motor memory. Once it is in motor memory, they no longer need to think about steering, pressing on the brakes, and stepping on the gas.

Every day for 6 weeks I drove 5 km to my aunt's mailbox and then another 5 km back, for a total of 10 km. I drove only on a dirt road without traffic. I then gradually began driving in traffic. It was a smooth transition. I don't have to think about steering, or breaking, or putting my foot on or off the gas. I actually learned to drive using a manual shift, and I no longer had to think about shifting gears. It is all in my motor memory.

Unfortunately, many students with autism are told to drive into traffic before their driving skills are developed in motor memory. This makes it very difficult when trying to learn to drive safely.

Like me, I suggest that parents have their children drive in the middle of a large empty field or parking lot where there is nothing to hit. I suggest they drive about 20 minutes a day for at least six weeks in a really safe place before going into traffic.

Again, I could not have a career without driving.

Edelson:

— Can you list the most common jobs appropriate for those on the autism spectrum.

Grandin:

— Let's start with visual thinkers like me. They can learn about art, graphic design, and computer-aided drafting. Skilled trades are also important to consider such as welders, machinists, and fine carpentry work. A good auto mechanic can visualize how the engine works and where it needs to be fixed.

Math thinkers can learn about computer programming, physics, statistics, and data analytics. Word thinkers will likely be successful writing for a living.

Edelson:

— How we make employers interested in hiring people with autism spectrum disorders?

Grandin:

— I started out as a freelancer. I simply showed customers my portfolio of drawings and photos of completed projects. If you watched the scene in the HBO movie about me (Mick Jackson, 2010), you probably remember when my drawings were placed on the desk and animated cattle walked on them. That was actually a copy of one of my drawings.

My advice: learn as much as you can about programming. Or make yourself really good at art and then show off your drawings. This is what I did and it worked.

In the area of computer science, a very good job is software testing website evaluation and programming. There was a company and their sales were down 20% after they upgraded their website. They could not figure the reason why and they hired an autistic man to test the website. Guess what? He

found that the contact phone number was off by one digit. It took a detailed-oriented person, like someone on the autism spectrum, to find it.

Edelson:

— What is important to consider when organizing an accessible environment in public space for people with ASD?

Grandin:

— Sensory is very important. Noisy spaces are not good. Visually, a lot of stripes and checkerboards can be difficult on the eyes. Thank goodness fluorescent lights are going away. But some on the autism spectrum can see a flicker in LED lights, especially with the cheap ones.

I was on a committee at school, and they wanted to make a space for people who had various sensory issues. They asked me about lighting. I told them to find someone who sees letters jiggle when reading print in a book. I suggested that this person walk around campus and identify lights that bothered him or her. For people who see the print jiggling, printing the book pages on pale colored paper such as tan, light gray, light blue, or lavender may be helpful.

Edelson:

— What is happiness for you?

Grandin:

— I am very happy when I design something and my client is very pleased that it is working. I am also very happy when a parent thanks me for the advice I gave them when their child was little. One parent wrote to me and said that I instructed her to push her child to do a lot of things. He now has a job, married, and lives in a house. I put this email on my wall. A good concept is to "stretch" and the child just outside their comfort zone. It is important to not force them into a situation where they will get overwhelmed.

A big problem I see is that some parents are overprotective. They are not letting their son or daughter go out and learn stuff. They get too much into a disability mindset. I once spoke to a mom whose 16-year-old teenager had never shopped. I suggested that he go into a store by himself and buy something. The mom started crying saying "I can't let go." The kid was overprotected and going nowhere.

I am also seeing some kids where their total identity is autism. Recently, an 8-year-old walked up to me, and all he wanted to do is to tell me about his autism. I would have preferred that he told me about the telescope he built, or a piece of artwork he had created. My mother had a very good sense about how to stretch me. She always gave me choices. But if I had not gone to live at my aunt's ranch, I would not have had a successful job working in the cattle industry. Children need to be exposed to many things so they can figure out what they are interested in. If you don't expose them, they are not going to get interested. It's that simple.

Edelson:

— Thank you Temple for your insight and advice.

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- **Special educators** (speech pathologists, psychologists and psychotherapists, art therapists, behavioral analysts)
- **Science journalists**
- **Government officials**
- **Various parent communities and NGOs**

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- **Диагностика и маршрутизация «аутизмов»:** потенциальные биомаркеры, тестовые инструменты, обследования
- **Коррекция и терапия аутизма:** доказательные методы, экспериментальные практики
- **Патогенез аутизма:** генетика и эпигенетика
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- **Epidemiology of autism**
- **Socioeconomic aspects of autism**
- **Diagnosing and classifying "autisms":** potential biomarkers, test protocols and assays
- **Autism intervention and therapy: evidence based methods and experimental practices**
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- **Behavioral science and autism**
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