BRAIN. Broad Research in Artificial Intelligence and Neuroscience
ISSN: 2068-0473 | e-ISSN: 2067-3957
Covered in: Web of Science (WOS); PubMed.gov; IndexCopernicus; The Linguist List; Google Academic; Ulrichs; getCITED; Genamics JournalSeek; J-Gate; SHERPA/RoMEO; Dayang Journal System; Public Knowledge Project; BIUM; NewJour; ArticleReach Direct; Link+; CSB; CiteSeerX; Socolar; KVK; WorldCat; CrossRef; Ideas RePeC; Econpapers; Socionet.

2021, Volume 12, Issue 2, pages: 335-341 | https://doi.org/10.18662/brain/12.2/211

Metabolomics in Pediatric Neuropsychiatry

Roberta PINTUS[1], **Angelica DESSI'**[2], **Alice BOSCO**[3], **Vassilios FANOS**[4]

[1] Department of Surgical Sciences, University of Cagliari and Neonatal Intensive Care Unit, AOU Cagliari, Cagliari, Italy, gomberta@icloud.com
[2] Department of Surgical Sciences, University of Cagliari and Neonatal Intensive Care Unit, AOU Cagliari, Cagliari, Italy, angelica.dessi@unica.it
[3] Department of Surgical Sciences, University of Cagliari and Neonatal Intensive Care Unit, AOU Cagliari, Cagliari, Italy, alicebosco88@gmail.com
[4] Department of Surgical Sciences, University of Cagliari and Neonatal Intensive Care Unit, AOU Cagliari, Cagliari, Italy, vafanos@tiscali.it

Abstract: *Metabolomics is one of the newest "omics" sciences that is being applied to date to investigate several aspects of pathologies and medical topics in general. It provides a snapshot of the metabolic state of an individual by the detection of metabolites in several biological fluids, such as saliva, blood and sweat. Our research group has more than a decade of experience in this field and we ourselves applied this technology to investigate, for instance, every aspect of breast milk, different neonatal diseases and neuropsychiatric disorders. In this paper, which is adapted from the lecture given by Professor Fanos at the 5th edition of the Galatia Congress (2021), we discuss the usefulness of metabolomics in the investigation of paediatric neuropsychiatric disorders. We are convinced that this technique, in the future, will provide all the answer to the infinite questions concerning the paediatric brain and its disorders, in order to help the clinicians and families of these children to give the best life possible to these little patients.*

Keywords: *metabolomics, pediatrics, neuropsychiatry, perinatal programming, autism.*

How to cite: Pintus, R., Dessi', A., Bosco, A., & Fanos, V. (2021). Metabolomics in Pediatric Neuropsychiatry. *BRAIN. Broad Research in Artificial Intelligence and Neuroscience, 12*(2), 335-341. https://doi.org/10.18662/brain/12.2/211

What is metabolomics?

Metabolomics is one of the newest omics sciences that analyzes the metabolites present in several biofluids (urine, blood, plasma serum, saliva CSF, etc..) through different techniques (LC/GC-MS or 1H-NMR). It provides a snapshot of the metabolic state of an individual in different conditions or under several treatments (Mussap et al., 2013). There are 50591 papers on PubMed (June 2014) on metabolomics applied to investigate every aspect of medicine and diseases. Moreover, the metabolomics market is project to reach USD 4.73 billion by 2027. It is the stethoscope for the 21th century. Our research group is performing metabolomics studies since 2011. We are interested in a wide spectrum of experimental and clinical topics starting from breast milk, sepsis, necrotizing enterocolitis and neuropsychiatric disorders. Why is it the medicine of the future? Because now clinicians practice with protocols that are meant for a "mean" of patients, but a "means" of patients does not actually exist. Every human being is unique and responds differently to treatment (Fanos, 2018). Furthermore, many pathophysiological mechanisms of several pathologies are still unclear. Thanks to metabolomics and the subsequent investigation of metabolites in biological fluids we could be able to find the answers to the open questions in medicine and above all in pediatrics (Bardanzellu & Fanos, 2020).

Autism: the plague of 21th century, could metabolomics be the cure?

In the context of neuropsychiatric disorder in pediatrics, metabolomics could be very useful. Especially in complex disorders such autism since many aspects of this neurodevelopmental alteration are still obscure. Our research group has performed several metabolomics studies concerning autism and other neuropsychiatric disorders. What we learnt and what is being acknowledged in recent years is the concept of perinatal programming of adult (and children) diseases, including neuropsychiatric disorders and neurobehavioral problems (Faa et al., 2016). It means that each and every adverse event that could happen during pregnancy can alter the development of the fetal brain leading to neurodevelopmental and neuropsychiatric disorders in childhood and later in life. In case of autism, it seems that neuroimmune insults in pregnancy and in infancy could be one of the most relevant adverse events, together with the exposure to endocrine disrupting chemicals (ECDs) (Goyal & Miyan, 2014; Street et al., 2018).

Furthermore, thanks to metabolomics we were able to make and hypothesis of the alterations that could lead to autism spectrum disorder

(ASD). We called it "The Bad Trio", meaning: a mitochondrial disfunction/oxidative stress, dysbiosis and immune activation (Panisi et al., 2021).

Indeed, in 2017 we performed a metabolomic study concerning autistic children and their unaffected siblings. We analyzed their urine metabolome and the ASD group displayed a completely different metabolism compared to the healthy group (Lussu et al., 2017). We found several metabolites related to the alteration of the gut microflora, especially hippurate, indicating an intestinal dysbiosis in ASD children. Many of these metabolites seems to be produced by Clostridium spp. Thus, metabolomics is able to tell whether there is a bacterial influence in the origins of neuropsychiatric disorders.

Moreover, some of our findings indicate an alteration of TCA cycle that could be a biomarker of mitochondrial dysfunction. Other authors correlated mitochondrial alterations with several neuropsychiatric disorder including autism (Morris & Berk, 2015).

Another key metabolite in our study was tryptophan, which was found altered in other studies as well (Gevi et al., 2016). It is metabolized both by humans and bacteria. It is a precursor of serotonin which is in turn, very important for the neural function and neuronal plasticity especially during pregnancy (Faa et al., 2016). Excessive bacterial degradation of tryptophan may lead to a depletion in serotonin production that may lead to ASD and other neuropsychiatric disorders (Gevi et al., 2016). Furthermore, altered tryptophan metabolism was found in individual with negative affectivity and social inhibition. Author relates these alterations to mental retardation, depression and anxiety states as well (Altmaier et al., 2013). Other amino acids were modified in our study, in particular: glycine, serine, glutamate and valine. These results are in line with other studies that have also shown that ASD children often suffer from dysregulated amino acid metabolism (Lussu et al., 2017).

Then we performed another study in which we were able to correlate the urine metabolism of ASD children with their clinical profile severity. Indeed, different scores in Repetitive Behavior Scale and Social Responsiveness Scale were correlated to different metabolic profiles (Mussap et al., 2020).

This study was preceded by another study in which the urine metabolome of 2 groups of ASD patients of different ages (toddlers and adolescents) with healthy controls. Interestingly, they displayed the same metabolic alterations and these were related to the clinical parameters (Noto et al., 2018).

Metabolomics could also be used to investigate whether the diet and which particular food could improve the ASD symptoms and why. There is only one paper concerning this topic so far in which ASD subject improved after the administration of broccoli thanks to the presence of sulforaphane (Bent et al., 2018).

Other neuropsychiatric disorders and metabolomics: where are we now?

Our group was involved in a project funded by the European Union and aggression. Aggressiveness is considered one of the biggest health issues in Europe. We performed the urinary metabolomics analysis of 1347 twins with different aggressiveness profiles. The discriminant metabolites, thought to be the biomarkers of aggression, were amines and organic acids (Hagenbeek et al., 2020).

Metabolomics is able to anticipate the occurrence of psychosis. Indeed, individuals that experience a psychotic episode at 18 years of age, show metabolic abnormalities already at 12 years of age (Madrid-Gambin et al., 2019).

Metabolomics is useful even when the neurobehavioral problems are caused by infections. Indeed, our group described a clinical case of a girl with pediatric acute onset neuropsychiatric syndrome after Mycoplasma spp. infection. Thanks to this technique we were able to verify her baseline metabolomics urinary profile and after treatment with subsequent symptoms improvement (Piras et al., 2020). Other authors studied the behavioral and cognitive modification due to other types of infections. It seems that the parasitic infection (helminths) modifies the microbiota composition in these children. Thus, since the microbiota has a role in neurodevelopment due the production of several neuroactive molecules, the parasitic infection itself alters the cognitive parameters (Guernier et al., 2017). Furthermore, it appears that enteric infections in small children exert a peculiar role in cognitive development as well. There could be a relationship between chronic systemic inflammation and alterations of the cognitive abilities in children due to an abnormal blood brain barrier and microglia activation (Orià et al., 2016).

The microbiota is involved in other neuropsychiatric disorders such as attention- deficit hyperactivity disorder in which it seems that the affected pediatric population has lower abundance of Fecalibacterium spp (Jiang et al., 2018). In addition, another study analyzed the association between microbiota and cognitive development in children of 1-2 years of age. They

found that the 3 different microbial clusters discovered, matched with different cognitive outcomes, not in a pathological sense (Carlson, 2018).

Conclusions

Metabolomics has proving to be exceptionally useful in the investigation of the neuropsychiatric disorders in pediatrics. It has provided unexpected link between the brain and the peripheral environment of an individual, highlighting the importance of several metabolites of different types. Furthermore, it has highlighted the role of microbiota in neuropsychiatric disorders in a very precise way. Even if the number of studies is limited, there is a growing interest of the application of this technique to investigate pediatric brain. We are convinced that in the future this technology could reach the patients bed and it will be a common tool to make diagnosis, prognosis and management of these small patients in order to give them the best life possible.

References

Altmaier, E., Emeny, R. T., Krumsiek, J., Lacruz, M. E., Lukaschek, K., Häfner, S., Kastenmüller, G., Römisch-Margl, W., Prehn, C., Mohney, R. P., Evans, A. M., Milburn, M. V., Illig, T., Adamski, J., Theis, F., Suhre, K., & Ladwig, K. H. (2013). Metabolomic profiles in individuals with negative affectivity and social inhibition: a population-based study of Type D personality. *Psychoneuroendocrinology, 38*(8), 1299–1309. https://doi.org/10.1016/j.psyneuen.2012.11.014

Bardanzellu, F., & Fanos, V. (2020). How could metabolomics change pediatric health? *Italian Journal of Pediatrics, 46*(1), 37. https://doi.org/10.1186/s13052-020-0807-7

Bent, S., Lawton, B., Warren, T., Widjaja, F., Dang, K., Fahey, J. W., Cornblatt, B., Kinchen, J. M., Delucchi, K., & Hendren, R. L. (2018). Identification of urinary metabolites that correlate with clinical improvements in children with autism treated with sulforaphane from broccoli. *Molecular Autism, 9*, 35. https://doi.org/10.1186/s13229-018-0218-4

Carlson, A. L., Xia, K., Azcarate-Peril, M. A., Goldman, B. D., Ahn, M., Styner, M. A., Thompson, A. L., Geng, X., Gilmore, J. H., & Knickmeyer, R. C. (2018). Infant gut microbiome associated with cognitive development. *Biological psychiatry*, *83*(2), 148-159. https://doi.org/10.1016/j.biopsych.2017.06.021

Faa, G., Manchia, M., Pintus, R., Gerosa, C., Marcialis, M. A., & Fanos, V. (2016). Fetal programming of neuropsychiatric disorders. *Birth Defects Research Part C: Embryo Today: Reviews, 108*(3), 207–223. https://doi.org/10.1002/bdrc.21139

Fanos, V. (2018). *Medicina di precisione: Cellule batteri metaboliti, energia* [Precision medicine: Metabolite bacteria cells, energy]. Hygeia Press

Gevi, F., Zolla, L., Gabriele, S., & Persico, A. M. (2016). Urinary metabolomics of young Italian autistic children supports abnormal tryptophan and purine metabolism. *Molecular Autism, 7*, 47. https://doi.org/10.1186/s13229-016-0109-5

Goyal, D. K., & Miyan, J. A. (2014). Neuro-immune abnormalities in autism and their relationship with the environment: A variable insult model for autism. *Frontiers in Endocrinology, 5*, 29. https://doi.org/10.3389/fendo.2014.00029

Guernier, V., Brennan, B., Yakob, L., Milinovich, G., Clements, A. C., & Soares Magalhaes, R. J. (2017). Gut microbiota disturbance during helminth infection: Can it affect cognition and behaviour of children? *BMC Infectious Diseases, 17*(1), 58. https://doi.org/10.1186/s12879-016-2146-2

Hagenbeek, F. A., Roetman, P. J., Pool, R., Kluft, C., Harms, A. C., van Dongen, J., Colins, O. F., Talens, S., van Beijsterveldt, C., Vandenbosch, M., de Zeeuw, E. L., Déjean, S., Fanos, V., Ehli, E. A., Davies, G. E., Hottenga, J. J., Hankemeier, T., Bartels, M., Vermeiren, R., & Boomsma, D. I. (2020). Urinary amine and organic acid metabolites evaluated as markers for childhood aggression: The ACTION biomarker study. *Frontiers in Psychiatry, 11*, 165. https://doi.org/10.3389/fpsyt.2020.00165

Jiang, H. Y., Zhou, Y. Y., Zhou, G. L., Li, Y. C., Yuan, J., Li, X. H., & Ruan, B. (2018). Gut microbiota profiles in treatment-naïve children with attention deficit hyperactivity disorder. *Behavioural Brain Research, 347*, 408–413. https://doi.org/10.1016/j.bbr.2018.03.036

Lussu, M., Noto, A., Masili, A., Rinaldi, A. C., Dessì, A., De Angelis, M., De Giacomo, A., Fanos, V., Atzori, L., & Francavilla, R. (2017). The urinary 1 H-NMR metabolomics profile of an italian autistic children population and their unaffected siblings. *Autism Research: Official Journal of the International Society for Autism Research, 10*(6), 1058–1066. https://doi.org/10.1002/aur.1748

Madrid-Gambin, F., Föcking, M., Sabherwal, S., Heurich, M., English, J. A., O'Gorman, A., Suvitaival, T., Ahonen, L., Cannon, M., Lewis, G., Mattila, I., Scaife, C., Madden, S., Hyötyläinen, T., Orešič, M., Zammit, S., Cagney, G., Cotter, D. R., & Brennan, L. (2019). Integrated lipidomics and proteomics point to early blood-based changes in childhood preceding later development of psychotic experiences: Evidence from the Avon longitudinal study of parents and children. *Biological Psychiatry, 86*(1), 25–34. https://doi.org/10.1016/j.biopsych.2019.01.018

Morris, G., & Berk, M. (2015). The many roads to mitochondrial dysfunction in neuroimmune and neuropsychiatric disorders. *BMC Medicine, 13*, 68. https://doi.org/10.1186/s12916-015-0310-y

Mussap, M., Antonucci, R., Noto, A., & Fanos, V. (2013). The role of metabolomics in neonatal and pediatric laboratory medicine. *Clinica Chimica Acta; International Journal of Clinical Chemistry, 426*, 127–138. https://doi.org/10.1016/j.cca.2013.08.020

Mussap, M., Siracusano, M., Noto, A., Fattuoni, C., Riccioni, A., Rajula, H., Fanos, V., Curatolo, P., Barberini, L., & Mazzone, L. (2020). The urine metabolome of young autistic children correlates with their clinical profile severity. *Metabolites, 10*(11), 476. https://doi.org/10.3390/metabo10110476

Noto, A., Fattuoni, C., Mussap, M., Barberini, L., Siracusano, M., Mazzone, L., Francavilla, R., Curatolo, P., & Fanos, V. (2018). Urinary GC-MS metabolomics comparison between two cohorts of toddler and adolescent subjects affected by autism spectrum disorder. In *Selected Lectures of the 14th International Workshop on Neonatology. Cagliari (Italy); October 24-28 2018, 7*(2):e070238. https://jpnim.com/index.php/jpnim/article/view/070238?articlesBySameAuthorPage=8

Oriá, R. B., Murray-Kolb, L. E., Scharf, R. J., Pendergast, L. L., Lang, D. R., Kolling, G. L., & Guerrant, R. L. (2016). Early-life enteric infections: Relation between chronic systemic inflammation and poor cognition in children. *Nutrition Reviews, 74*(6), 374–386. https://doi.org/10.1093/nutrit/nuw008

Panisi, C., Guerini, F. R., Abruzzo, P. M., Balzola, F., Biava, P. M., Bolotta, A., Brunero, M., Burgio, E., Chiara, A., Clerici, M., Croce, L., Ferreri, C., Giovannini, N., Ghezzo, A., Grossi, E., Keller, R., Manzotti, A., Marini, M., Migliore, L., Moderato, L., … Fanos, V. (2021). Autism spectrum disorder from the womb to adulthood: Suggestions for a paradigm shift. *Journal of Personalized Medicine, 11*(2), 70. https://doi.org/10.3390/jpm11020070

Piras, C., Pintus, R., Pruna, D., Dessì, A., Atzori, L., & Fanos, V. (2020). Pediatric acute-onset neuropsychiatric syndrome and mycoplasma pneumoniae infection: A case report analysis with a metabolomics approach. *Current Pediatric Reviews, 16*(3), 183–193. https://doi.org/10.2174/1573396315666191022102925

Street, M. E., Angelini, S., Bernasconi, S., Burgio, E., Cassio, A., Catellani, C., Cirillo, F., Deodati, A., Fabbrizi, E., Fanos, V., Gargano, G., Grossi, E., Iughetti, L., Lazzeroni, P., Mantovani, A., Migliore, L., Palanza, P., Panzica, G., Papini, A. M., Parmigiani, S., … Amarri, S. (2018). Current knowledge on endocrine disrupting chemicals (EDCs) from animal biology to humans, from pregnancy to adulthood: Highlights from a national Italian meeting. *International Journal of Molecular Sciences, 19*(6), 1647. https://doi.org/10.3390/ijms19061647