

BEHAVIORAL ASPECTS IN CHILDREN'S BROTHERS AFFECTED BY AUTISM SPECTRUM DISORDERS

MICHELE SORRENTINO¹, GABRIELE TRIPI^{2,3}, MARGHERITA SALERNO⁴, DANIELA RUSSO⁵, SERENA MARIANNA LAVANO⁷, FRANCESCO CERRONI⁸, PALMIRA ROMANO⁹, BEATRICE GALLAI¹⁰, ROSA MAROTTA⁷, FRANCESCO LAVANO⁷, ROSARIA MARTINA MAGLIULO¹¹, LUCREZIA D'ORO¹², ANNABELLA DI FOLCO⁶, DAVIDE TESTA⁶, GABRIELLA MARSALA¹³, ANGELO MONTANA¹⁴, SABRINA FRANCO¹⁴, DIEGO GERACI¹⁴, MARIO GIUSEPPE CHISARI¹⁵, ELISABETTA PICCIOCCHI^{16,17}, ANNA NUNZIA POLITO¹⁸, PAOLO MURABITO¹⁹, MARIA RUBERTO², LUCIA PARISI⁶

¹NICU -Preterm and High Risk Newborn Neurodevelopmental Follow-up Service; Pineta Grande Hospital Castel Volturno (CE), Italy - ²Department PROSAMI, University of Palermo, Italy - ³Childhood Psychiatric Service for Neurodevelopmental Disorders, CH Chinon, France - ⁴Sciences for Mother and Child Health Promotion, University of Palermo, Italy - ⁵Centro di Riabilitazione La Filanda LARS; Sarno, Italy - ⁶Department of Psychology, Educational Science and Human Movement, University of Palermo, Italy - ⁷Department of Health Sciences, University "Magna Graecia", Catanzaro, Italy - ⁸Centro Manzoni s.r.l., Napoli, Italy - ⁹Centro di Riabilitazione LARS, Sarno, Italy - ¹⁰Department of Surgical and Biomedical Sciences, University of Perugia, Perugia, Italy - ¹¹Centro Studi Della Scoliosi S.R.L, Italy - ¹²Centro Ambulatoriale Santo Stefano, Pesaro, Italy - ¹³Struttura Complessa di Farmacia, Azienda Ospedaliero-Universitaria, Ospedali Riuniti di Foggia, Foggia, Italy - ¹⁴Department of Medical, Surgical and Advanced Technology Sciences G.F. Ingrassia, University of Catania, Catania, Italy - ¹⁵Istituto nazionale della previdenza sociale (INPS), Catania, Italy - ¹⁶Department of Clinical and Experimental Medicine, University of Foggia, Foggia, Italy - ¹⁷Casa di Cura Villa dei Fiori Acerra, Napoli, Italy - ¹⁸Complex Structure of Neuropsychiatry Childhood-Adolescence of Ospedali Riuniti of Foggia, Foggia, Italy - ¹⁹Università degli Studi di Catania, Catania, Italy - ²⁰CRD Santa Maria del Pozzo, Somma Vesuviana, Italy

ABSTRACT

Introduction: Autistic Spectrum Disorder (ASD) is a permanent and complex disability arising within the first three years of life characterized by a socio-communicative disorder and by fixed interests and repetitive behaviors. The present pilot study aims to evaluate behavioral aspects in a small population of siblings of ASD children.

Material and methods: Population: 5 school-aged children (2 males, 3 females) (mean age 9.235 ± 2.041) were enrolled, as siblings of ASD children, and for comparison, 12 healthy (7 males, 5 females) children (average age 9.528 ± 3.351). All subjects underwent evaluation of the behavioral with Child Behavior Checklist (CBCL) scale.

Results: The two groups were statistically comparable by age ($p = 0.86$) and gender distribution ($p = 0.87$). From the behavioral point of view evaluated with the CBCL scale, siblings of ASD have a higher degree of overall problem (Total problems) compared to control children ($p=0.003$), in addition they have significantly higher scores in the subscales of behavior examined (Anxious/Depressed, Withdrawn, Somatic Complaints, Social, Thought, Attention, Delinquent, Aggressive) as well as a greater share of disturbances both internalizing ($p=0.004$) and externalizing ($p = 0.007$) (Table 1).

Conclusions: The present preliminary data confirm the need for a global management of the entire family structure for the correct management of Autistic Disorders.

Keywords: Autism spectrum disorders, siblings, behavior.

DOI: 10.19193/0393-6384_2018_4s_324

Received July 17, 2018; Accepted September 20, 2018

Introduction

Autistic Spectrum Disorder (ASD) is a permanent and complex disability that arises within the

first three years of life characterized by a socio-communicative disorder and by fixed interests and repetitive behaviors. The symptoms of autism vary widely: under the term "autism" there are, in fact, personal

situations with some common factors, but they are completely particular and cannot be reduced to a prototype. Each subject exhibits an intensity and a variable expressiveness of his symptoms. For this reason terms such as “autism” or “autistic spectrum” are used to indicate complexity, while “continuum” to represent the progression of severity levels from mild to very serious. Further complexity derives from the fact that the symptomatic picture can change in the same individual at different stages of life (e.g. appearance of behavioral excitement at the entrance into adolescence)⁽¹⁻¹⁰⁾.

People with autism avoid the gaze of others and human contact, have difficulty in interpreting the tone of the voice or facial expressions, are unable to develop relationships with peers appropriate to the level of development, appear unaware of the feelings of others in their comparisons and the negative impact of one's own behavior on others, have difficulties in the understanding of one's own and others' emotions⁽¹⁻¹⁰⁾. They have a delay or absence of verbal language, an inability to start or hold a conversation, use of stereotypies and deficits in imaginative play⁽¹¹⁻¹⁴⁾. Some, moreover, speak in a sing-song voice of a limited number of subjects they prefer and can refer to themselves with their own name rather than with “me” or “me”⁽¹⁵⁻¹⁶⁾.

Finally, subjects affected by autism are dedicated to one or more restricted, stereotypical and anomalous interests, some of them persistently turned to parts of objects. We observe typical motor stereotypies such as repetitive swaying or “flickering” of the hands near the head, and an attachment to specific habits and rituals⁽¹⁷⁻²¹⁾.

In about 75% of the autistic subjects there is also a mental retardation that can be of variable entity. Both in the cases of intellectual disability and in those with normal intelligence, the cognitive profile is often very inhomogeneous: in addition to the deeply compromised areas, it is possible to detect great cognitive-perceptive abilities indicated by Kanner as “islet of ability”⁽²²⁾, that is, islands of geniality relative to the peculiarity of interest, to the mechanical memory (eg ability to remember structures and complex sequences), to visual elaboration (eg graphic abilities in copying environments and objects and accuracy in reproducing proportions and details). Very often they are associated with striking behavioral alterations such as hyperactivity and auto and / or hetero aggressiveness, particularly in the most serious conditions. The regulation of affects is very primitive, with intense and acute

anguish crises apparently unmotivated or triggered by excessive environmental stimuli or changes in the environment⁽²³⁻²⁸⁾. The mood is very changeable, with rapid and sudden oscillations from flattening and apathy to excitement. Finally, serious and early alterations of food and sleep are very frequent⁽²⁹⁻³⁵⁾.

Often there are clinical conditions associated with autistic syndrome: in particular, it has been found that about 25% of individuals develop epileptic disorders⁽³⁶⁻³⁸⁾.

The prognosis in terms of development of personal and social autonomies and, in general, of quality of life is strongly conditioned by the degree of impairment of cognitive functioning and in particular of language development, but also by the presence of serious behavioral disorders.

The improvement in prognosis appears mainly linked to the precociousness of the diagnosis and the possibility of receiving an adequate intervention. There is no cure for autism, but it is possible to aim at improving the adaptive capacity of the subject, and then to significant improvements in the living conditions not only of the individual, but of the entire family unit. These improvements can, however, only take place through a continuous and coordinated multidisciplinary take-up that forms on the specific needs of the individual⁽³⁹⁻⁴⁵⁾.

About epidemiology. Autism does not seem to present geographic and / or ethnic prevalences, as it has been described in all the populations of the world, of every race or social environment; presents, on the contrary, a prevalence of sex, as it affects males in a measure 3 to 4 times higher than females, a difference that increases even more when examining the Asperger syndrome pictures, one of the forms of ASD. A prevalence of 10-13 cases per 10,000 seems to be the most reliable estimate for the classic forms of autism, while if we consider all the autism spectrum disorders the prevalence reaches 40-50 cases per 10,000. However, further studies have to be conducted in relation to the prevalence of autistic diseases that have recently been reported mainly by the English-speaking countries and which would bring the prevalence of autism spectrum disorders to 90 / 10,000. There is no shared explanation of this constant increase in cases: the increase we are witnessing may reflect a better identification and recognition of autism and its variants, but could also be attributed to changes in diagnostic practice, such as an effective increase in prevalence.

The causes of Autism are still unknown today and between aetiology and symptomatology, a chain of largely undefined events is grafted. Moreover, on this chain of events there are “internal” and “external” factors to the nervous system, which are equally ill-defined, capable of conditioning the expressiveness of the pathology⁽⁴⁶⁻⁴⁹⁾. It follows that the same cause can give rise to very different symptomatological pictures, just as different causes can give rise to the same symptomatic picture. In fact, the current difficulties in defining the mechanisms that underlie autistic behavior, and the factors that can interfere on them, represent only one aspect of a much more general problem: the problem, that is, of complex mind-brain relationships⁽⁵⁰⁻⁵³⁾.

Trying to summarize the data currently available should be broken down, referring to four areas of research. A first area of research is the deepening of observable behavior, that is to say the definition of the ways of conducting an individual or group of individuals in certain situations⁽⁵⁴⁻⁵⁶⁾.

A second area of research refers instead to the possible explanations of behaviors detected in certain circumstances. This level of depth, that is, tries to “understand” the observed behavior, reading it within general functional systems. In fact, the aim of this level of research is the attempt to define the functional systems of which the behaviors observed represent the expression “visible”.

The third area of research concerns the study of the structural components of the functions. This is a level that addresses the possible neuroanatomical, neurobiological and / or neurochemical bases of the various functional systems; of those functional systems, that is, that in turn are believed to underlie certain behaviors. The fourth area of research, finally, addresses the factors capable of affecting the structural components. It is an area that are still moving on parallel binaries: the failure to define the chain of events interposed between a given potentially pathogenic agent and a given behavior, prevents the integration of the data relating to the different areas for the development of a unitary interpretative model⁽⁵⁷⁻⁵⁹⁾.

Genetic component may be also relevant in ASD referring to the high concordance between monozygotic twins, ranging from 86% to 92%, and in dizygotic ones is about 26%, while in brothers the ASD incidence would be about 2%, with a risk 100 times higher than estimated in the general population (0,02%).

Moreover, ASD is frequently associated with genetic syndromes such as tuberous sclerosis, neurofibromatosis, phenylketonuria, Fragile X syndrome. The indications that emerged from these epidemiological investigations have reduced the search for candidate genes, responsible, at least, for a situation of “vulnerability”. The methodology is generally represented by association studies which use specific markers. These studies are conducted on families with more than one affected person or even in families with more than one affected child, evaluating the intra-family transmission⁽⁶⁰⁻⁶²⁾.

The present pilot study aims to evaluate behavioral aspects in a small population of siblings of ASD children.

Material and methods

Population

For the present study, 5 children (2 males, 3 females) of school age (mean age 9.235 ± 2.041) were enrolled, as siblings of children with ASD, and for comparison, 12 healthy (7 males, 5 females) children (average age $9,528 \pm 3,351$). All subjects underwent evaluation of the behavioral setting through the use of a specific validated assessment scale for school-age subjects .

Behavioral evaluation scale

All subjects were subjected to behavioral assessment through the Child Behavior Checklist (CBCL) scale. The CBCL questionnaires are part of the “empirical evaluation system” of T. Achenbach⁽⁶³⁾ and allow a description of the behavioral and emotional repertoire of the child through the reports provided by parents, teachers and / or children, to evaluate the presence of potentially problematic pipelines listed in behavioral scales.

They allow to gather information from different sources:

- parents in the form 1 ½ - 5 years and 6-18 years (CBCL 1 ½ -5, CBCL 6-18)
- educators or teachers in the form 1 ½ - 5 years (Caregiver 1 ½), and 6-18 years (TRF 6-18)
- boy aged 11 and up (YSR 11-18)

The response form is multiple-choice on a scale of three values: 0 = not true; 1 = sometimes true; 2 = very true. The evaluation refers to the present / last six months for the forms completed by the parents and self reports while for teachers the reference time is present / last 2 months.

The scales allow to investigate a broad spectrum of characteristics of the evolutionary age, both in reference to the skills and involvement in the activities, both in relation to the presence of emotional and behavioral problems.

The Italian CBCL versions scale consists of 103 items, grouped into 8 syndromic dimensional scales:

- Anxiety and depression,
- Withdrawal and depression,
- Somatic Complaints,
- Social problems,
- Thought problems,
- Attention problems,
- Behavior of transgression of rules,
- Aggressive behavior.

Moreover, it is possible to evaluate the behavior through three other general problems scales:

- Internalizing,
- Externalizing,
- Total Scale

For the present study the questionnaire was administered to the mothers of all subjects.

Statistic analysis

For the comparison between the two groups, t-test and Chi-square tests were used when appropriated. p value ≤ 0.05 was considered statistically significant.

Results

The two groups are statistically comparable by age ($p = 0.86$) and gender distribution ($p = 0.87$). From the behavioral point of view evaluated with the CBCL scale (Table 1), siblings of subjects with ASD have a greater degree of overall problem (Total problems) compared to control children ($p = 0.003$), in addition they have significantly higher scores in the subscales of behavior examined (Anxious / Depressed, Withdrawn, Somatic Complaints, Social, Thought, Attention, Delinquent, Aggressive) as well as a greater share of disturbances both internalizing ($p=0.004$) and externalizing ($p = 0.007$) (Table 1).

Discussion

Most studies evaluating psychoeducational interventions recruited siblings along with other family members. However, the proportion of siblings in these studies was low and outcomes for sib-

	ASD Siblings N=5	Controls N=12	p
Activities	30.147±6.306	36.955±7.073	0.083
Social	39.206±7.923	44.022±6.757	0.221
School	44.294±8.615	48.225±5.383	0.267
Competence	30.676±8.022	39.494±7.515	0.047*
Anxious/Depressed	64.235±8.389	52.697±5.793	0.005**
Withdrawn	62.353±8.998	52.978±7.722	0.046*
Somatic Complaints	64.059±6.555	53.236±5.112	0.002**
Social	61.324±7.881	53.506±5.945	0.040*
Thought	62.676±9.184	51.124±3.557	0.002**
Attention	61.294±8.709	52.472±4.076	0.011*
Delinquent	59.176±7.280	51.854±4.138	0.018*
Aggressive	61.706±11.358	51.101±2.768	0.007**
Internalizing	65.824±6.672	48.899±9.975	0.004**
Externalizing	59.235±10.246	44.629±8.104	0.007**
Total Problems	63.853±8.479	45.876±10.062	0.003**

Table 1: shows the results of the comparison between sibling children of subjects with Autism Spectrum Disorder (ASD) and control subjects at the Child Behavior Checklist (CBCL).

Legend: * = p values $< .05$; ** = p values $< .01$

lings were not reported independently from those of other types of family members. Indeed, only data from one study with nine siblings were available for the review. The limited study data we obtained provides no clear good quality evidence to indicate psychoeducational is beneficial for siblings' wellbeing or for clinical outcomes of people affected by SMI. More randomized studies are justified and needed to understand the role of psychoeducational in addressing siblings' needs for information and support⁽⁶⁴⁻⁶⁵⁾.

As reported in the international literature in recent years is focusing on the study of psychopathological impairment in the family of individuals with ASD, in this light our preliminary data confirm the idea that the brothers of ASD children seem to present anomalies behaviors of various kinds compared to subjects of the same age who have no sibs affected by ASD⁽⁶⁶⁻⁷⁵⁾.

Although less pronounced, social, cognitive, and personality characteristics associated with autism spectrum disorders (ASD) may be present in people who do not meet ASD diagnostic criteria, especially in first-degree relatives of individuals with ASD. Research on these characteristics, referred to as broader autism phenotype (BAP), provides valuable data on potential expressions of autism-specific deficits in the context of family relations. This paper offers a review of research on BAP in siblings of individuals with ASD, focusing on reports regarding social, communication, and cognitive deficits, published from 1993 to 2014.

The studies are divided into two groups based on participants' age: papers on preschool and older siblings of individuals with ASD; and publications on infants at risk for ASD. On the basis of this review, suggestions are offered for further research and its significance for our understanding of the genetic determinants of autism. Although sibling interactions play an important role in children's early development, they are rarely studied in very young children with an older brother or sister with autism spectrum disorder (ASD)⁽⁷⁶⁻¹⁰⁰⁾.

In this picture, our preliminary data confirm and strongly reaffirm the need for a global management of the entire family structure for the correct management of Autistic Disorders.

References

- 1) Messina A, Monda V, Sessa F, Valenzano A, Salerno M, Bitetti I, Precenzano F, Marotta R, Lavano F, Lavano SM, Salerno M, Maltese A, Roccella M, Parisi L, Ferrentino RI, Tripi G, Gallai B, Cibelli G, Monda M, Messina G, Carotenuto M. (2018) Sympathetic, Metabolic Adaptations, and Oxidative Stress in Autism Spectrum Disorders: How Far From Physiology? *Front Physiol.* Mar 22; 9: 261. doi: 10.3389/fphys.2018.00261
- 2) Esposito M, Ruberto M, Pascotto A, Carotenuto M. (2012) Nutraceuical preparations in childhood migraine prophylaxis: effects on headache outcomes including disability and behaviour. *Neurol Sci.* Dec; 33(6): 1365-8. doi: 10.1007/s10072-012-1019-8
- 3) Smirni D, Beadle JN, Paradiso S. An Initial Study of Alexithymia and Its Relationship With Cognitive Abilities Among Mild Cognitive Impairment, Mild Alzheimer's Disease, and Healthy Volunteers. *J Nerv Ment Dis* 2018, 206 (8): 628-636. doi: 10.1097/NMD.0000000000000853
- 4) Esposito M, Verrotti A, Gimigliano F, Ruberto M, Agostinelli S, Scuccimarra G, Pascotto A, Carotenuto M. (2012) Motor coordination impairment and migraine in children: a new comorbidity? *Eur J Pediatr.* Nov; 171(11): 1599-604. doi: 10.1007/s00431-012-1759-8.
- 5) Chieffi S, Messina G, Villano I, Messina A, Esposito M, Monda V, Valenzano A, Moscatelli F, Esposito T, Carotenuto M, Viggiano A, Cibelli G, Monda M. (2017) Exercise Influence on Hippocampal Function: Possible Involvement of Orexin-A. *Front Physiol.* Feb 14; 8: 85. doi: 10.3389/fphys.2017.00085
- 6) Esposito M, Roccella M, Gallai B, Parisi L, Lavano SM, Marotta R, Carotenuto M. (2013) Maternal personality profile of children affected by migraine. *Neuropsychiatr Dis Treat.* 9 :1351-8. doi: 10.2147/NDT.S51554
- 7) Esposito M, Marotta R, Gallai B, Parisi L, Patriciello G, Lavano SM, Mazzotta G, Roccella M, Carotenuto M. (2013) Temperamental characteristics in childhood migraine without aura: a multicenter study. *Neuropsychiatr Dis Treat.* 9: 1187-92. doi: 10.2147/NDT.S50458
- 8) Esposito M, Gallai B, Parisi L, Castaldo L, Marotta R, Lavano SM, Mazzotta G, Roccella M, Carotenuto M. (2013) Self-concept evaluation and migraine without aura in childhood. *Neuropsychiatr Dis Treat.* 9: 1061-6. doi: 10.2147/NDT.S49364
- 9) Esposito M, Parisi L, Gallai B, Marotta R, Di Dona A, Lavano SM, Roccella M, Carotenuto M. (2013) Attachment styles in children affected by migraine without aura. *Neuropsychiatr Dis Treat.* 9: 1513-9. doi: 10.2147/NDT.S52716
- 10) Carotenuto M, Gallai B, Parisi L, Roccella M, Esposito M. (2013) Acupressure therapy for insomnia in adolescents: a polysomnographic study. *Neuropsychiatr Dis Treat.* 9:1 57-62. doi: 10.2147/NDT.S41892
- 11) Carotenuto M, Gimigliano F, Fiordelisi G, Ruberto M, Esposito M. (2013) Positional abnormalities during sleep in children affected by obstructive sleep apnea syndrome: the putative role of kinetic muscular chains. *Med Hypotheses.* Aug; 81(2): 306-8. doi: 10.1016/j.mehy.2013.04.023
- 12) Esposito M, Pascotto A, Gallai B, Parisi L, Roccella M, Marotta R, Lavano SM, Gritti A, Mazzotta G, Carotenuto M. (2012) Can headache impair intellectual abilities in children? An observational study. *Neuropsychiatr Dis Treat.* 8: 509-13. doi: 10.2147/NDT.S36863.
- 13) Esposito M, Gallai B, Parisi L, Roccella M, Marotta R, Lavano SM, Gritti A, Mazzotta G, Carotenuto M. (2013) Maternal stress and childhood migraine: a new perspective on management. *Neuropsychiatr Dis Treat.* 9: 351-5. doi: 10.2147/NDT.S42818.
- 14) Esposito M, Parisi P, Miano S, Carotenuto M. (2013) Migraine and periodic limb movement disorders in sleep in children: a preliminary case-control study. *J Headache Pain.* Jul 1; 14: 57. doi: 10.1186/1129-2377-14-57
- 15) Esposito M, Gallai B, Parisi L, Roccella M, Marotta R, Lavano SM, Mazzotta G, Patriciello G, Precenzano F, Carotenuto M. (2013) Visuomotor competencies and primary monosymptomatic nocturnal enuresis in prepubertal aged children. *Neuropsychiatr Dis Treat.* 9: 921-6. doi: 10.2147/NDT.S46772
- 16) Esposito M, Carotenuto M. (2011) Ginkgolide B complex efficacy for brief prophylaxis of migraine in school-aged children: an open-label study. *Neurol Sci.*

- Feb; 32(1): 79-81. doi: 10.1007/s10072-010-0411-5
- 17) Esposito M, Roccella M, Parisi L, Gallai B, Carotenuto M. (2013) Hypersomnia in children affected by migraine without aura: a questionnaire-based case-control study. *Neuropsychiatr Dis Treat.* 9: 289-94. doi: 10.2147/NDT.S42182
 - 18) Carotenuto M, Esposito M, Pascotto A. (2011) Facial patterns and primary nocturnal enuresis in children. *Sleep Breath.* May;15(2): 221-7. doi: 10.1007/s11325-010-0388-6
 - 19) Carotenuto M, Esposito M. (2013) Nutraceuticals safety and efficacy in migraine without aura in a population of children affected by neurofibromatosis type I. *Neurol Sci. Nov;* 34(11): 1905-9. doi: 10.1007/s10072-013-1403-z
 - 20) Carotenuto M, Esposito M, Parisi L, Gallai B, Marotta R, Pascotto A, Roccella M. (2012) Depressive symptoms and childhood sleep apnea syndrome. *Neuropsychiatr Dis Treat.* 8: 369-73. doi: 10.2147/NDT.S35974
 - 21) Carotenuto M, Bruni O, Santoro N, Del Giudice EM, Perrone L, Pascotto A. (2006) Waist circumference predicts the occurrence of sleep-disordered breathing in obese children and adolescents: a questionnaire-based study. *Sleep Med. Jun;* 7(4): 357-61
 - 22) Esposito M, Carotenuto M, Roccella M. (2011) Primary nocturnal enuresis and learning disability. *Minerva Pediatr.* Apr; 63(2): 99-104
 - 23) Perillo L, Esposito M, Contiello M, Lucchese A, Santini AC, Carotenuto M. (2013) Occlusal traits in developmental dyslexia: a preliminary study. *Neuropsychiatr Dis Treat.* 9: 1231-7. doi: 10.2147/NDT.S49985
 - 24) Esposito M, Marotta R, Roccella M, Gallai B, Parisi L, Lavano SM, Carotenuto M. (2014) Pediatric neurofibromatosis 1 and parental stress: a multicenter study. *Neuropsychiatr Dis Treat.* Jan 22;10:141-6. doi: 10.2147/NDT.S55518.
 - 25) Carotenuto M, Esposito M, Pascotto A. (2010) Migraine and enuresis in children: An unusual correlation? *Med Hypotheses.* Jul; 75(1): 120-2. doi: 10.1016/j.mehy.2010.02.004
 - 26) Verrotti A, Carotenuto M, Altieri L, Parisi P, Tozzi E, Belcastro V, Esposito M, Guastaferrò N, Ciuti A, Mohn A, Chiarelli F, Agostinelli S. (2015) Migraine and obesity: metabolic parameters and response to a weight loss programme. *Pediatr Obes.* Jun; 10(3): 220-5. doi: 10.1111/ijpo.245
 - 27) Carotenuto M, Guidetti V, Ruju F, Galli F, Tagliente FR, Pascotto A. (2005) Headache disorders as risk factors for sleep disturbances in school aged children. *J Headache Pain.* Sep; 6(4): 268-70
 - 28) Esposito M, Carotenuto M. (2010) Borderline intellectual functioning and sleep: the role of cyclic alternating pattern. *Neurosci Lett.* Nov 19; 485(2): 89-93. doi: 10.1016/j.neulet.2010.08.062
 - 29) Carotenuto M, Santoro N, Grandone A, Santoro E, Pascotto C, Pascotto A, Perrone L, del Giudice EM. (2009) The insulin gene variable number of tandem repeats (INS VNTR) genotype and sleep disordered breathing in childhood obesity. *J Endocrinol Invest.* Oct; 32(9): 752-5. doi: 10.3275/6398.
 - 30) Carotenuto M, Esposito M, Cortese S, Laino D, Verrotti A. (2016) Children with developmental dyslexia showed greater sleep disturbances than controls, including problems initiating and maintaining sleep. *Acta Paediatr. Sep;* 105(9): 1079-82. doi: 10.1111/apa.13472
 - 31) Carotenuto M, Esposito M, D'Aniello A, Ripa CD, Precenzano F, Pascotto A, Bravaccio C, Elia M. (2013) Polysomnographic findings in Rett syndrome: a case-control study. *Sleep Breath.* Mar; 17(1): 93-8. doi: 10.1007/s11325-012-0654-x. Epub 2012 Mar 7. Erratum in: *Sleep Breath.* 2013 May; 17(2):877-8
 - 32) Verrotti A, Agostinelli S, D'Egidio C, Di Fonzo A, Carotenuto M, Parisi P, Esposito M, Tozzi E, Belcastro V, Mohn A, Battistella PA. (2013) Impact of a weight loss program on migraine in obese adolescents. *Eur J Neurol.* Feb; 20(2): 394-7. doi: 10.1111/j.1468-1331.2012.03771.x
 - 33) Esposito M, Carotenuto M. (2014) Intellectual disabilities and power spectra analysis during sleep: a new perspective on borderline intellectual functioning. *J Intellect Disabil Res.* May; 58(5): 421-9. doi: 10.1111/jir.12036
 - 34) Carotenuto M, Esposito M, Precenzano F, Castaldo L, Roccella M. (2011) Cosleeping in childhood migraine. *Minerva Pediatr.* Apr; 63(2): 105-9
 - 35) Coppola G, Licciardi F, Sciscio N, Russo F, Carotenuto M, Pascotto A. (2004) Lamotrigine as first-line drug in childhood absence epilepsy: a clinical and neurophysiological study. *Brain Dev.* Jan; 26(1): 26-9
 - 36) Verrotti A, Greco M, Varriale G, Tamborino A, Savasta S, Carotenuto M, Elia M, Operto F, Margari L, Belcastro V, Selicorni A, Freri E, Matricardi S, Granata T, Ragona F, Capovilla G, Spalice A, Coppola G, Striano P. (2018) Electroclinical features of epilepsy monosomy 1p36 syndrome and their implications. *Acta Neurol Scand.* Aug 14. doi: 10.1111/ane.13006
 - 37) Esposito M, Precenzano F, Sorrentino M, Avolio D, Carotenuto M. (2015) A Medical Food Formulation of Griffonia simplicifolia/Magnesium for Childhood Periodic Syndrome Therapy: An Open-Label Study on Motion Sickness. *J Med Food.* Aug; 18(8): 916-20. doi: 10.1089/jmf.2014.0113
 - 38) Esposito M, Ruberto M, Gimigliano F, Marotta R, Gallai B, Parisi L, Lavano SM, Roccella M, Carotenuto M. (2013) Effectiveness and safety of Nintendo Wii Fit Plus™ training in children with migraine without aura: a preliminary study. *Neuropsychiatr Dis Treat.* 9:1803-10. doi: 10.2147/NDT.S53853
 - 39) Di Filippo T, Orlando MF, Concialdi G, La Grutta S, Lo Baido R, Epifanio MS, Esposito M, Carotenuto M, Parisi L, Roccella M. (2013) The quality of life in developing age children with celiac disease. *Minerva Pediatr.* Dec; 65(6): 599-608.
 - 40) Carotenuto M, Parisi P, Esposito M, Cortese S, Elia M. (2014) Sleep alterations in children with refractory epileptic encephalopathies: a polysomnographic study. *Epilepsy Behav.* Jun; 35: 50-3. doi: 10.1016/j.yebeh.2014.03.009
 - 41) Esposito M, Gimigliano F, Ruberto M, Marotta R, Gallai B, Parisi L, Lavano SM, Mazzotta G, Roccella M, Carotenuto M. (2013) Psychomotor approach in children affected by nonretentive fecal soiling (FNRFs): a new rehabilitative purpose. *Neuropsychiatr Dis Treat.* 9: 1433-41. doi: 10.2147/NDT.S51257
 - 42) Parisi L, Di Filippo T, La Grutta S, Lo Baido R,

- Epifanio MS, Esposito M, Carotenuto M, Roccella M. (2013) Sturge-weber syndrome: a report of 14 cases. *Ment Illn.* Jun 3;5(1):e7. doi: 10.4081/mi.2013.e7
- 43) Coppola G, Auricchio G, Federico R, Carotenuto M, Pascotto A. (2004) Lamotrigine versus valproic acid as first-line monotherapy in newly diagnosed typical absence seizures: an open-label, randomized, parallel-group study. *Epilepsia.* Sep; 45(9): 1049-53
- 44) Esposito M, Gallai B, Roccella M, Marotta R, Lavano F, Lavano SM, Mazzotta G, Bove D, Sorrentino M, Precenzano F, Carotenuto M. (2014) Anxiety and depression levels in prepubertal obese children: a case-control study. *Neuropsychiatr Dis Treat.* Oct 3; 10: 1897-902. doi: 10.2147/NDT.S69795
- 45) Perillo L, Esposito M, Caprioglio A, Attanasio S, Santini AC, Carotenuto M. (2014) Orthodontic treatment need for adolescents in the Campania region: the malocclusion impact on self-concept. *Patient Prefer Adherence.* Mar 19; 8: 353-9. doi: 10.2147/PPA.S58971
- 46) Esposito M, Antinolfi L, Gallai B, Parisi L, Roccella M, Marotta R, Lavano SM, Mazzotta G, Precenzano F, Carotenuto M. (2013) Executive dysfunction in children affected by obstructive sleep apnea syndrome: an observational study. *Neuropsychiatr Dis Treat.* 9: 1087-94. doi: 10.2147/NDT.S47287
- 47) Villano I, Messina A, Valenzano A, Moscatelli F, Esposito T, Monda V, Esposito M, Precenzano F, Carotenuto M, Viggiano A, Chieffi S, Cibelli G, Monda M, Messina G. (2017) Basal Forebrain Cholinergic System and Orexin Neurons: Effects on Attention. *Front Behav Neurosci.* Jan 31; 11: 10. doi: 10.3389/fnbeh.2017.00010
- 48) Gallelli L, Cione E, Caroleo MC, Carotenuto M, Lagana P, Siniscalchi A, Guidetti V. (2017) microRNAs to Monitor Pain-migraine and Drug Treatment. *Microna.* Dec 6;6(3):152-156. doi: 10.2174/221153660666170913152821
- 49) Matricardi S, Darra F, Spalice A, Basti C, Fontana E, Dalla Bernardina B, Elia M, Giordano L, Accorsi P, Cusmai R, De Liso P, Romeo A, Ragona F, Granata T, Concolino D, Carotenuto M, Pavone P, Pruna D, Striano P, Savasta S, Verrotti A. (2018) Electroclinical findings and long-term outcomes in epileptic patients with inv dup (15). *Acta Neurol Scand.* Jun; 137(6): 575-581. doi: 10.1111/ane.12902
- 50) Esposito M, Messina A, Monda V, Bitetti I, Salerno F, Precenzano F, Pisano S, Salvati T, Gritti A, Marotta R, Lavano SM, Lavano F, Maltese A, Parisi L, Salerno M, Tripi G, Gallai B, Roccella M, Bove D, Ruberto M, Toraldo R, Messina G, Carotenuto M. (2017) The Rorschach Test Evaluation in Chronic Childhood Migraine: A Preliminary Multicenter Case-Control Study. *Front Neurol.* Dec 12; 8: 680. doi: 10.3389/fneur.2017.00680
- 51) Sperandeo R, Monda V, Messina G, Carotenuto M, Maldonato NM, Moretto E, Leone E, De Luca V, Monda M, Messina A. (2017) Brain functional integration: an epidemiologic study on stress-producing dissociative phenomena. *Neuropsychiatr Dis Treat.* Dec 19; 14:11-19. doi: 10.2147/NDT.S146250
- 52) Messina A, Bitetti I, Precenzano F, Iacono D, Messina G, Roccella M, Parisi L, Salerno M, Valenzano A, Maltese A, Salerno M, Sessa F, Albano GD, Marotta R, Villano I, Marsala G, Zammit C, Lavano F, Monda M, Cibelli G, Lavano SM, Gallai B, Toraldo R, Monda V, Carotenuto M. (2018) Non-Rapid Eye Movement Sleep Parasomnias and Migraine: A Role of Orexinergic Projections. *Front Neurol.* Feb 28; 9: 95. doi: 10.3389/fneur.2018.00095.
- 53) Esposito M, Gimigliano F, Barillari MR, Precenzano F, Ruberto M, Sepe J, Barillari U, Gimigliano R, Militerni R, Messina G, Carotenuto M. (2017) Pediatric selective mutism therapy: a randomized controlled trial. *Eur J Phys Rehabil Med.* Oct 53(5): 643-650. doi: 10.23736/S1973-9087.16.04037-5
- 54) Bellini B, Arruda M, Cescut A, Saulle C, Persico A, Carotenuto M, Gatta M, Nacinovich R, Piazza FP, Termine C, Tozzi E, Lucchese F, Guidetti V. (2013) Headache and comorbidity in children and adolescents. *J Headache Pain.* Sep 24;14:79. doi: 10.1186/1129-2377-14-79
- 55) Esposito M, Gallai B, Parisi L, Roccella M, Marotta R, Lavano SM, Mazzotta G, Carotenuto M. (2013) Primary nocturnal enuresis as a risk factor for sleep disorders: an observational questionnaire-based multicenter study. *Neuropsychiatr Dis Treat.* 9: 437-43. doi: 10.2147/NDT.S43673
- 56) Monda V, La Marra M, Perrella R, Caviglia G, Iavarone A, Chieffi S, Messina G, Carotenuto M, Monda M, Messina A. (2017) Obesity and brain illness: from cognitive and psychological evidences to obesity paradox. *Diabetes Metab Syndr Obes.* Nov 21; 10: 473-479. doi: 10.2147/DMSO.S148392
- 57) Parisi P, Vanacore N, Belcastro V, Carotenuto M, Del Giudice E, Mariani R, Papetti L, Pavone P, Savasta S, Striano P, Toldo I, Tozzi E, Verrotti A, Raucci U; "Pediatric Headache Commission" of Società Italiana di Neurologia Pediatrica (SINP). (2014) Clinical guidelines in pediatric headache: evaluation of quality using the AGREE II instrument. *J Headache Pain.* Sep 1; 15: 57. doi: 10.1186/1129-2377-15-57
- 58) Toldo I, Rattin M, Perissinotto E, De Carlo D, Bolzonella B, Nosadini M, Rossi LN, Vecchio A, Simonati A, Carotenuto M, Scalas C, Sciruicchio V, Raieli V, Mazzotta G, Tozzi E, Valeriani M, Cianchetti C, Balottin U, Guidetti V, Sartori S, Battistella PA. (2017) Survey on treatments for primary headaches in 13 specialized juvenile Headache Centers: The first multicenter Italian study. *Eur J Paediatr Neurol.* May; 21(3): 507-521. doi: 10.1016/j.ejpn.2016.12.009
- 59) Verrotti A, Casciato S, Spalice A, Carotenuto M, Striano P, Parisi P, Zamponi N, Savasta S, Rinaldi VE, D'Alonzo R, Mecerani F, Ritaccio AJ, Di Gennaro G. (2017) Coexistence of childhood absence epilepsy and benign epilepsy with centrotemporal spikes: A case series. *Eur J Paediatr Neurol.* May; 21(3): 570-575. doi: 10.1016/j.ejpn.2017.02.002
- 60) Matricardi S, Spalice A, Salpietro V, Di Rosa G, Balistreri MC, Grosso S, Parisi P, Elia M, Striano P, Accorsi P, Cusmai R, Specchio N, Coppola G, Savasta S, Carotenuto M, Tozzi E, Ferrara P, Ruggieri M, Verrotti A. (2016) Epilepsy in the setting of full trisomy 18: A multicenter study on 18 affected children with and without structural brain abnormalities. *Am J Med Genet C Semin Med Genet.* Sep; 172(3) :288-95. doi: 10.1002/ajmg.c.31513
- 61) Gallelli L, Avenoso T, Falcone D, Palleria C, Peltrone

- F, Esposito M, De Sarro G, Carotenuto M, Guidetti V. (2014) Effects of acetaminophen and ibuprofen in children with migraine receiving preventive treatment with magnesium. *Headache*. Feb; 54(2): 313-24. doi: 10.1111/head.12162
- 62) Elia M, Amato C, Bottitta M, Grillo L, Calabrese G, Esposito M, Carotenuto M. (2012) An atypical patient with Cowden syndrome and PTEN gene mutation presenting with cortical malformation and focal epilepsy. *Brain Dev*. Nov; 34(10): 873-6. doi: 10.1016/j.braindev.2012.03.005
- 63) Achenbach TM, Ruffle TM. The Child Behavior Checklist and related forms for assessing behavioral/emotional problems and competencies. *Pediatr Rev*. 2000; 21(8): 265-271. doi: 10.1542/pir.21-8-265
- 64) Sin J, Jordan CD, Barley EA, Henderson C, Norman I. Psychoeducation for siblings of people with severe mental illness. *Cochrane Database Syst Rev*. 2015 May 8; (5): CD010540. doi: 10.1002/14651858.CD010540
- 65) Filliter JH, Longard J, Lawrence MA, Zwaigenbaum L, Brian J, Garon N, Smith IM, Roncadin C, Roberts W, Bryson SE. Positive affect in infant siblings of children diagnosed with autism spectrum disorder. *J Abnorm Child Psychol*. 2015 Apr; 43(3): 567-75. doi: 10.1007/s10802-014-9921-6
- 66) Finan LJ, Ohannessian CM, Gordon MS. Trajectories of depressive symptoms from adolescence to emerging adulthood: The influence of parents, peers, and siblings. *Dev Psychol*. 2018 Aug; 54(8): 1555-1567. doi: 10.1037/dev0000543
- 67) Pisula E, Ziegart-Sadowska K. Broader Autism Phenotype in Siblings of Children with ASD-A Review. *Int J Mol Sci*. 2015 Jun 10; 16(6): 13217-58. doi:10.3390/ijms160613217
- 68) Bontinck C, Warreyn P, Van der Paelt S, Demurie E, Roeyers H. The early development of infant siblings of children with autism spectrum disorder: Characteristics of sibling interactions. *PLoS One*. 2018 Mar 15; 13(3): e0193367. doi: 10.1371/journal.pone.0193367
- 69) Pomara, C., D'Errico, S., Riezzo, I., De Cillis, G.P., Fineschi, V. Sudden cardiac death in a child affected by Prader-Willi syndrome. (2005) *International Journal of Legal Medicine*, 119 (3), pp. 153-157. DOI: 10.1007/s00414-004-0513-9
- 70) Fineschi, V., Neri, M., Di Donato, S., Pomara, C., Riezzo, I., Turillazzi, E. An immunohistochemical study in a fatality due to ovarian hyperstimulation syndrome. (2006) *International Journal of Legal Medicine*, 120 (5), pp. 293-299. DOI: 10.1007/s00414-006-0104-z
- 71) Turillazzi, E., Baroldi, G., Silver, M.D., Parolini, M., Pomara, C., Fineschi, V. A systematic study of a myocardial lesion: Colliquative myocytolysis. (2005) *International Journal of Cardiology*, 104 (2), pp. 152-157. DOI: 10.1016/j.ijcard.2004.10.051
- 72) Mazzeo F, Motti ML, Messina G, Monda V, Ascione A, Tafuri D, et al. Use of nutritional supplements among south Italian students of physical training and sport university. *Curr Top Toxicol*. 2013; 9: 21-6
- 73) Messina G, Monda V, Moscatelli F, Valenzano AA, Monda G, Esposito T, et al. Role of orexin system in obesity. *Biol Med*. 2015; 7(4)
- 74) Messina G, Di Bernardo G, Viggiano A, De Luca V, Monda V, Messina A, et al. Exercise increases the level of plasma orexin A in humans. *J Basic Clin Physiol Pharmacol*. 2016; 27(6): 611-6
- 75) Messina G, Palmieri F, Monda V, Messina A, Dalia C, Viggiano A, et al. Exercise causes muscle GLUT4 translocation in an insulin-independent manner. *Biol Med*. 2015; 7(Special issue)
- 76) Messina G, Viggiano A, Tafuri D, Palmieri F, De Blasio S, Messina A, et al. Role of orexin in obese patients in the intensive care unit. *J Anesth Clin Res*. 2014; 5(3)
- 77) Monda M, Viggiano A, Viggiano A, Viggiano E, Messina G, Tafuri D, et al. Quetiapine lowers sympathetic and hyperthermic reactions due to cerebral injection of orexin A. *Neuropeptides*. 2006; 40(5): 357-63
- 78) Chieffi S, Messina G, Villano I, Messina A, Esposito M, Monda V, et al. Exercise influence on hippocampal function: Possible involvement of orexin-a. *Front Physiol*. 2017; 8
- 79) Valenzano A, Moscatelli F, Triggiani AI, Capranica L, De Ioannon G, Piacentini MF, et al. Heart-rate changes after an ultraendurance swim from Italy to Albania: A case report. *Int J Sports Physiol Perform*. 2016; 11(3): 407-9
- 80) Viggiano E, Monda V, Messina A, Moscatelli F, Valenzano A, Tafuri D, et al. Cortical spreading depression produces a neuroprotective effect activating mitochondrial uncoupling protein-5. *Neuropsychiatr Dis Treat*. 2016; 12: 1705-10
- 81) Rinaldi B, Guida F, Furiano A, Donniacuo M, Luongo L, Gritti G, et al. Effect of Prolonged Moderate Exercise on the Changes of Nonneuronal Cells in Early Myocardial Infarction. *Neural Plast*. 2015; 2015;
- 82) Monda V, Valenzano A, Moscatelli F, Salerno M, Sessa F, Triggiani AI, et al. Primary motor cortex excitability in karate athletes: A transcranial magnetic stimulation study. *Front Physiol*. 2017; 8
- 83) Triggiani AI, Valenzano A, Ciliberti MAP, Moscatelli F, Villani S, Monda M, et al. Heart rate variability is reduced in underweight and overweight healthy adult women. *Clin Physiol Funct Imaging*. 2017; 37(2): 162-7;
- 84) Messina G, Di Bernardo G, Viggiano A, De Luca V, Monda V, Messina A, et al. Exercise increases the level of plasma orexin A in humans. *J Basic Clin Physiol Pharmacol*. 2016; 27(6): 611-6
- 85) De Luca V, Viggiano E, Messina G, Viggiano A, Borlido C, Viggiano A, et al. Peripheral amino acid levels in schizophrenia and antipsychotic treatment. *Psychiatry Investig*. 2008; 5(4): 203-8
- 86) Messina G, Dalia C, Tafuri D, Monda V, Palmieri F, Dato A, et al. Orexin-A controls sympathetic activity and eating behavior. *Front Psychol*. 2014; 8(5): 997
- 87) Messina A, Monda V, Avola R, Moscatelli F, Valenzano A, Ruberto M, et al. Role of the orexin system on arousal, attention, feeding behaviour and sleep disorders. *Acta Medica Mediterr*. 2017; 33(4): 645-649
- 88) Monda M, Viggiano A, Viggiano A, Viggiano E, Messina G, Tafuri D, et al. Sympathetic and hyperthermic reactions by orexin A: role of cerebral catecholaminergic neurons. *Regul Pept*. 2007; 139(1-3): 39-44
- 89) Monda M, Messina G, Scognamiglio I, Lombardi A, Martin GA, Sperlongano P, et al. Short term diet and moderate exercise in young overweight men modulate cardiocyte and hepatocarcinoma survival by oxidative

- stress. *Oxid Med Cell Longev*. 2014; 2014: 131024
- 90) Monda M, Messina G, Vicidomini C, Viggiano A, Mangoni C, De Luca B. Activity of autonomic nervous system is related to body weight in pre-menopausal, but not in post-menopausal women. *Nutr Neurosci*. 2006; 9(3-4): 141-5
- 91) Di Bernardo G, Messina G, Capasso S, Del Gaudio S, Cipollaro M, Peluso G, et al. Sera of overweight people promote in vitro adipocyte differentiation of bone marrow stromal cells. *Stem Cell Res Ther*. 2014; 5(1): 4
- 92) Chieffi S, Carotenuto M, Monda V, Valenzano A, Villano I, Precenzano F, et al. Orexin System: The Key for a Healthy Life. *Front Physiol*. 2017; 31(8): 357
- 93) Panico A, Messina G, Lupoli GA, Lupoli R, Cacciapuoti M, Moscatelli F, et al. Quality of life in overweight (Obese) and normal-weight women with polycystic ovary syndrome. *Patient Prefer Adherence*. 2017; 11: 423-9
- 94) Viggiano A, Chieffi S, Tafuri D, Messina G, Monda M, De Luca B. Laterality of a second player position affects lateral deviation of basketball shooting. *J Sports Sci*. 2014; 32(1): 46-52
- 95) Moscatelli F, Messina G, Valenzano A, Petito A, Triggiani AI, Ciliberti MAP, et al. Relationship between RPE and blood lactate after fatiguing handgrip exercise in taekwondo and sedentary subjects. *Biol Med*. 2015; 7(Special issue)
- 96) Chieffi S, Iachini T, Iavarone A, Messina G, Viggiano A, Monda M. Flanker interference effects in a line bisection task. *Exp Brain Res*. 2014; 232(4): 1327-34;
- 97) Parisi L, Faraldo M, Ruberto M, Salerno M, Maltese A, Di Folco A, et al. Life events and primary monosymptomatic nocturnal enuresis: A pediatric pilot study. *Acta Medica Mediterr*. 2017; 33(1), 23-27
- 98) Parisi L, Salerno M, Maltese A, Tripi G, Romano P, Di Folco A, et al. Emotional intelligence And Obstructive Sleep Apnea Syndrome In Children: Preliminary Case-Control Study. *Acta Medica Mediterr*. 2017; 33: 485-489
- 99) Moscatelli F, Messina G, Valenzano A, Monda V, Viggiano A, Messina A, et al. Functional Assessment of Corticospinal System Excitability in Karate Athletes. *PLoS One*. 2016; 24(5): e0155998
- 100) Turillazzi E, Greco P, Neri, M., Pomara, C., Riezzo, I., Fineschi, V. Anaphylactic latex reaction during anaesthesia: The silent culprit in a fatal case. (2008) *Forensic Science International*, 179 (1), pp. e5-e8. DOI: 10.1016/j.forsciint.2008.03.021

Corresponding author

LUCIA PARISI

Department of Psychology, Educational Science and Human Movement

University of Palermo

(Italy)