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COORDINATORE Prof. Renato Corradetti

EARLY MOTOR SIGNATURE IN AUTISM SPECTRUM DISORDER

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Dottorando
Dott.ssa Francesca Fulceri

Tutori
Prof. Filippo Muratori

Dott.ssa Maria Luisa Scattoni

Coordinatore
Prof. Renato Corradetti

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THESIS'S STRUCTURE

My Ph.D. experimental activities have been performed in Rome (Italy), at the Istituto Superiore di Sanità (ISS), and in Pisa (Italy), at the Scientific Institute Stella Maris. During the first seven months of my Ph.D. (from November 2014 to May 2015), my research activities were held at the Scientific Institute Stella Maris under the supervision of Professor Filippo Muratori. In September 2016, after the one-year-suspension for pregnancy leaving, I obtained the authorization from the Ph.D.'s Council to retrieve my Ph.D. activities under the supervision of Doctor Maria Luisa Scattoni at the ISS.

The present thesis consists of three chapters:

The first chapter provides an analysis of the literature related to the Autism Spectrum Disorder (ASD). In this chapter, the updated literature on early signs and associated features of ASD condition have been reported.

The second chapter presents an overview of data on ASD motor deficits across childhood, including a section focused on infants at high risk of having ASD.

The third chapter describes experimental activities performed within the Italian network for early detection of autism spectrum disorder (NIDA) and the European project called "Brainview – fetal ultrasound screening for neurodevelopmental disorders in normal and high-risk pregnancies" Marie Sklodowska – Curie Actions, Innovative Training Networks (ETN), H2020 –MSCA- ETN-2014. Dr. Maria Luisa Scattoni (ISS) is the coordinator of the cited projects, and the Stella Maris Scientific Institute took part at both projects as clinical center.

The overall objective of my experimental activities was to identify early predictors of ASD through the investigation of antenatal and postnatal motor development in fetuses and infants at low- and high-risk for ASD. The underlying hypothesis is that assessment of motor performances might be effective in predicting abnormal outcomes in infants at risk for neurological development.

We performed two specific experimental studies to assess this aim:

- experiment 1. Analysis of early motor repertoires in infants at low and high risk for ASD;

- experiment 2. Analysis of fetal movements in pregnancies at low and high risk for ASD through 2D-3D-4D ultrasound (US) techniques.

ABSTRACT

Several evidences showed atypical gross and fine motor functions in infants and children with Autism Spectrum Disorder (ASD). For this reason, motor impairments or abnormalities should be investigated as potential early signs of the disorder and correlated to the severity of its core symptoms. Thus, the early detection of motor abnormalities may be potentially useful to diagnose later social impairments.

Main aim of the present PhD project is to identify early predictors of ASD through the investigation of antenatal and postnatal motor development in fetuses and infants at low- and high-risk for ASD. The underlying hypothesis is that assessment of motor performances may be effective in predicting abnormal outcomes in infants at risk for neurological development.

To this aim, two specific experiments have been performed:

Experiment 1. Analysis of early motor repertoire in infants at low and high risk for ASD.

Experiment 2. Analysis of fetal movements in pregnancies at low and high risk for ASD through ultrasound (US) techniques.

All the experimental activities have been performed at the Istituto Superiore di Sanità (ISS) within the Network for early detection of autism spectrum disorders (NIDA) and the European project “Brainview – fetal ultrasound screening for neurodevelopmental disorders in normal and high-risk pregnancies” Marie Sklodowska – Curie actions, Innovative Training Networks (ETN), H2020 –MSCA- ETN-2014. During the Ph.D., I collaborated with Prof. Andrea Guzzetta and his staff at the Stella Maris Foundation on the analysis of infant’s spontaneous movements and with Dr. Maria Bulgheroni (Ab. Acus company) and her staff of bio-engineers on the development and implementation of a software for the kinematic analysis of infant’s movements. To investigate antenatal neurobehaviours of fetuses at risk for ASD, I have collaborated with Dr. Laura Iaconianni, head gynecologist of the “Ultrasound Diagnostic Centre Eco.B.I.” in Rome.

Given the importance of further exploring the early motor trajectories in infants with ASD, this study had the overall purpose to collect longitudinal data on motor development of infants at high risk for ASD. The present work has several strengths and gave light to novel findings. First, data from the first experimental study supported the importance of carefully exploring the developmental trajectories of the spontaneous movements in the first 5-6 months of life of infants at high-risk for ASD since potentially predictive of later social impairments. Second, the development of the MOVIDEA software provided the possibility of detecting spontaneous movements for future application in clinical settings. Finally, the standard operative procedures developed to collect and analyze fetal movements and basal biometrical data during 2D and 4D ultrasound recording allow to evaluate possible indicators of an adequate fetal health during the gynecological examination of pregnant women during the first and second trimester.

In conclusion, the present work defined motor prenatal and postnatal trajectories to detect early signs of ASD in at-risk populations. In fact, given the well-established link between motor development and social competencies, it is possible to use this protocol as screenings in clinical settings to identify children at risk for neurodevelopmental disorders early in life and provide them and their families adequate care, services and interventions. Even if the low number of high risk with ASD prevents us from any consideration regarding the comparison between groups and the detection of early markers of ASD, the current protocols and techniques may be considered valuable tools to investigate motor developmental trajectories in infants.

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Quando un impegno ti accompagna nel tempo può diventare molto difficile ringraziare tutti coloro che ne sono stati coinvolti.

In questo percorso, iniziato con paure e incertezze, ho avuto la fortuna di avere vicino persone di valore, merito e umanità. Guardare alle prossime esperienze con lo stesso rispetto e la stessa fiducia che ho ricevuto è sicuramente uno dei modi più autentici per dire grazie.

Sono stati preziosi i suggerimenti di chi ha discusso, criticato e migliorato il mio lavoro. Sono state fondamentali l'incoraggiamento e la complicità di chi si è seduto a lavorare accanto a me insegnandomi il valore del metodo. Grazie per aver nutrito con costanza e fatto crescere la mia curiosità. Tra tutti, un ringraziamento speciale alla *mia Jacqueline.*

Questa tesi è dedicata ad un nuovo arrivo, nato nella collaborazione e con l'aiuto delle famiglie con cui ho condiviso attese, preoccupazioni e gioie.

Sicuramente non avrei potuto concludere questa strada senza la gioia, la pazienza e l'affetto di cui la mia famiglia mia ha circondata.

Chapter 1

Autism Spectrum Disorder

Introduction

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by persistent impairments in reciprocal social communication and social interactions along with the presence of restricted, repetitive patterns of behaviors, interests, or activities (American Psychiatric Association, APA 2013; DSM-5, 2013). According to the DSM-5, symptoms are present from early childhood, but they may be masked by camouflaging strategies that may delay the diagnosis also in adulthood (DSM-5; APA, 2013; Lai & Baron-Cohen, 2015).

The clinical manifestations of ASD may vary greatly depending on the condition's severity, developmental level, and chronological age (APA 2013; DSM-5, 2013). The term "spectrum" indicates a vast spectrum of different clinical conditions that may vary over time and across individuals. The DSM-5 lists the diagnostic criteria for ASD along with a detailed description of the full spectrum of symptoms. "Children with ASD present deficits in social-emotional reciprocity (i.e., the ability to engage with others and share thoughts and feelings) and they may show little or no initiation of social interaction along with reduced or absent imitation of others' behavior. Language deficits range from complete lack of speech through language delays, poor comprehension of speech, echoed speech, or stilted and overly literal language. Moreover, even if formal language skills are intact, children with ASD may present the use of language for reciprocal social communication. Language is often one-sided, lacking in social reciprocity, and used to request or label rather than to comment, share feelings, or converse. Deficits in nonverbal communicative behaviors are manifested by absent, reduced, or atypical use of eye contact, gestures, facial expressions, body orientation, or speech intonation" (DSM-5, APA, 2013).

Early clinical manifestations of ASD may be extremely heterogeneous (APA 2013; DSM-5, 2013). Some children are described as having behavioral abnormalities from the earliest months of life, whereas others are described as becoming withdrawn

and losing skills after a period of relatively typical development into the second year of life (APA 2013; DSM-5, 2013). A recent meta-analysis on this topic reported a rate of developmental regression of 32.1 %, occurring on average at 1.78 years old (Barger, Campbell, & McDonough, 2013). However, the prevalence of regression differed significantly depend on the regression's definition and to the sampling method (e.g.., 21,8% in clinical population-based studies and 40.8 % in parent survey-based studies) (Barger, Campbell, & McDonough, 2013).

Retrospective studies using home videos' coding revealed atypical behaviors appearing from the first year of life and other studies on high-risk infants (siblings of children with a ASD diagnosis) identified an ASD prodrome including reduced motor control, attention, and emotional regulation problems before the development of social communication impairments and repetitive behaviors (Zwaigenbaum & Penner, 2018). In the second year of the child's life, the most consistently reported findings were an impaired language development, a reduced orienting to name, a deficit in joint attention behaviors, and an atypical use of objects and visual exploration (Jones, Gliga, Bedford, Charman, & Johnson, 2014).

According to the DSM-5, "common early features of ASD are impaired joint attention (as manifested by lack of pointing, showing, or bringing objects to share interest with others, or failure to follow someone's pointing or eye gaze), poor integration of eye contact, gestures, body posture, prosody, and facial expressions for social communication. Stereotyped or repetitive behaviors include simple motor stereotypies, repetitive use of objects, and repetitive speech. Excessive adherence to routines and restricted patterns of behavior may be manifest in resistance to change or ritualized patterns of verbal or nonverbal behaviors. Highly restricted, fixated interests in individuals with ASD tend to be abnormal in intensity or focus. Some fascinations and routines may relate to apparent hyper- or hyporeactivity to sensory input manifested through extreme responses to specific sounds or textures, excessive smelling or touching of objects, fascination with lights or spinning objects, and sometimes apparent indifference to pain, heat, or cold. Extreme reaction to or rituals involving taste, smell, texture, or appearance of food or excessive food restrictions are typical and may be a presenting feature of ASD" (DSM-5, APA, 2013). Even if symptoms are often noted in the second year of life, the current average age for ASD childhood diagnosis in the

United States is 52 months and do not differ significantly by sex or race/ethnicity (Baio et al., 2018).

In 2014, the overall **prevalence of ASD** among 11 sites in the United States was estimated to be 16.8 per 1,000 (one in 59) children aged eight years (Baio et al., 2018). The Autism and Developmental Disabilities Monitoring (ADDM) Network is an active surveillance system that provides estimates of the prevalence of the ASD condition among children aged 8 years residing within 11 ADDM sites in the United States[1]. The ASD prevalence has been recently investigated in school-aged children in the province of Pisa (Italy) within the European Union (ASDEU) project. Results indicate a prevalence of ASD in children aged 7-9 years around one in 87 (Narzisi et al., 2018). The interpretation of the possible increase over the past 20 years of the ASD condition remains controversial and it is still not clear if this growth is real or due to more awareness or improved ascertainment. The ASD condition occurs about 4 times more often in males compared to females with an even higher range (from 6:1 8 to 10:1) in high functioning individuals with autism (HFA) (Fombonne, 2003). Hiller, Young and Weber (2016) observed that also pre-diagnosis concerns were significantly different between genders, with a disadvantage for females. It is worth noticing that there is an underrepresentation of females with ASD in the scientific literature (Lai, Baron-Cohen & Buxbaum, 2015). The gender ratio discrepancy in pre-diagnosis concerns, diagnosis and in research may be due to false negative or misdiagnosis. Affective disorders, anxiety disorders, personality disorders or eating disorders are usually attributed to females with ASD (Young, Oreve & Speranza, 2018). A lack of diagnosis or a misdiagnosis may lead to absence or to inappropriate treatments that may have negative consequences on the development of the individual (Micai et al., 2019).

To date, the **causes of ASD** are still unknown. There is growing evidence supporting that the ASD condition mainly results from a complex interaction between an individual's genetic profile and environmental exposure (Hunter, 2005). The latter may cause profound changes in brain development and may influence neurological processes such as cell differentiation, synaptogenesis and axon myelination (Lyall, Schmidt, & Hertz-Picciotto, 2014). It has been reported that maternal lifestyle and diet

[1] (Arizona, Arkansas, Colorado, Georgia, Maryland, Minnesota, Missouri, New Jersey, North Carolina, Tennessee, and Wisconsin)

may have beneficial effects on the fetal brain development (Lyall, Schmidt, & Hertz-Picciotto, 2014), whereas maternal deficiencies in essential nutrients and fatty acids may be associated with neurodevelopmental negative consequences, including the onset of an ASD condition (Al-Farsi et al., 2013; Lyall, Schmidt, & Hertz-Picciotto, 2014). The tobacco smoking and the exposure to alcohol or drugs during pregnancy may be related to structural brain anomalies observed in children with ASD (Eliasen et al., 2010; Tran et al., 2013). In addition, the chronic use of medications during pregnancy has been associated with the perturbation of the fetal brain development, increasing the risk for exposed children to have ASD (Croen, Grether, Yoshida, Odouli, & Hendrick, 2011). Moreover, nutritional disorders, exposure to air pollutants, maternal infections during pregnancy, poor socioeconomic status, and low maternal educational level have been considered as potential ASD risk factors (Grant & Cannell, 2013; Chaste & Leboyer, 2012; Lyall et al., 2014; Randolph-Gips & Srinivasan, 2012). A recent study reported that a low concentration of vitamin D in typically developing (TD) children could affect brain development causing morphological and functional changes also observed in individuals with ASD (Jia et al., 2015). Environmental factors may directly act with some susceptibility genes, leading to epigenetic changes in gene expression that could increase the risk to have ASD (Lyall et al., 2014; Volk et al., 2014). In this regard, it is well known that new epigenetic modifications, including DNA methylation, could interfere with the neurodevelopment (Schaevitz & Berger-Sweeney, 2012; Tordjman et al., 2014). The fact that ASD is a complex and heterogeneous disease is supported by several studies that demonstrated that one single environmental factor is not sufficient and responsible for the ASD predisposition. It is more likely that a combination of several environmental factors has a significant impact on ASD suscetibility (Gardener, Spiegelman, & Buka, 2011).

Associates conditions to ASD such as psychiatric disorders, medical problems and developmental delay may severely impact individuals with ASD life. According to Soke and colleagues (2018), over 95% of the children diagnosed with ASD had at least one **co-occurring condition/symptom** with a higher prevalence in 8- than 4-year-olds children. According to the ADDM Network, the 31% of children with ASD were in the range of intellectual disability (intelligence quotient IQ < 70), 25% were in the borderline range (IQ 71-85), and 44% had IQ scores in the average or above the average range (i.e., IQ >

85) (Baio et al., 2010). As previously mentioned, individuals with ASD may present several physical health problems. The most frequent include gastrointestinal disorders, feeding difficulties, seizures, and sleep problems, all which impact health-related quality of life (Klukowski, Wasilewska & Lebensztejn, 2015; Coury, Jones, Klatka, Winklosky & Perrin, 2009). Emblematic examples of associate ASD condition are the gastrointestinal (GI) problems that are nearly eight times more likely to suffer from one or more of them compared to other children (https://www.autismspeaks.org).

The literature reported that the prevalence of **gastrointestinal disorders in ASD** 1 to 18 years old samples ranges from 9% to 91% (Buie et al., 2010). This striking heterogeneity may be due to several reasons: different methodological approaches, various measures for GI symptoms, different criteria to define GI problem or numbers of GI symptoms considered to estimate prevalence, study design and different characteristics of study population (Fulceri et al., 2016). Moreover, a source of conflicting results may derive from the clinical features of the ASD samples since children with ASD and severe language/communicative impairment could have problems to communicate GI symptoms (Buie et al., 2010; Carr & Owen-Deschryver, 2007). A meta-analysis on this topic (McElhanon, McCracken, Karpen, & Sharp, 2014) revealed a higher prevalence of GI symptoms among ASD children compared to control peers with higher rates of constipation, diarrhea, and abdominal pain. Children with ASD suffering from GI symptoms may also present problem behaviors, sensory sensitivity (Mazurek et al., 2013), sleep problems (Maenner et al., 2012), rigid-compulsive behaviors (Peters et al., 2014), irritability, anxiety, affective problems and externalizing behaviors (Nikolov et al., 2009; Chaidez, Hansen, & Hertz-Picciotto, 2014).

These findings have been recently confirmed also in a sample of 230 Italian children with ASD (Fulceri et al., 2016). The authors explored the type and the prevalence of GI symptoms in children with ASD compared to TD. Parental report of behavioral problems and GI symptoms were assessed through the Child Behavior Check List 1½–5 (Achenbach & Rescorla, 2000). Four groups of children were evaluated: ASD individuals suffering from GI symptoms (ASD/GI+), ASD subjects without GI symptoms (ASD/GI−), TD peers with (TD/GI+) and without (TD/GI−) GI symptoms. GI symptoms was observed in a significant higher percentage of ASD (37.4%) versus TD (14.8%). 'Constipated' and 'Not-Eat' were the most frequent GI symptoms both in ASD and in TD

groups, but they were evaluated as more severe in ASD patients. Differently from the TD group, ASD/GI+ children had more anxiety problems, somatic complaints, externalizing and total problems than ASD/GI− individuals. Overall, the findings suggested that GI symptomatology should be accurately assessed, especially in ASD children with anxiety and/or externalizing behavioral problems. In addition to its clinical significance, the association between GI dysfunction and ASD may be crucial also from a theoretical point of view. Indeed, it has been hypothesized that gut-based processes may have a direct pathophysiologic role in ASD and that GI symptoms may represent the visible expression of a gut-brain axis disruption. At IRCCS Stella Maris Foundation (Pisa, Italy) it is ongoing a clinical trial that investigates the role of probiotics on clinical, biochemical and neurophysiological parameters (Santocchi et al., 2016). The gut-brain axis represents a complex bidirectional network of communication between the brain and the gut, and it emerged as a critical player in typical neurodevelopment. By contrast, several studies had discussed dysbiosis or altered composition of intestinal microbiota in children with ASD which could represent a crucial determinant for neurodevelopmental alterations (Santocchi et al., 2016).

Chapter 2

Motor abnormalities in Autism Spectrum Disorder

Introduction

Atypical motor function among infants and children with ASD are well established early signs of atypical development (Esposito, Venuti, Apicella, & Muratori, 2011; Landa & Garrett-Mayer, 2006; Esposito & Venuti, 2008; Phagava et al., 2008; Esposito, Venuti, Maestro, & Muratori, 2009). Moreover, motor disturbances in ASD might be related to the severity of core symptoms (Hilton, Zhang, Whilte, Klohr, & Constantino, 2012; Jasmin et al., 2009; MacDonald, Lord, & Ulrich, 2013; Mac-Donald et al., 2014; Purpura, Fulceri, Puglisi, Masoni, and Contaldo, 2016; Sipes, Matson, & Horovitz, 2011). For these reasons, the detection of early motor abnormalities may be useful to diagnose later social impairments (Fournier et al. 2010; Kindregan, Gallagher, & Gormley, 2015; Kovaniemi et al., 2018).

To date, a single early motor marker as a universal sign or prodrome for ASD has not been identified. Findings in this field are mixed reflecting the heterogeneity of the motor markers measurements. Some studies approached the analysis of motor development through parental reports (Matson et al., 2010a), others assessed directly the motor skills using developmental tests (Landa & Garrett-Mayer, 2006; Landa et al., 2013; Libertus et al., 2014) or specific motor batteries (e.g., the Movement Assessment Battery for Children, Green et al., 2009; Whyatt & Craig, 2012; the Peabody Developmental test, Jasmin et al., 2009; Provost et al., 2007; Fulceri et al., 2015). Other studies measured walking/prehension movement using the kinematic analysis (Campione et al., 2016; Eggleston et al., 2017; Glazebrook et al., 2006) or the electronic balance board (Travers et al., 2013; Stins et al., 2015).

We are going to illustrate the most relevant findings on motor impairment in children with ASD according the following schema:

Section 2.1 Motor abnormalities in children with ASD. This section gives an overview of the literature on motor abnormalities that may appear in children with ASD. The full spectrum of the potential motor abnormalities is presented across three broad categories: gross motor skills, fine motor skills and restricted and repetitive behaviors (RRBs).

Section 2.2 Early motor development in infants later diagnosed with ASD. The present section describes the early motor signs detected in infants and toddlers that were later in time diagnosed with ASD.

Section 2.3 Early motor markers in siblings at risk for ASD. Finally, this section defines the importance of investigating motor disturbances in siblings of children with ASD defined as high risk infants.

2.1 Motor abnormalities in children with ASD

The assessment of motor skills in children is a research and clinical challenge because the young children may not be able to comply with structured instructions given their not yet fully developed cognitive and language skills. Despite this limitation, some interesting results on motor skills in preschoolers have been found. Provost and colleagues (2007) documented gross and fine motor impairments in toddlers with ASD (21-41 months), especially in the Locomotion and Visual-Motor Integration subscales of the Peabody Developmental Motor Scale-2 (PDMS-2; Folio and Fewell, 2000). The levels of motor functioning in children with ASD were significantly lower than expected for age even if not significantly different from the scores of matched for gender and chronological age children with Developmental delay (DD). Using a similar methodological approach, Jasmin and colleagues (2009) confirmed the presence of motor disorders in preschoolers with ASD aged from 3 to 4 years old. The authors detected a gross motor impairment in the 63% of the sample and a general delay of fine motor skills in the 53% of the sample and they identified the locomotion, object manipulation and grasping as the most impaired skills.

Grasping and locomotion skills have been found to be the most vulnerable motor areas in a sample of Italian preschoolers with ASD aged 30 - 60 months, using the PDMS-2 test (Fulceri et al., 2015). Motor impairment in children with ASD and its correlation with developmental and clinical features of ASD was explored in the study by Fulceri and collaborators (2015). Thirty-five male preschoolers with ASD completed the PDMS- 2 and were assessed in a multidisciplinary setting that included a medical examination, standardized assessment of the cognitive profile, investigation of the autistic symptomatology using the Autism_Diagnostic_Observation_Schedule (ADOS-G; Lord, 2000), and parental interview on child's adaptive skills. Results revealed that locomotion and grasping are the most impaired skills in children with ASD and motor development

may be detected at preschool age. These findings suggest that professionals must assess motor skills in preschoolers with ASD in addition to other developmental skills.

A recent review (Moseley & Pulvermüller, 2018) found that motor dysfunction in children with ASD occurs very often. The review analyzed the findings of 49 studies, and included studies with the following inclusion criteria: control sample matched for chronological and/or mental age and/or Intelligence Quotient (IQ) with their ASD peers, and samples with more than 30 individuals for each group (Abu-Dahab, Skidmore, Holm, Rogers, & Minshew, 2013; Ament et al., 2015; Dewey, Cantell, & Crawford, 2007; Dowell, Mahone, & Mostofsky, 2009; Duffield et al., 2013; Dziuk et al., 2007; Floris et al., 2016; Sumner, Leonard, & Hill, 2016; Travers et al., 2015). These findings confirmed a 41 studies previous meta-analysis reporting that TD participants were significantly outperforming motor coordination, arm movements, gait and postural stability scores of individuals with ASD (Fournier, Hass, Naik, Lodha, & Cauraugh, 2010). In addition, numerous types of motor development disorders have been reported in children with ASD such as deficits in gross and fine motor areas, motor coordination, postural control and standing balance (Esposito et al., 2011; Fournier et al., 2010; Travers et al., 2013; May et al., 2016).

Gross motor skills

Gait patterns alterations has been consistently observed in children with ASD, but it is still not clear how walking differs between children with and without ASD. In a recent review, Kindregan and colleagues (2015) identified 11 studies investigating gait patterns in children with ASD aged 4–18 years. The most consistent finding was that individuals with ASD showed abnormalities in step width (Nayate et al., 2012; Nobile et al., 2011; Shetreat-Klein, Shinnar, & Rapin, 2014), and in stride length (Nayate et al., 2012; Nobile et al., 2011; Rinehart et al., 2006). In addition, Vilensky, Damasio, and Maurer (1981) showed that children with ASD had a reduced stride lengths and knee extension, increased stance times and hip-flexion at toe-off, and ankle dorsiflexion at ground contact. The authors suggested that gait in children with ASD could resemble those of Parkinsonian patients and may be related to a specific dysfunction of the motor system involving the basal ganglia. In contrast, Hallett et al. (1993) measured a standard velocity of gait, step length, cadence, step width, stance time and vertical ground reaction forces in five adult patients with ASD. The only significant abnormality was the decreased range of ankle's motion. The velocity of the gait and the step length at average range suggested a motor dysfunction of the cerebellum.

The kinematic analysis of the gait provides a quantitative assessment of the locomotion and postural control taking into consideration different motor features integrated into the same locomotor act. The motor features consisting on one hand in basic motor skills, assessed by gait parameters; parameters related to such as equilibrium, body orientation and postural control, and, on the other hand, in motor planning of a goal-directed behavioral parameters, evaluated as the ability to define the best trajectory to reach the goal (Nayate, Bradshaw & Rinehart, 2005; Nobile et al., 2011). Vernazza-Martin and colleagues (2005) investigated basic gait parameters such as equilibrium, body orientation parameters, and walking orientation towards an experimenter-imposed goal in nine children with ASD and six typical controls aged 4 to 6 years, using the kinematic analysis of gait. Results showed that the main components

affected in children with ASD during locomotion were the orientation towards goals and the definition of trajectories (i.e., planning of movements) and not the gait parameters or the balance control. These data suggested that the prefrontal, parietal cortex and other structures may be involved in the compromised motor components. The authors did not investigate the cognitive level of functioning and its possible contribution to the impairment of movements' planning. In addition, difficult to measure using qualitative analysis, even with an expert clinical examination, were the abnormalities in the muscular tone, motor controls, praxes, and postural control.

Rinehart and collaborators (2006a; 2006b) used quantitative and qualitative analysis of gait to investigate motor function in two groups of children with ASD and without intellectual disabilities (ASD group one: children aged 4 to 6 years; ASD group 2: children aged 6 to 14 years). On one hand, regarding the quantitative analysis, the first group of children with ASD, aged 4 to 6 years, showed greater difficulty walking along a stride line and greater stride-length and stride-time variability than the control group. On the other hand, with regard to the qualitative analysis, the children with ASD appear to be uncoordinated and less smoothed in movements, with postural abnormalities in the head and trunk. In the same direction, the second group with ASD, aged 6 to 14 years, had significantly greater stride length variability compare to the typical developing control group. Qualitative analysis showed abnormal arm posturing, and lack in motor smoothness. The authors underlined the stability of abnormal gait features across developmental periods and suggested the involvement of both cerebellar and front- striatal basal ganglia regions.

More recently, Nobile and colleagues (2011) investigated the linear gait parameters upper body kinematic parameters, walk orientation and smoothness using an automatic motion analyzer in 16 children with ASD (mean age and standard deviation (SD): 10.56 ± 2.50 years; range: 6 - 14 years) and 16 controls without ASD (mean age and SD: 9.99 ± 2.28 years; range: 6 - 14 years). The authors observed a trend towards slower gait velocity that might reflect the presence of compensatory strategies that help to maintain balance control. Overall findings revealed that children with ASD had and impaired walking modality on a wide variety of motor parameters confirming the presence of basic and complex motor dysfunction in the ASD condition. In addition, it was hypothesized a complex motor dysfunction involving both the cortical and the

subcortical area or a deficit in the integration of the sensory-motor information within the motor networks (i.e., anomalous interconnections in the frontal-cerebellum-thalamo-frontal network). The movements impairments in individuals with ASD may involve not only basic motor skills such as linear gait parameters, but also motor control strategies based on the processing and integration of sensory-motor information (Nobile et al., 2011). Biffi and colleagues (2018) have recently investigated the gait pattern of school-aged children with ASD compared to TD peers using some novel advanced technologies that use treadmills together with virtual reality environments and motion capture systems. In the Biffi's study, gait analysis was carried out in an immersive virtual environment. In particular, each participant was exposed to trials with a discrete gait perturbation and various gait peculiarities have been detected in children with ASD compared to TD peers.

Gross motor function includes the ability to maintain the body position and to move around by changing body position. Thus, the achievement of **postural control** plays a pivotal role in the child's development (Mijna Hadders-Algra, 2018). A well-functioning postural control system is important for walking (Horak 2006), and evidences suggest that children with ASD exhibit difficulties with postural control (Nickel, Thatcher, Keller, Wozniak, & Iverson, 2013; Memari, Ghanouni, Shayestehfar, & Ghaheri, 2014). It has been reported that children with ASD demonstrated larger excursions in postural sway than controls in quiet standing (Fournier, Amano, Radonovich, Bleser, & Hass, 2014; Memari, Ghanouni, Shayestehfar, Ziaee, & Moshayedi, 2014; Minshew, Sung, Jones, & Furman, 2004). Findings in this field, vary depending on the afferent inputs: the addition of a visual or auditory input; the absence of vision or the modification of somatosensory cues (Greffou et al., 2012; Kohen-Raz, Volkman, & Cohen, 1992; Minshew, Sung, Jones, & Furman, 2004; Molloy, Dietrich, & Bhattacharya, 2003; Travers, Powell, Klinger, & Klinger, 2013).

Lim, Partridge, Girdler, and Morris (2017) recently reviewed the literature to compare the effect of different sensory conditions on static standing postural control between individuals with ASD and TD individuals. The 19 studies meta-analysis indicated a large difference in postural control between groups across all the sensory conditions revealing sensorimotor and multiple sensorial processing deficits in individuals with ASD. Moreover, it has been suggested that the type of sway used by children with ASD

to maintain balance is different from the sway in TD children: the clinical sample appeared to have a greater instability in the medial-lateral axis compared their controls, who were more unstable in the anterior-posterior axis (Downey & Rapport, 2012; Lim, Partridge, Girdler, & Morris, 2017). Memari and colleagues highlighted that it is not possible to write definitive conclusions could on determinants of the posture due to the heterogeneity of ASD groups studied (Memari, Ghanouni, Shayestehfar, & Ghaheri, 2014). Their review suggested that clinical and demographical variables (i.e., the severity of the disorder, the level of IQ, the co-occurrence of other psychiatric or neurological disorders, and the socio-demographic variables) along with the general motor impairments might contribute to postural control patterns in children with ASD. The large magnitude of postural sway in standing, combined with increased step width and variation in stride length during walking in individuals with ASD, implies a global impairment of postural control.

Even if different hypothesizes have been advanced to explain the impairment in postural control in the ASD condition (Fournier et al., 2010; Mostofsky & Ewen 2011; Iwanaga, Kawasaki, & Tsuchida, 2000; Marco et al. 2011), the mechanism underlying remains uncertain.

Fine motor skills

Fine motor function is the ability to reach, to lift, carry, and manipulate object. Typically, these actions are performed by the upper extremities and often involve a transport component that moves the hand from the starting position to the object (reaching) and a manipulation component in which the object is grasped (manipulation) (Mijna Hadders-Algra, 2018).

Impairments in fine motor skills and differences in the manual dexterity performances have been detected in children and adolescents with ASD using the Movement Assessment Battery for Children (Movement ABC-2) or other motor skills standardized instruments (Green et al., 2009; Hilton et al., 2007; Liu & Breslin, 2013; Whyatt & Craig, 2012; Purpura, Fulceri, Puglisi, Masoni, & Contaldo, 2016). Different studies that used the Peabody Developmental Motor Scales- 2 edition (PDMS-2; Folio and Fewell 2000) revealed poor fine motor skills in children with ASD such as specifically handling, grasping and visual-motor tasks (Jasmin et al., 2009; Provost et al., 2007; Fulceri et al., 2015). Impairments in fine motor skills may affect learning in every day actions such as grooming, dressing, writing, and using implements (Jasmin et al., 2009). Moreover, through fine motor activities children explore the world (David, Baranek, Wiesen, Miao, & Thorpe, 2012). Indeed, disturbances in these skills may affect the children's ability to play, explore, use tools, and engage in social relationships. The development of sensorimotor skills also relies on grasp objects and manipulate skills allow children to explore physical features of the objects (Sacrey et al., 2015). This panorama suggests that the atypical object exploration modality observed in infants (12 months-old) later diagnosed with ASD is particularly relevant (Ozonoff et al., 2008). Indeed, typical developing infants are able to grasp objects, observe, feel the texture with the touch, and place objects in their mouth to taste it. In this direction, Gernsbacher, Sauer, Geye, Schweigert, and Hill Goldsmith (2008) investigated the retrospective parent reports of oral- and manual-motor skills from primary caregivers of children with ASD (n = 172) and TD children (n = 44) suggesting that impaired oral-motor

abilities and manual-motor abilities could differ between children with ASD and TD children during infancy and toddlerhood.

The ability to plan, execute, and monitor ongoing movements is fundamental in order to complete goal directed movements (Schmitz, Martineau, Barthélémy, & Assaiante, 2003). Sacrey, Germani, Bryson, and Zwaigenbaum (2014) have reviewed literature findings in ASD population on motor planning that used reaction times and reach to grasp tasks, motor execution measured by grasping tasks, and motor control that used load-lifting tasks, adaptation tasks, and motor knowledge. Overall, their findings suggested that motor planning, motor execution and motor correction are impaired in children with ASD (Sacrey, Germani, Bryson, and Zwaigenbaum 2014). Children with ASD showed longer reaction times (i.e., the time taken by children to elaborate a motor plan) (Mari, Castiello, Marks, Marraffa, & Prior, 2003; Glazebrook, Elliott, & Szatmari, 2008; Nazarali, Glazebrook, & Elliott, 2009), they showed more variable reaction times (Dowd, McGinley, Taffe, & Rinehart, 2012), and more variable end-points (Papadoupolus et al., 2012) compared to the control group, suggesting the presence of impairment in motor planning. It should be noted that the high variability of reaction times has also been reported in children with Attention Deficit Hyperactivity Disorder (ADHD; Epstein et al., 2011).

Children with ASD may present symptoms referring to the ADHD symptomatology (Carpenter, Loo, Yang, Dang, & Smalley, 2009; Grzadzinski et al., 2011; Nijmeijer et al., 2009; Sinzig, Morsch, Bruning, Schmidt, & Lehmkuhl, 2008). To date, the research on potential indicators of later ADHD symptomatology, detected using the motor domain indicators during infancy, is scarce (Kern et al., 2015). Early motor indicators of ADHD, if present, are non-specific, and therefore not yet useful in the clinical screening. Spontaneous motility seems to be a promising measure for early ADHD detection, although further studies with large cohorts are needed to determine its clinical role in populations at risk of having ADHD (Athanasiadou et al., 2019).

Little is known about the neurophysiological and functional mechanisms that underlie motor deficits in children with ASD, but one current hypothesis is that the impairments in hierarchical action planning have a relevant role (Gowen & Hamilton, 2013). In the functional hierarchy of goal-directed behavior, the final goal of an action is the selection of an immediate goal in order to support a smooth and integrated

organization between subsequent movements (Rosenbaum, Vaughan, Barnes, & Jorgensen, 1992; van Schie & Bekkering, 2007). Moreover, a movement is planned effectively when begin an action with an uncomfortable grasp, but end it with a comfortable grip. Hughes (1996) revealed that children with ASD tended to not plan a series of movements resulting in a comfortable end-grasp posture suggesting impairments in simultaneous representation and coordination of multiple consecutive actions. The same impairment may account for the deficits in identifying other's intentions toward objects rather than to note only the merely final effect of the visible action. One example of this impairment may be that the child fails in the interpretation of the intention to phone when a phone is reached, and tends to see only the physical contact with the phone (Boria et al. 2009; Sacrey, Germani, Bryson, & Zwaigenbaum, 2014). However, van Swieten and colleagues (2010) did not confirm the presence of a motor planning impairment in children with ASD, but they suggested that a task that encouraged a comfortable hand posture reflected motor experience rather than predictive planning.

Internal models for actions provide a prediction of the upcoming sensory consequences of actions and use deviations from what was expected to be generated as new motor commands that allows to reach the anticipated goals (Wolpert and Flanagan 2001; Gowen & Hamilton, 2013). Internal models seemed able to support the functional integration between the perception and the action (Wolpert and Flanagan 2001; Gazzola and Keysers 2009). Forti and colleagues (2011), using a grasp and place task, found that children with ASD (mean age: 3.5 years) needed more time to complete the movements and were faster at the movement terminus. Although children with ASD accurately performed the task, they made corrections at least once after reaching the goal. This pattern may be indicative of their difficulty in anticipating the perceptual consequences (Gowen & Hamilton, 2013). In a similar study, Stoit, van Schie, Slaats-Willemse, and Buitelaar (2013) revealed that movement reaction times were significantly longer for children with ASD compared to TD children and no differences in the initiation errors or time to respond were observed.

Schmitz, Martineau, Barthélémy, and Assaiante (2003) had previously advanced that children with ASD are impaired in generating feed-forward predictions. They investigated children's ability to make anticipatory postural adjustments revealing that

children with ASD primarily used feedback rather than a feed-forward motor control. Feed-forward movements rely on internal models for accuracy and do not require the online use of sensory feedback evolving during the action (Sacrey et al., 2014). A similar deficit in feed-forward modeling has been observed to negatively affect the spoon's use anticipation in feeding behavior reported by Brisson, Warreyn, Serres, Foussier, and Adrien-Louis (2012) in infants aged between 4 and 6 months later diagnosed with ASD. Mari et al. (2003) suggested that the deficit in the simultaneous and coordinated activation of independent motor components also emerged at the level of single-step motor acts. The authors reported that children with ASD presented the reaching and grasping kinematics uncoupled movements and executed them in a successive non-overlapping manner. Moreover, the "lower functioning" group (IQ ranging between 70–79 scores) showed a desynchronization between the reaching and grasping components, whereas the "higher functioning" group (IQ ranging between 80–109 scores) demonstrated closely integrated and overlapping movements. These results highlight the importance of including IQ and/or developmental matched controls to determine the specificity of ASD movements' patterns.

Joint action is defined as "form of social interaction in which two or more individuals coordinate their actions in space and time to bring about a change in the environment" (Knoblich & Sebanz, 2008; Sebanz et al., 2006). In everyday life, we do several actions requiring the movements coordination with other individuals. Two different types of coordination may occur when people act together: emergent and planned coordination. Emergent coordination occurs spontaneously between individuals who have no plan to perform actions together. Planned coordination arises when individuals plan their actions toward others' actions in order to reach a shared goal, and strongly implies the use of shared intentions (Knoblick and Sebanz, 2008; Knoblich et al., 2011). The ability to smoothly coordinate actions with others gradually develops during childhood, from early imitative interactions that play a crucial role in social development to more complex joint actions (Meltzoff and Moore, 1983; Meyer, Bekkering, Paulus & Hunnius, 2010). This ability to smoothly coordinate with each other's during a joint action implies that an individual should present a range of motor and social cognitive competencies: joint attention, turn-taking, goals and intentions sharing, actions understanding, motor planning, and predictive abilities. All these

competencies are based on the sensory-motor processes emerging very early in life (Falck-Ytter et al., 2006; Yu & Smith, 2013; Zoia et al., 2007). Recently emerged a new research field which studies the interplay between sensory-motor processes and social competencies, particularly in those people with early impairment in their ability to establish appropriate social interactions, as occurs in people with ASD (Cerullo, Fulceri, Muratori, Contaldo: under revision).

Castiello and collaborators (2010) described that the propensity to interact with others is present before birth. The authors studied the kinematics of movements of twin fetuses using four-dimensional ultrasound at the 14th and the 18th gestational week. Results showed that already at the 14th week twin fetuses display movements toward the co-twin and these movements increased between the 14th and 18th week range. The kinematics of movements toward the co-twin are different from those directed to the uterine wall because they are longer, have a prolonged deceleration time and a higher degree of accuracy. This study has shown that the social actions already appear in the second trimester of pregnancy, and provided important information about the social dimension of motor planning and control in fetal life. Some hours after birth, newborns socially interact by imitating adult facial gestures (Meltzoff & Moore, 1983). During infancy, the ability to coordinate a common focus of attention with another person (joint attention), share goals, intentions, and psychological states and engage in cooperative action gradually develops.

The fundamental ability to coordinate one's own actions with those of others develops considerably within the first three years of life (Brownell et al., 2006). Importantly, social development is based on the maturation of those sensory-motor systems. The sub sequential development of higher cognitive skills such as inhibitory control, cognitive flexibility, and perspective-taking, play an important role in integrating the actions of others toward an action plan and in adjusting one's action plans to one's partner. A simplified image of this process is shown in Figure 1.

Fig.

Figure 1 Joint action's developmental milestones.

A growing body of research on ASD revealed difficulties in sensory-motor processes (Cook, 2016; Downey & Rapport, 2012; Paquet et al., 2016) and recent literature focusing on bidirectional process during interaction between people with and without ASD emphasize the role of sensory-motor processes that consequently guide and determine the social interaction (Brewer et al., 2016; Cook, 2016). The monitoring process determines to what extent a task goal is being achieved or whether actions are unfolding as wanted. Predictive mechanisms allow the agents to smoothly interact with each other. Kinematics is very important for the simplifying coordination. An exemplification of the simplifying coordination is shown in Figure 2.

Fig

Figure 1 Simplified mechanisms of joint action coordination.

In order to interact and coordinate actions with other individuals should share a common goal (i.e., “what”), engage in joint attention (i.e., “where”) and predict the timing of the other’s actions and finally, plan their own actions in order to achieve a temporal coordination (i.e., “when") (Sebanz & Knoblich, 2009). Prediction in successful joint actions relies on the a priori knowledge about the action’s goal and on the movement’s kinematic features (Cuijpers, van Schie, Koppen, Erlhagen, & Bekkering, 2006; Kilner, Friston & Frith, 2007). Observing kinematics helps us to understand the actions of others (Stapel, Hunnius & Bekkering, 2012). Moreover, kinematics guides the co-actors in predicting the temporal and spatial aspects of the joint action in order to coordinate accurately with each other. Some evidence of intact goal-directed imitation in children with ASD have been observed, together with a failure to use kinematic cues to predict other’s actions. This pattern has been suggested to be the key sensorimotor problem in this population (Gowen, 2013).

To date, only few studies have investigated joint action coordination in children with ASD. Some studies reported that individuals with ASD are able to coordinate their actions with others and share common goals (Fitzpatrick, Diorio, Richardson, & Schmidt, 2013). They can also understand the goal of others and help them to achieve them (Liebal, Colombi, Rogers, Warneken, & Tomasello, 2008). However, impairments emerge when the task difficulty increases (Dowd, McGinley, Taffe & Rinehart, 2012;

Glazebrook et al., 2008). It is possible that people with ASD show impairment in planning their movements considering the other's motor plans (Gonzales et al., 2013; Sharoun & Bryden, 2016). Moreover, they perform poorly in cooperative tasks compared to children with developmental delay, (Liebal et al., 2008; Colombi et al., 2009) and this deficit seems to be linked to imitation and joint attention impairments (Colombi et al., 2009).

Recently, Fulceri and colleagues (2018) explored whether children with ASD fail to use kinematic information during joint actions. They enrolled eleven children with ASD and eleven typically developing (TD) children assessed for interpersonal motor coordination during a joint action task. Participants performed two cooperative tasks that were implemented by the authors. In the first test called Clear End- Point, children received a priori information on movement end-point. In the second test called Unclear End-Point, the end-point was unknown and the children had to use kinematic cues in order to accomplish shared goal. Findings revealed no between-group differences in the first task, even if children with ASD displayed greater reaction time variability. In the second task, children with ASD showed less accurate and slower movements compared to the TD children. Moreover, the ASD movement features did not differ between the two tasks. Contrarily, the TD children showed reduced reaction time variability and less number of errors in the second task. In conclusion, children with ASD appeared to be impaired in joint action coordination when they had to rely only on kinematic information, suggesting that they were not able to pay additional attention to the kinematic cues in absence of a visual goal.

Repetitive behaviors

The presence of repetitive behaviors (RRB) is currently a diagnostic criterion of ASD (DSM5; APA, 2013). There is evidence that young children later diagnosed with ASD demonstrated RRBs toward objects, body, and sensory behaviors more frequently and for more extended periods of time compared to age-matched TD children (Watt, Wetherby, Barber, & Morgan, 2008). Moreover, higher frequency and greater diversity of RRB in young children with ASD compared age-matched TD have been recently detected (Harrop, McConachie, Emsley, Leadbitter, & Green, 2013). Some studies suggest that RRB may be among the earliest behavioral manifestations of ASD (Kim & Lord, 2010; Ozonoff et al., 2008). Ozonoff et al. (2008) reported atypical way of object exploration in one-year-old children subsequently diagnosed with ASD, whereas Wolff et al. (2014) observed, in 12-month-old infants, a broad range of repetitive behaviors frequently occurred in toddlers who will receive an ASD diagnosis.

Even if data have not yet replicated, some studies reported that certain RRBs could be ASD-specific, since TD children rarely roll or wobble objects, or demonstrate careful placement of objects or spinning objects (Barber, Wetherby, & Chambers, 2012; Watt, Wetherby, Barber, & Morgan, 2008). Wetherby and colleagues (2004) highlighted the warning role of repetitive actions with objects and repetitive movements of the body/arms/hands as a red flag for the ASD diagnosis in the second year of life. Recent findings suggest that bilateral Repetitive Movement Episodes (RMEs), might differentiate infants with ASD from infants with DD and TD aged between 6 and 12 months with a satisfactory diagnostic efficiency (i.e., higher in infants with ASD) (Purpura et al., 2017). No significant difference was found between the distributions of unilateral RMEs between ASD and DD/TD. Thus, the presence, at an early age, of ASD-specific pattern such as bilateral repetitive movements might suggest a continuum between this pattern and the lack of variability in finalized and communicative movements and gestures observed in children with ASD at the second year of life.

Despite their strong diagnostic significance, most of the research on ASD core symptoms has been directed to explore the social- communicative impairment rather than the RRBs and therefore RRBs profiles, and associated features that were not fully elucidated. The lower interest for RRBs could be primarily due to their supposed poor specificity and underestimated diagnostic role in the ASD profile. RRBs are not unique to ASD, but are evident in other clinical populations and in TD individuals (for reviews see: Langen, Durston, Kas, van Engeland, & Staal, 2011; Leekam, Prior, & Uljarevic, 2011). Moreover, according to the DSM-IV-TR (American Psychiatric Association, 2000), RRBs were not mandatory, but just ‘‘possible’’ feature in the large Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS) category.

Recently, repetitive behaviors have been explored in a relatively large sample of children with ASD (Fulceri et al., 2016). The Italian version of the Repetitive Behavior Scale-Revised (RBS-R; Bodfish, Symons, Parker, & Lewis, 2000) was applied to 79 preschool-aged children with ASD who underwent a comprehensive clinical assessment at IRCCS Stella Maris Institute. The relationship between RRB and sex, age, non- verbal IQ, autism severity, as well as the diagnostic accuracy of the RBS-R were explored. Findings revealed that Stereotyped and Ritualistic/Sameness behaviors were the most common RRBs in preschoolers with ASD, without widespread differences between males and females. No significant correlations between RRBs and chronological age, or non-verbal IQ were detected. The expressiveness of ritualistic/sameness behaviors positively correlated with autism severity, assessed through the Calibrated Severity Score derived from the ADOS (Lord, 2000). Finally, the scores on RBS-R of the ASD sample were compared with those of 79 TD controls. The Receiver Operator Characteristic (ROC) analysis showed high diagnostic accuracy using the Global Rating Score, which represents the judgment of the parents given the impact of RRBs on the child’s life.

Recent findings seem also to suggest that the RRB severity may be related to the severity of motor problems the motor skills in individuals with ASD (Purpura et al., 2016). Indeed, using the Movement Assessment Battery for Children – 2 edition Checklist (Henderson, SugdeN & Barnett, 2007), motor skills abilities were assessed in a sample of 22 Italian children with a diagnosis of ASD (aged between 5 and 13.5 years). Findings revealed that over the 70% of the sample has motor difficulties and poorer performance

was related to higher frequency and intensity of repetitive and stereotyped behaviors assessed through the RBS-R).

Regarding the relationship between motor impairment and RRBs or other clinical features of ASD, the literature data are not still conclusive. Both the different methodological approaches assessing motor skills and the heterogeneity of the clinical features of the participants analyzed have been implicated as contributors for mixed results. First, different studies have examined motor skills through various instruments (Wilson et al., 2018) including home-video analysis (Gernsbacher et al., 2008; Ozonoff et al., 2008; Phagava et al., 2008; Zappella et al., 2015), parent reports (Kopp et al., 2010; Hedgecock et al., 2018; LeBarton & Iverson, 2013), developmental tests (Landa & Garrett- Mayer, 2006; Landa et al., 2013; Libertus et al., 2014), specific motor batteries as the Movement Assessment Battery for Children (Green et al., 2009; Whyatt & Craig, 2012) and the Peabody Developmental test (Jasmin et al., 2009; Provost et al., 2007; Fulceri et al., 2015), kinematic analysis during walking or prehension movement (Campione et al., 2016; Eggleston et al., 2017; Glazebrook et al., 2006) and electronic balance board (Travers et al., 2013; Stins et al., 2015). Secondly, some studies enrolled infants and young children (Esposito et al., 2009; Phagava et al., 2008; Jasmin et al., 2009; Landa & Garrett-Mayer, 2006; Provost et al., 2007), whereas others involved school-aged children, adolescents, and adults (Green et al., 2009; Staples & Reid, 2010; Minshew et al., 2004). Moreover, some studies enrolled children without intellectual disabilities (MacDonald et al., 2013; Miller et al., 2014) whereas others enlisted children with a wide range of cognitive functioning (Fulceri et al., 2015; Green et al., 2009; Vanvuchelen et al., 2007). In this regard, it has been reported that lower intellectual functioning may be related to reduced motor skills (Dowell et al., 2009; Dziuk et al., 2007; Green et al., 2009; Hilton et al., 2012; Mari et al., 2003; Fulceri et al., 2015; Vanvuchelen et al., 2007).

The largest meta-analysis on this issue to date (Fournier et al., 2010) was unable to determine the impact of intellectual functioning on motor skills. Analogously, the relationship between motor impairments and language abilities in children with ASD has not been yet clarified. The observation of motor impairments in children with poor language skills has been associated with the coexistence of intellectual impairment (Moseley and Pulvermuller, 2018). The interconnection between motor and language

skills during development has been clearly defined in TD children (Libertus & Violi, 2016), and this evidence may be relevant also for children with ASD (Bedford et al., 2015; Kim, 2008; Srinivasan & Bhat, 2016). indeed, studies on infants at high familial risk for ASD (infants who have an older sibling with a diagnosis of ASD) revealed that the level of fine motor skills in the first years of life was able to predict the language development (LeBarton & Iverson, 2013; Garrido et al., 2017). Finally, the degree of ASD severity has been found to be related to the severity of motor problems (Hilton et al., 2012; Jasmin et al. 2009; MacDonal et al. 2013; Purpura et al., 2016), even if contrasting data have been reported (Fulceri et al., 2015; Zachor et al., 2010). It has to be noted that the traditional statistical analysis approach performed in these mentioned studies are not free of criticisms due to the heterogeneity in clinical expression of ASD (i.e., different degree of symptoms severity along with various co-morbidities).

These research issues have been recently supplied through an innovative approach (Fulceri et al., 2018). A dataset including data on both motor and clinical features of a sample of children with ASD has been analyzed through the Artificial Neural Networks (ANNs) approach. ANNs are computational adaptive systems inspired by the functioning processes of the human brain particularly adapted to solve non-linear problems (Krogh, 2008; Manning et al., 2014). The findings revealed that poor motor skills were a common clinical feature of preschoolers with ASD, correlated with the high level of repetitive behaviors and the low level of expressive language. Moreover, in the study by Fulceri and collaborators (2018) unobvious trends among motor, cognitive and social skills have been detected. Since the ANNs is based on an adaptive learning style, this technique appears to be a powerful tool for data analysis also in the presence of relatively small samples (Buscema et al., 2015).

2.2 Early motor development in infants later diagnosed with ASD

Motor delays or impairments have repeatedly been reported in infants and toddlers later diagnosed with ASD. Different types of instruments have been administrated to measure motor skills in infancy and childhood as parent report, standardized assessments, and behavioral coding schemes (Matson et al., 2010a; Landa & Garrett-Mayer, 2006). Different methodological approaches may partly explain some of the variability in findings. Gillberg and colleagues (1990) suggested that before the age of 3 years, children with ASD have intact motor skills, despite their lower IQ profile. Indeed, motor quotients of children with ASD enrolled in this study were 15 points higher than their IQ scores. However, findings that show that motor abilities of the ASD children were within the normal range have to be considered in light of the fact that the exact motor quotients were not reported, and 16 of the 20 children with ASD had an IQ lower than 70, with nine children having a score lower than 50 (Provost et al., 2007).

Using a retrospective clinical record review, Ming and colleagues (2007) showed that a cohort of 154 children with ASD had a delay in walking. Matson and colleagues (2010a) observed significant differences in the attainment of milestones between toddlers with Autistic Disorder, PDD-NOS and atypical development (1044 participants) using a parental questionnaire. Differences between groups emerged in the age of the first word and the onset of crawling, but no for walking or first phrase. More recently, Shetreat-Klein, Shinnar, and Rapin (2014) retrospectively recorded the age at walking suggesting that children with ASD attained independently walking on average 1.6 months later than age- and gender-matched TD peers. Moreover, children with ASD had significantly greater joint mobility and higher gait abnormalities compared to peers. Lloyd et colleagues (2013) founded that motor milestones of children with ASD fall within the typical ranges for children without developmental disabilities (ASD sitting: mean age of 7.19 months; ASD walking: mean age of 13.73 months; children without

developmental disabilities walking: 12–18 months; children without developmental disabilities sitting: 6–9 months), using the Autism Diagnostic Interview-Revised (ADI-R, Rutter, 2003). However, comparing the gross motor and fine motor skills of a cross-sectional group of 162 children with ASD (12–36 months) through the Mullen Scale of Early Learning (MSEL), the authors showed that the gross motor age equivalents for all the children in each age group were below the expected chronological age level. Moreover, 58 children with ASD were longitudinally assessed over two-time points (approximately 12 months apart) suggesting that the differences between chronological age and gross motor age equivalent increased progressively from 12 to 36 months. Previously, Matson and colleagues (2010b) observed that children with ASD have significantly lower fine and gross motor scores compared to a group of 168 TD children through the administration of the Battelle Developmental Inventory, 2nd Edition (BDI-2; Newborg, 2005).

Interesting findings also emerged in the retrospective examination of home videotapes of children later diagnosed with ASD. Assessing the home videos of 11 children with ASD at 9–12 months of age, Baranek (1999) found subtle yet salient sensory-motor deficits, including excessive mouthing of objects. Again, using home videotapes analysis, Adrien and colleagues found hypotonia, hypoactivity, and unusual postures in children later diagnosed with ASD while Teitelbaum and colleagues (1998, 2004) observed disturbances of movement at 4–6 months age and aberrant motor patterns, including persistence of primitive reflexes and delays in head righting reactions. Ozonoff and colleagues (2008) examined the early trajectories of motor development in infants later diagnosed with ASD. Findings revealed that the ASD group showed a slower rate of development of walking, supine lying and sitting compared to the TD group even if no differences emerged in the number of movement abnormalities or a in the presence of protective reactions.

Aside from delay in milestones, static and dynamic postural asymmetries have been detected in infants with ASD (Esposito et al., 2009; Esposito et al., 2011). Esposito and colleagues (2009) retrospectively examined videotapes of infants aged 12 to 21 weeks and showed a more significant presence of static and dynamic asymmetries in laying in infants later diagnosed with ASD compared to two control groups: infants with TD and DD. Additionally, Esposito and Venuti (2008) retrospectively investigated

through video analysis the first unsupported gait in 20 toddlers with ASD (mean age: 14.2 months) compared to that of 20 toddlers with TD (mean age: 12.9months) and 15 toddlers with DD of mixed etiology (mean age: 13.1 months). The authors revealed significant differences in gait patterns between ASD and the two control groups for both the Walking Observation Scale which include items that analyze gait through three axes (foot movements, arm movements and general movements) and the Positional Pattern for Symmetry during walking which analyses static and dynamical symmetry during gait.

Paquet, Olliac, Golse, and Vaivre-Douret (2016) have reviewed the literature focusing on early motor symptoms in ASD and West and colleagues (2018) have recently published a meta-analysis on motor development in ASD. Overall, findings showed that motor abilities in infants later diagnosed with ASD diverged from those of infant with TD. In detail, the meta-analysis examined data from 26 studies, which included individual data from 1,953 infants with ASD and 78,473 TD infants. It should be noted that the meta-analysis's authors included the Lemcke, Juul, Parner, Lauritsen, and Thorsen, (2013) study that explored the child development at 6 and 18 months prospectively collected from 76,441 mothers. West and collaborators (2018) reported that excluding this study, data from 1,233 infants with ASD and 2,032 infants with TD did not change the results of the meta-analysis. According to this meta-analysis (West et al., 2018), the motor development of infants later diagnosed with ASD was found to be less advanced than in neurotypical peers. The 30.7% of the included studies examined gross motor skills, the 52.5% fine motor skills, and the 16.8% were a combination of gross and fine motor skills. Three types of instruments were mainly used to measure motor skills in infants: standardized assessments (45,5%), parent report (38,6) and behavioral coding schemes (15,8%). Moreover, West (2018) highlighted that the majority of the included studies (81%) presented a gender bias with an average of 74.5% male in the ASD samples compared to the 60.3% in the TD samples. Concerning infant age, 20 studies (77%) reported the mean age for each cohort and the average age was 18.6 months for infants with ASD, and 17.9 months for TD infants.

2.3 Early motor markers in siblings at risk for ASD

Siblings of children with ASD are at increased risk (~20 %) of developing ASD compared to the 1 % rate for the general population (Ozonoff et al., 2011). The probability to receive a diagnosis of ASD in a younger sibling with an older sibling diagnosed with ASD, differs in male and female. Indeed, recurrence is more likely in a male sibling compared to a female sibling (Palmer et al., 2017).

Studies exploring at-risk infants (HR infants), consistently reported that infants who later developed ASD exhibited clinical signs starting from 12 months of age (e.g., lack of eye contact, reciprocal smiling, and social engagement). To date, no developmental differences have been reliably detected at 6 months in HR infants compared with infants who later did not develop ASD (Bölte et al., 2013). However, given the evidence of motor abnormalities in children with ASD, a growing interest has been focused on the evaluation of measures of early motor development as potential markers for early ASD detection in HR infants (Landa, Gross, Stuart, and Faherty, 2013).

Some studies revealed that HR risk infants presented motor developmental differences compared to low risk (LR) -infants (siblings of children without a diagnosis of ASD) already at 6 months of age (Bryson et al. 2007; Flanagan, Landa, Bhat, & Bauman, 2012; Iverson & Wozniak, 2007; Nickel, Thatcher, Keller, Wozniak, & Iverson, 2013). Thus, the systematic observation of motor functioning at an early age of development may be useful to indicate some impairments, even before that the ASD core deficits emerge (Libertus and Violi, 2016).

Zwaigenbaum and colleagues (2005) identified a reduced activity level in some 6-month-old HR infants diagnosed with ASD at 24 months using a parent-report questionnaire. Results indicated that by 12 months of age, HR infants later diagnosed with ASD presented a pattern of early temperament, defined by marked passivity and decreased activity at 6 months, followed by extreme distress reactions, a tendency to

fixate on objects in the environment, and decreased expressions of positive affect by the age of 12 months. Other differences emerged in the eye contact, visual tracking, disengagement of visual attention, orienting to own name, imitation, social smiling, reactivity, social interests, and sensory-oriented behaviors, delayed expressive and receptive language. Heathcock, Tanner, Robson, Young, and Lane (2015) observed fewer midline behaviors with the upper extremities and delayed motor skills in the upper-extremity in 25 HR compared to 14 LR infants at 2, 4, 6 months. Differences emerged especially at four months.

Even if very informative, retrospective works are methodologically limited since parents' reports or videotapes may be selectively influenced by parental memory and influence of the interviewers (Jones et al., 2014). Prospective studies tried to overcome this challenge by focusing on the early development through longitudinal approaches. Landa and Garrett-Mayer (2006), investigated the development of 87 HR-infants using the Mullen Scales of Early Learning (MSEL; Mullen, 1995) at 6, 14, and 24 months. Findings revealed poor motor skills in children diagnosed with ASD at 14 months with a further worsening between 14 and 24 months. Iverson and Wozniak (2007) prospectively evaluated HR and LR infants from 5 to 14 months. HR infants were delayed in the onset of motor milestones and spent significantly less time in a higher number of postures. Also, they demonstrated attenuated patterns of change in the rhythm of arm activity around the time of reduplicated babble onsets; HR infants were also highly likely to exhibit delayed language development at 18 months. Loh et colleagues (2007) examined motor behaviors in a longitudinal cohort of HR infants. Stereotypic movements and postures occurring during standardized observational assessments at 12 and 18 months were coded from videotapes and showed that at 12 and 18 months the group with ASD "arm waved" more frequently, and that at 18 months, the posture "hands to ears" was more frequent in the ASD and non-diagnosed group compared to controls. Overall, the siblings subsequently diagnosed with ASD and the comparison groups had considerable overlap in their repertoires of stereotyped behaviors. Authors suggested that more sensitive testing might be required to identify motor impairments. Bryson and colleagues (2008) prospectively assessed a sample of 9 HR infants starting from 6 months of age identifying two broadly subgroups according to the development of IQ (i.e., group one showed a decrease in IQ scores between 12 and 24-36 months,

group two continued to perform IQ scores on or near average). In all children, early impairment in social-communicative development coexisted with atypical sensory and/or atypical motor behaviors.

Brian and colleagues (2008) longitudinally assessed 155 HR infants and 73 LR infants showing that the motor control skills measured at 18 months of age predicted the later clinical ASD diagnosis using the ADOS and the ADI-R at three years of age. Ozonoff et al. (2010) examined the developmental trajectories of 50 infants classifying their development at 36 months. Diagnosis of ASD occurred in 25 infants. In detail, participants were prospectively evaluated at 6, 12, 18, 24, and 36 months of age. The authors reported that the frequency of gaze to faces, shared smiles, and vocalizations to others were highly comparable between groups at 6 months of age, but were also present significantly declining trajectories over time that emerged in the 25 infants later diagnosed with ASD. Group differences were significant by 12 months of age on most variables including scores on the fine motor subscale of the MSEL. Mulligan and White (2012) compared data on 10-minutes videotaped sensory and motor behaviors of 13 HR infants and 12 TD infants, infant-mother play sessions, and 5 minutes of spoon- feeding session at 12 months-old infants. The results indicated that HR infants had fewer movement transitions and object manipulation compared to LR infants.

Landa, Gross, Stuart, and Bauman (2012) prospectively assessed 204 HR infants with the MSEL from the age of 6 months to 36 and found that early receptive language and early motor development were vulnerable in HR infants regardless their clinical outcome. The authors underlined 4-types of development trajectories respectively characterized by 1) accelerated development (25.7% of the sample); 2) normative development with the above-average nonverbal cognitive outcome (40.0% of the sample); 3) receptive language and gross and fine motor delay (22.3% of the sample); 4) widespread delayed skill acquisition (12.0% of the sample). Children with an outcome diagnosis of ASD were spread across Types 2 (normative development), 3 (receptive language, gross and fine motor delay), and 4 (widespread delayed skill acquisition). Flanagan and colleagues (2012) evaluated the development of 40 HR infants from 6 to 36 months. In this study, a presence of head lag along with other early developmental alterations was significantly associated with ASD diagnosis at 36 months.

More recently, Lebarton and Iverson (2013) investigated whether fine motor

skills correlates with expressive language in 34 HR infants longitudinally assessed from 12 to 36 months. The authors used a parent report and a standardized observation measures to assess fine motor skills from 12 to 24 months in HR infants (Study 1) and its relationship with the later expressive vocabulary at 36 months (Study 2). HR infants exhibited fine motor delays between 12 and 24 months and expressive vocabulary delays at 36 months. Further, fine motor skill significantly predicted expressive language at 36 months. These findings have been recently confirmed by Choi, Leech, Tager-Flusberg, and Nelson (2018). Indeed, in this recent study, the authors prospectively investigated the developmental trajectories of the fine motor skills between 6 and 24 months related to expressive language outcomes using the MSEL at 36 months in 71 infants at HR without ASD diagnosis, in 30 HR infants later diagnosed with ASD, and in 69 LR infants without ASD diagnoses. Findings revealed that HR infants who later developed ASD showed significantly slower growth in fine motor skills between 6 and 24 months, compared to their TD peers. Moreover, fine motor skills at six months predicted expressive language outcomes at three years of age.

Nickel, Thatcher, Keller, Wozniak, and Iverson (2013) prospectively investigated early posture development in 22 HR infants (four were diagnosed with ASD at 36 months) and in 18 LR infants. Infants were videotaped at home at 6, 9, 12, and 14 months during everyday activities and infant postures were coded. Compared to the LR infants, HR infants were slower to develop sitting and standing positions. HR infants later diagnosed with ASD exhibited substantial delays in the arising of more advanced postures and initiated fewer posture changes. It should be noted that postural delays may impact the opportunities for infant to explore and learn from the environment (Libertus and Violi, 2016). Leonard et al. (2014) investigated the profile of motor development in HR and LR infants between 6 and 24 months. Data of the gross and fine motor scales of the MSEL and the Vineland Adaptive Behavior Scales (VABS; Sparrow, Cicchetti & Balla, 2005) were examined. LR and HR infants differed significantly on motor scales at all visits, with substantially lower motor scores in the HR group which was evident from the early age of 6 months (as assessed by a parental report), and 12 months (as measured by a standardized assessment). Later, Sacrey and colleagues (2015) prospectively investigated parents' concerns for their HR children at multiple time points in the first two years and evaluated the scores with the diagnostic outcomes

at three years. The total number of concerns predicted a subsequent diagnosis of ASD at 12 months, and the concerns regarding sensory behaviors and motor development predicted a subsequent diagnosis of ASD at 6 months, whereas concerns about social communication and repetitive behaviors did not anticipate the diagnosis of ASD until after the 12 months.

Chapter 3

Early detection of motor abnormalities in Autism Spectrum Disorder

Introduction

The overall objective of my current project is to investigate antenatal and postnatal motor development in fetuses and infants at low- and high-risk for ASD aiming to identify early predictors of ASD. The hypothesis is that assessment of motor performances may be effective in predicting abnormal outcome in infants at risk for neurological development. To this aim, two specific experiments have been planned:

- **Experiment 1**. Analysis of early motor repertoire in infants at low and high risk for ASD.
- **Experiment 2**. Analysis of fetal movements in pregnancies at low and high risk for ASD through ultrasound (US) techniques.

My experimental activities have been performed within the Network for early detection of autism spectrum disorders (NIDA) and the European project "Brainview – fetal ultrasound screening for neurodevelopmental disorders in normal and high-risk pregnancies" Marie Sklodowska – Curie actions, Innovative Training Networks (ETN), H2020 –MSCA- ETN-2014.

The NIDA network shares consolidated expertise in infant neurology and child neuropsychiatry through the involvement of the largest pediatric hospital and clinical-research centers of the Italian territory. The NIDA Network aims at identifying early risk indexes of ASD by a clinical/biological standardized protocol for monitoring in HR infants (i.e., siblings of children with a diagnosis of ASD, preterm newborns and small for gestational age newborns) and LR infants (i.e., siblings of typically developing children) between 0 to 36 months. The NIDA Network has been active since 2012 thanks to the funding of the Ministry of Health, Centre for Disease Control and Prevention and currently through the Network Project of the Directorate General of Research and Innovation in Health of the Ministry of Health, the European project BRAINVIEW, MARIE SKŁODOWSKA-CURIE ACTIONS, Innovative Training Networks (H2020-MSCA- ETN-2014), and the Italian Foundation Autism Onlus.

The NIDA network is enrolling LR and HR infants after delivery with the aim of assessing preferences for social stimuli and recording infant crying and spontaneous movements at 10 days, 6, 12, 18 and 24 weeks of age. In addition, a comprehensive clinical evaluation assessing several areas of development is provided at 6, 12, 18, 24 and 36 months of age. The NIDA partners are currently collecting prospective data on motor, vocal and interactive features to detect potential behavioral abnormalities within the first 36 months of life.

3.1 Experiment 1

Analysis of early motor abilities in infants at low and high risk for ASD

Introduction

During my PhD activities at ISS, I was involved in the analysis of the early motor abilities in infants at low and high risk for ASD within the NIDA Network under the supervision of Dr. Maria Luisa Scattoni.

Firstly, I collaborated with the Prof. Andrea Guzzetta and his staff to the analysis of early spontaneous and intentional motor movements in infants at low and high risk for ASD. In detail, I have been committed in the statistical analysis of data on infant's spontaneous movements collected by ISS and scored by the Stella Maris's staff of Andrea Guzzetta. Moreover, Dr. Jessica Tealdi trained me in the theoretical and technical aspect of the Infant Assessment of Intentional Motor Schemes (A-IAM) developed as part of the activities of the BRAINVIEW project and the Italian Ministry of Health Young Researchers' project entitled "Non-invasive tools for the early detection of autism spectrum disorders autistic". The aim of the scale is to detect the first signs of newborn's exploratory behaviors through the video recordings of spontaneous motor activity of infants at low and high risk for autism spectrum disorder (i.e. siblings of children with an autism spectrum disorder) from 10 days to 6 months of life. I am currently involved in the scoring of early intentional movements based on the analysis of video-recording collected by ISS among the NIDA Network.

Secondly, I have collaborated with Dr. Maria Bulgheroni (Ab.acus) and her staff of bio-engineers to elaborate and implement a software for the kinematic analysis of infant's movements. By MOVIDEA, I coded video-recordings acquired within the NIDA network.

Finally, under the supervision of Dr. Maria Luisa Scattoni, I reviewed the literature on motor assessment in sibling of children with ASD with the final aim to introduce in the existing NIDA clinical protocols an additional tool to assess motor development from infancy to 36 months of age (named *Early Motor Questionnaire* and described below).

In the present Chapter, a detailed description of the data collection and analysis is presented.

3.1.1 General movements and their relevance in the research field of ASD

General Movements (GMs) consist of movements in which all parts of the body participate. They emerge during early fetal life and gradually disappear when goal-directed arm movements develop between the age of 3 to 5 months corrected age. Typical general movements are characterized by complexity and variation, whereas atypical general movements exhibit a limited repertoire of movement variants (Hadders-Algra, 2018b).

Fig

Figure 2 General movements (Ferrari et al., 2002)

The earliest GMs are gross movements that involve the whole body; they may last from a few seconds to several minutes. The **writhing movements** appear early in gestation (9-10 weeks' postmenstrual age) and are the most complex of the whole repertoire of endogenously generated distinct movements. The distinctive pattern of GMs is that normal GMs presents variable sequence of arm, neck, and trunk movements. They wax and wane in intensity, force, and speed, and they have a gradual beginning and end.

Most the sequence of extension and flexion movements of arms and legs is complex, with superimposed rotations and, often, slight changes in the direction of the movement. These additional components make the movement fluent and elegant and create the impression of complexity and variability. Despite this variability, GMs must be considered as a distinct coordinated pattern that is possible to recognize each time it occurs. (Ferrari et al., 2002). The **fidgety movements** are an ongoing stream of small, circular, and elegant movements of the neck, trunk, and limbs; they emerge at 6 to 9 weeks' and disappear around 15 to 20 weeks' post-term age. Abnormal fidgety movements look like normal fidgety movements, but their amplitude, speed, and jerkiness are moderately or greatly exaggerated (Ferrari et al., 2002).

There is a consensus that GMs are a major expression of the young developing brain and, according to the current update and review of knowledge (Hadders-Algra, 2018b), the quality of general movements reflects the integrity of the complex cortical-subcortical networks in which the cortical subplate, the cortical plate (at the fidgety age)– and the connecting white matter play a dominant role (Hadders-Algra, 2017).

Fig

Figure 3 Schematic presentation of the processes underlying the subplate and cortical plate modulation hypothesis (Hadders-Algra, 2018)

GMs evaluated according to visual Gestalt perception are proved to predict cerebral palsy with a sensitivity greater than 91% and a specificity greater than 81% (Einspieler et al., 2014). Anyway, since the GMs quality reflects the integrity of extensive neural networks involving not only cortical areas, but also their connectivity with subcortical relay stations, the quality of GMs reflects the interconnective integrity of complex cortical-subcortical networks explaining why atypical GMs quality has been not only associated with cerebral palsy but also with cognitive impairment, attention-deficit-hyperactivity disorder, and minor neurological dysfunction (Hadders-Algra, 2007; Einspieler, Bos, Libertus & Marschik, 2016).

Einspieler and colleagues (2014) have recently reviewed the literature identifying an association between motor abnormality in the first 5 months of infancy and later diagnosis of ASD. Conclusions revealed that even if GMs are a diagnostic tool that has repeatedly proven to be valuable in detecting early markers for different neurodevelopmental disorders, overall data were not conclusive especially for ASD. Indeed, even if the rate of occurrence of abnormal GMs was found exceedingly high in infants later diagnosed with ASD, the author strongly recommended further prospective studies including HR population. The studies reported by Einspieler and colleagues (2014) are following described.

The retrospective study of Phagava and colleagues (2008) was performed by analyzing the family videos provided by parents of 20 children (male 17, female 3) later diagnosed as ASD and by parents of a control group of healthy children (n=20; male 10, female 10) matched for age. Findings revealed significant differences between the ASD and the control groups in both GMs and in optimality scores. In detail, during the writhing movement period, the 70.0% sequences of infants with ASD showed poor repertoire GMs whereas the poor repertoire GMs were seen in only 12.5% of the sequences in the control group. Moreover, in the fidgety movement period 20.8% of sequences of ASD group were assessed as absent fidgety movements and 29.2% as abnormal fidgety movements. Conversely, the large majority of the videos for the

control cases were scored as normal (88.9%). Finally, the optimality scores were lower in the ASD group mainly due to a lack of variable sequences, amplitude and speed of writhing GMs and an altered quality of fidgety and other spontaneous movements in the ASD group. However, some methodological limitations should be discussed as the lack of the longitudinal data (only four individuals were recorded several times), the high degree of variation in available GM trajectories, and the lack of detailed information about outcome and severity of the phenotype.

The prospective study of Hadders-Algra, Bouwstra & Groen (2009) explored the relationships between abnormal GMs and ADHD with or without psychiatric co-morbidity at school-age. 25 LR full term infants and 16 infants at high risk for neurodevelopmental disorder were enrolled evaluating the GMs (writhing and fidgety). Both parents and teachers completed a questionnaire on ADHD-like behavior, Child Behavior Checklist (CBCL) and Teachers Report Form (TRF) when the children were 9-12 years. Findings revealed that abnormal GMs were related to the presence of ADHD with psychiatric co-morbidity but not to isolated ADHD.

Recently, Zappella and colleagues (2015) suggested that abnormal GMs were the sign clearly distinguishing between individuals displaying autistic behaviors during the second year of life with and without a later diagnosis of ASD. The Authors reported that the abnormal monotonous writhing GMs in infants later diagnosed with ASD were usually followed by abnormal monotonous fidgety movements. Moreover, they suggested that the fast and exaggerated fidgety movements or monotonously slow fidgety movements with a higher amplitude seemed to be more specifically related to ASD. Even if some findings seemed to confirm previous published data (Yuge et al., 2011; Palchik et al., 2013), it should be noted that several limitations should be mentioned as the sample selection bias and the criticisms relating to the quality of home video.

More recently, Hamer, Bos and Hadders-Algra (2016) investigated whether specific characteristics of abnormal GMs were associated with developmental outcome at school age. The study has indicated that in 40 children with abnormal GMs (median gestational age 30.3 weeks; birth weight 1243 g), the absence of fidgety movements and the presence of stiff movements were related to worse functional motor outcome at school age, including cerebral palsy. In addition, a lack of complexity and movement variation was associated with the presence of behavioural problems. Overall these

findings confirmed previous published data according to with early monotonous movements and behavioural problems (evaluated through CBCL) may be associated (Hitzert et al. 2014).

3.1.2 Kinematic analysis of movements through the MOVIDEA software

At ISS I have been involving in the development of an advanced software for the analysis of spontaneous motor performances. In particular, I have the opportunity to collaborate with one of the largest Italian companies in the information technology sector for its specialization in the field of biomedical sciences (Ab.Acus, Milan). I have collaborated with the director of the same company (the engineer Dr. **Maria Bulgheroni**, who for years has been focusing his research on the development of advanced technologies for the study of movements), and with her staff of bio-engineers to elaborate and implement a software for the kinematic analysis of infant's movements.

The MOVIDEA software analyzes the 2D videos of newborns by implementing a semi-automatic trajectory of the limbs, from which it is possible to extract and calculate several parameters based on literature on this argument (see table 1). The interface of MOVIDEA has been implemented to support the operator in identifying and selecting the arm of interest.

Fig

Figure 4 Interface of MOVIDEA and motor trajectories provided by MOVIDEA

Table 1 Features extracted by MOVIDEA

Tab. 1

The cross-correlation indexes aim to determine whether movement of arms proceeds in the same direction at the same time. The Periodicity aim to determine the regularity with which intersections of the trajectory with the mean occur and the frequency of intersections (Meinecke et al., 2006).

The centroid of motion is the spatial center of the positive pixels in the motion image, and may be a correlate to the center point of the movements of the infant. Quantity of motion ranging between 0 and 1, where 1 means that all pixels changed between the two frames, and 0 means that no pixels changed between frames. Quantity of motion can therefore be used as an estimate of movement from a video sequence. The variability of velocity and acceleration of the centroid of motion were given as time derivate (Adde et al., 2009).

3.1.3 Early motor questionnaire

During my Ph.D. activities, I reviewed the literature focusing on the instruments elaborated to assess the development of early motor skills selecting the "Early motor questionnaire" (Libertus and Landa, 2013). Under the supervision of Dr. Maria Luisa Scattoni, I have been involved in translating and adapting the questionnaire "Early motor questionnaire" in collaboration with a developmental psychologist (English mother tongue) for the back-translation (English-Italian). We discussed each item of the questionnaire to achieve agreement. Additionally, I managed the presentation of the draft to five Italian parents to ascertain possible misunderstanding. The questionnaire is currently included in the NIDA clinical protocol used by all the clinical centers of the NIDA network.

The Early Motor Questionnaire (EMQ) is a parent-questionnaire focusing on early motor development. The EMQ has been elaborated and published by Libertus and Landa (2013). The EMQ provides a measure of early motor development, and it is organized around different 'contexts' a child encounters during everyday situations (e.g., sitting at a table, playing on the floor). The items included on the EMQ describe motor behaviors typically emerging within the first two years of life (0–24 months). Other primary caregivers (e.g., a grandparent or a nanny) may also complete the EMQ even if it is not targeted toward teachers. The EMQ uses a 5-point scale ranging from −2 to +2 to quantify parents' certainty. A behavior is rated -2 if the parent is sure the child does not show the behavior yet and +2 if parent remembers an instance where the child exhibited the behavior in question. Further, the EMQ is divided into three sections, a Gross Motor section (GM: 49 items), a Fine Motor section (FM: 48 items), and a Perception-Action section (PA: 31 items).

In the study of Libertus and Landa (2013), participants were 94 parent of children (age range 3-24 months) who had been enrolled in a longitudinal study on the early detection of ASD. About 59% of the children are younger siblings of a child with a diagnosis of ASD. Findings revealed that the EMQ scores increased linearly with age, showed high concurrent validity with two separate examiner-administered measures

(Mullen Scales of Early Learning -MSEL- and the PDMS-2), had good predictive validity with MSEL and PDMS-2 scores obtained nearly five months later, and had good test-retest reliability.

The questionnaire has been introduced in the NIDA protocol starting from 6 months of age expecting several advantages. The parent questionnaires are structured tools providing access to parent's knowledge about their children (Libertus and Landa, 2013). Even if some concerns regarding their validity mainly due to the retrospective nature of parent report (Seifer, 2008; Kennedy, Brown, & Chien, 2012) and more doubts remain in the field of research of younger children (Libertus and Landa, 2013), those kinds of questionnaires require minimal time for scoring and are thought to be low-expensive in contrast to examiner-administered assessments. To date, few questionnaires are elaborated to investigate early motor development (Duby et al., 2006; Libertus and Landa, 2013) and, the EMQ may be a valuable tool to understanding motor development in very young children.

Fig

Figure 5 Italian Version of Early Motor Questionnaire

Methods

The NIDA network is the largest Italian cohort of infants at risk for ASD. The NIDA network is enrolling LR and HR infants after delivery with the aim of recording infant spontaneous movements at 10 days, 6, 12, 18 and 24 weeks of age. A comprehensive clinical evaluation assessing several areas of development is provided at 6, 12, 18, 24 and 36 months of age. Up to now, NIDA recruited 247 siblings and 114 low risk infants.

Based on the available clinical outcome, this study included 103 infants. Specifically:

- 62 LR infants assessed as “Typical development” between 24-36 months,
- 26 HR infants assessed as “No diagnosis” between 24-36 months,
- 12 HR infants assessed as “Neurodevelopmental disorder” between 24-36 months,
- 3 HR infants assessed as “ASD” between 24-36 months.

Spontaneous movements of LR and HR infants enrolled in the NIDA Network have been coded by the researchers of Stella Maris and ISS. In detail, the assessment of spontaneous movements was performed by:

- **General Movements Optimality score** analyzed by the GM Optimality List for Preterm GMs and Writhing Movements scale (Ferrari et al., 1990_ modified). This scale provided information on the quality of spontaneous movements included in the writhing repertoire. The final score, the GM Optimality score (ranging from 8 to 18), it is calculated summing the scores provided in terms of quality, sequence, amplitude, speed, space, rotatory components, onset and offset, and tremulous movements.
- **Motor Optimality score** - analyzed by the Assessment of Motor repertoire - 3 to 5 months scale (Einspieler, Prechtl, Bos, Ferrari & Cioni 2004). This scale provided information on the quality of spontaneous movement included in the fidgety repertoire. The final score, the Motor Optimality score (ranging from 5 to 28), it is calculated by collapsing scores from 5 categories: fidgety movements (max 12 points), repertoire of co-existent other movements (max 4 points), quality of

other movements (max 4 points), posture (max 4 points) and movement character (max 4 points).

- **MOVIDEA softwar**e

Statistical analysis

Differences between groups (Typical development, HR_ASD, HR_NDD and HR_No diagnosis), time of testing (10 days and 6 weeks; 12, 18 and 24 weeks) and interaction between groups and time of testing were evaluated by ANOVA (repeated measures) for GM optimality score (10 days and 6 weeks) and the Motor optimality score (12, 18, 24 weeks).

The permutation test has been applied to compare the GM optimality score of HR_ASD group with the GM optimality score of TD group, HR_ NDD group and HR_No diagnosis group both at 10 days and 6 weeks.

The total number of infants for each analysis differ according to the availability of the videos. The level of significance was set at 0.05. Statistical analysis was carried out by Stata 13.1.

Results

General Movements analysis: Enspieler and Ferrari scales

Mean values of the Writhing GM optimality score (10 days and 6 weeks) and the Fidgety Motor Optimality Score (12-18-24 weeks) for each group are presented in table 2.

Table 2 Mean values of GM Optimality Score and Motor Optimality Score

Tab. 2

The Writhing GM optimality score (mean value) of the ASD group at 6 weeks of age is lower than scores of the other groups (HR-NDD, HR-No diagnosis, TD). The optimality score was calculated from the following categories: Quality (max 4 points), sequence (max 2 points), amplitude (max 2 points), speed (max 2 points), space (max 2 points), rotary components (max 2 points), onset and offset (max 2 points), tremulous movements (max 2 points). Figure 6 showed the developmental trajectories of the GM optimality score between 10 days and 6 weeks.

While the developmental trajectory of writhing movements of infants with typical development and HR_No diagnosis infants did not differ between 10 days and 6 weeks, ASD and HR_NDD showed a different trajectory with a reduction of the GM optimality score from 10 days to 6 weeks.

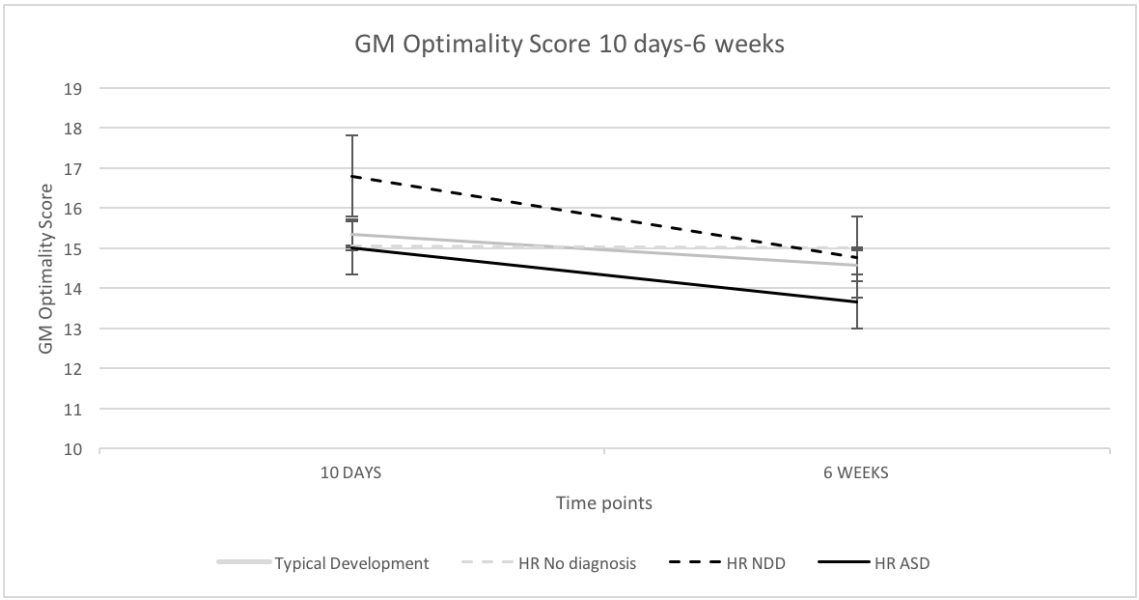

Figure 6 Mean values of GM Optimality Score. Bars are standard errors

The statistical analysis detected a significant effect of diagnosis at 10 days and 6 weeks [F (3,21) = 3.04, p= 0.03]. No significant effect emerged for time of testing [F (1,66) = 3.75, p= 0.06)] or for the two-way-interaction between diagnosis and time of testing [F (3,66) = 0.40, p= 0.76)]. The permutation statistical test did not reveal significant differences between groups at 10 days or 6 weeks presumably due to the small sample size of HR-ASD and HR-NDD groups. Results of permutation test are summarized in table 3.

Table 3 Results of the permutation test at 10 days and 6 weeks

Tab. 3

Figure 7 showed the developmental trajectory of the Fidgety Motor optimality score between 12 and 18 weeks. As specified in the Methods Section, the motor optimality score was derived from 5 categories: fidgety movements (max 12 points), repertoire of co-existent other movements (max 4 points), quality of other movements (max 4 points), posture (max 4 points) and movement character (max 4 points). The Fidgety Motor optimality score has a max of 28 points.

The Motor optimality score (mean value) did not differ between 12 weeks and 18 weeks in the TD and HR_No diagnosis groups, while HR_ASD infants increased their score at the second time point of recording (18 weeks). Statistical analysis of the Fidgety Motor Optimality Score did not reveal a significant effect at 12 and 18 weeks for diagnosis [F (3,89) = 0.01, p= 0.9991], time of testing [F (1,89) = 2.93, p= 0.0904] and the two-way-interaction diagnosis and time of testing [F (3,89) = 0.84, p= 0.4732].

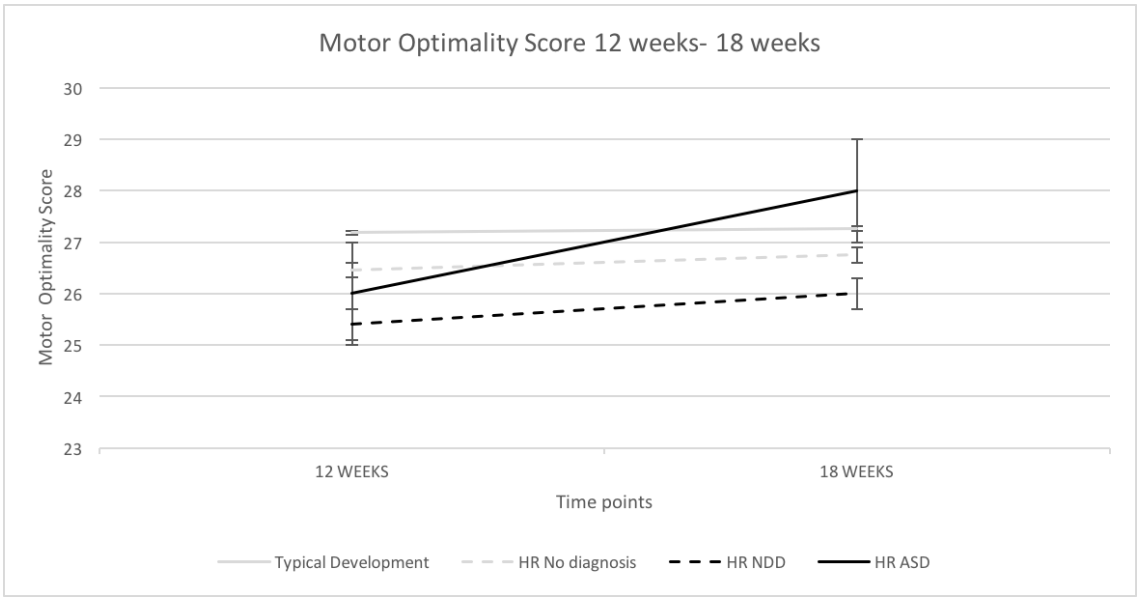

Figure 7 Fidgety Motor Optimality Score. Bars are standard errors

The developmental trajectory of the **Fidgety Motor optimality score** across 18 and 24 weeks has been evaluated. Results are showed in figure 8.

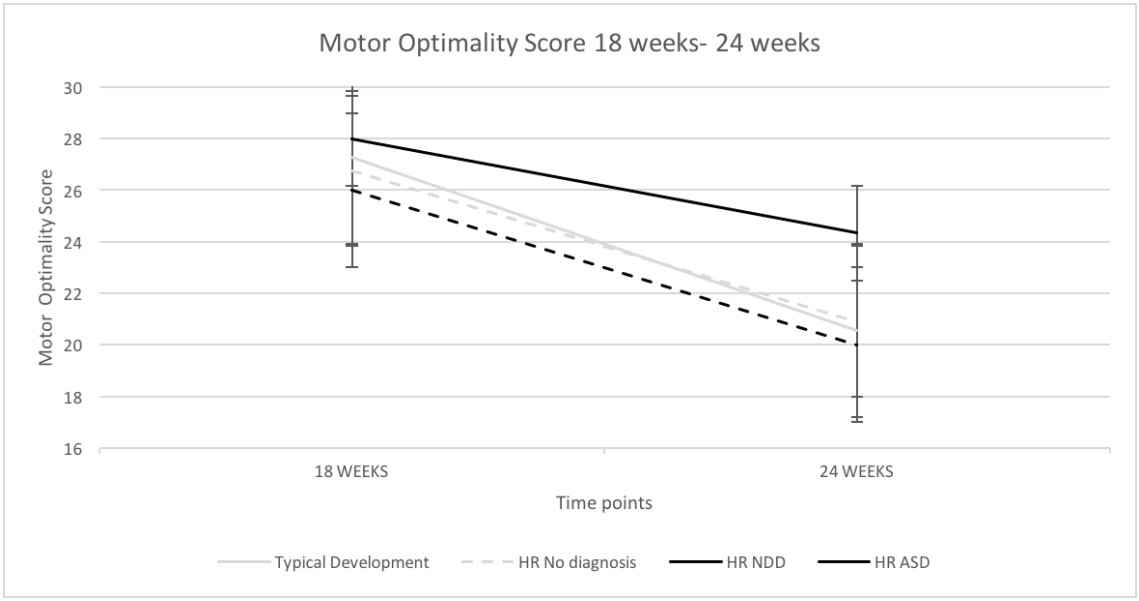

Figure 8 Mean values of Motor Optimality Score at 18 and 24 weeks. Bars are standard errors

Each group showed a developmental trajectory characterized by a lower mean value of the Motor optimality score at 24 weeks of age. The statistical analysis detected a significant effect of time of testing [$F(1,85) = 18.60$, $p < 0.05$]. No significant effect emerged for diagnosis [$F(3,85) = 0.89$, $p = 0.45$] or for the two-way-interaction diagnosis and time of testing [$F(3,85) = 1.15$, $p = 0.33$].

Kinematic Movements analysis: MOVIDEA

Table 4 shows features extracted by MOVIDEA at 10 days, 6-12-18-24 weeks for HR_ASD, HR_ NDD and HR_ No diagnosis group.

Table 4 Mean values of Features extracted by MOVIDEA

Tab. 4

Figures 9-15 show the developmental trajectories of the features extracted by MOVIDEA (Quantity of centroid of motion, Velocity of centroid of motion, Acceleration of centroid of motion, Periodicity hand, Periodicity foot, Cross correlation hand, Cross correlation foot) for HR_NDD and HR_No diagnosis group across time of testing. Since only one /two infants compose the HR_ASD group, their score is provided as a circle marker.

As for the category *'Quantity of motion'*, HR_ASD infants showed a quantity of centroid of motion lower than HR_ No diagnosis group at 10 days, 18 and 24 weeks (Figure 9).

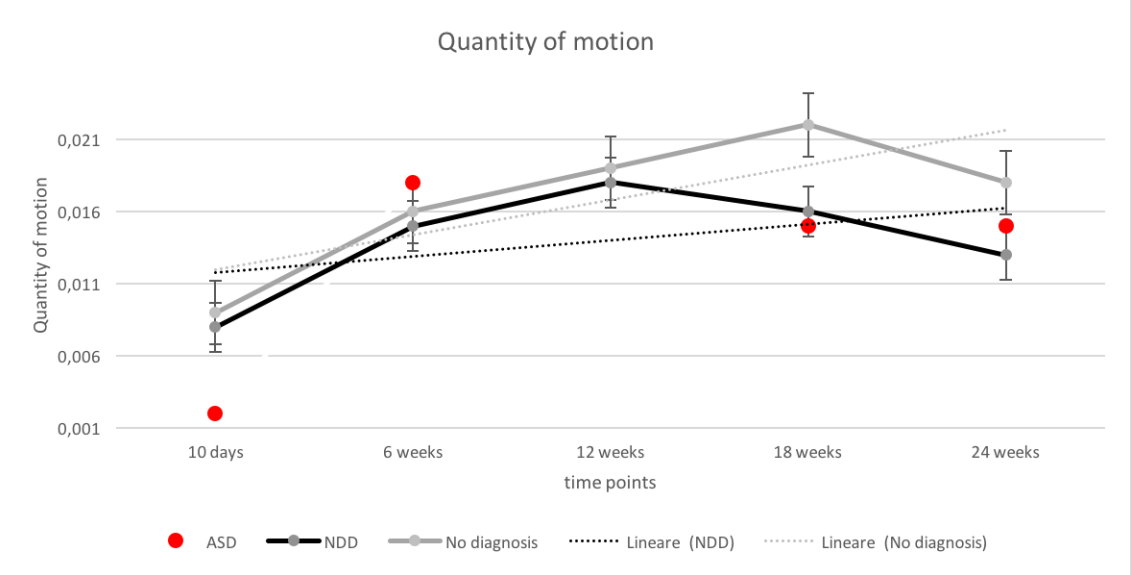

Figure 9 Quantity of Centroid of Motion. Bars are standard errors

As for the category *'Velocity of motion'*, HR_ASD infants showed a velocity of centroid of motion higher than HR_ No diagnosis group at 10 days, 6, 18 e 24 weeks (Figure 10).

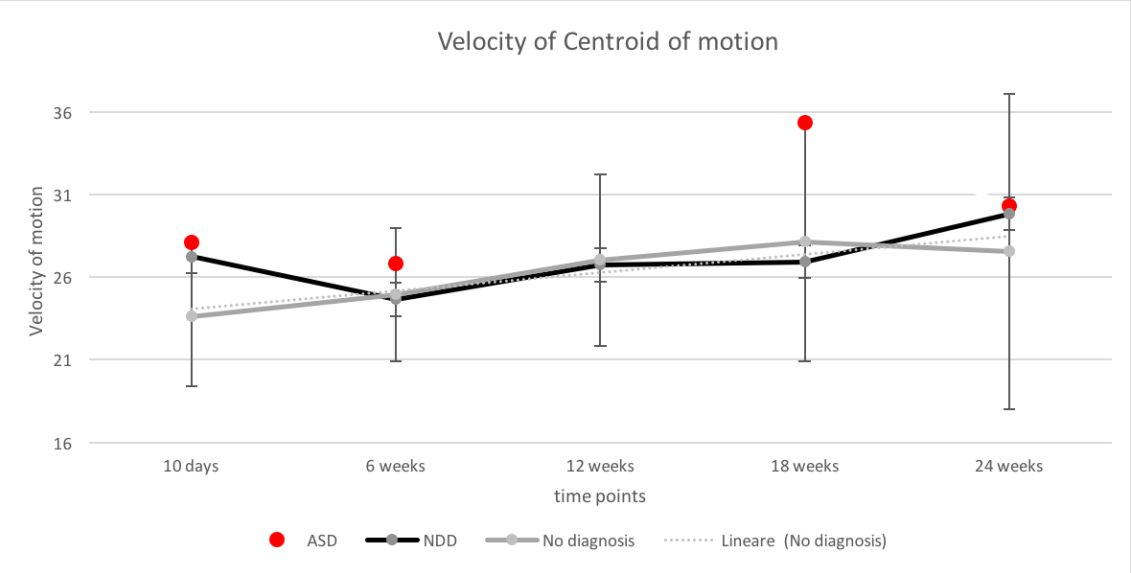

Figure 10 Velocity of Centroid of motion. Bars are standard errors

As for the category '*Acceleration of motion'*, HR_ASD infants showed an accelleration of centroid of motion higher than HR_ No diagnosis group at 10 days and 6,24 weeks (Figure 11).

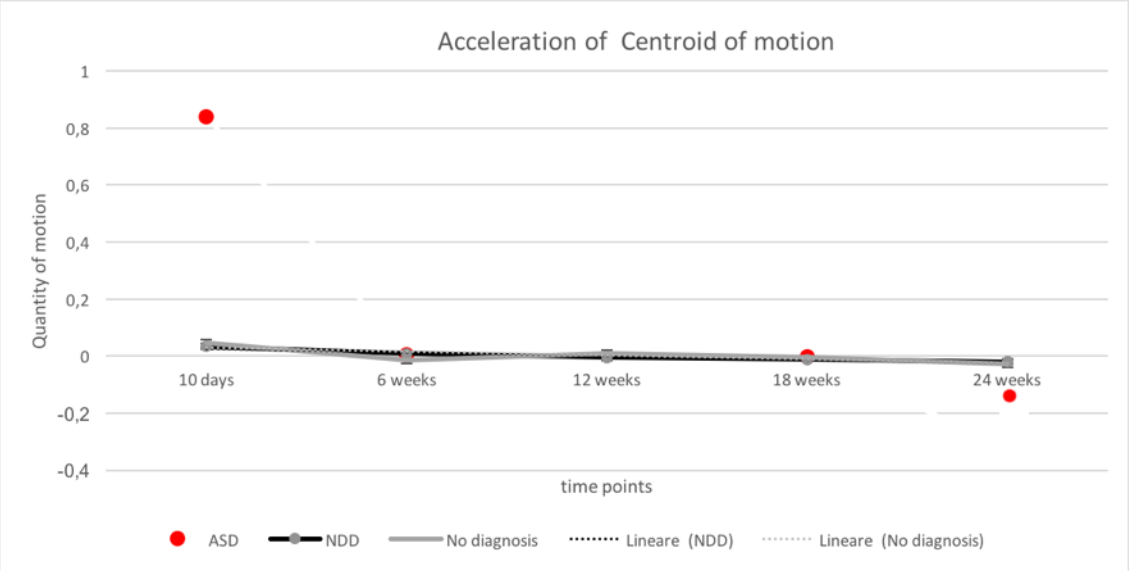

Figure 11 Acceleration of Centroid of motion. Bars are standard errors

As for the category of '*Periodicity of hand*' HR_ASD infants showed a periodicity of hand higher than HR_ No diagnosis group at 6, 24 weeks of testing (Figure 12).

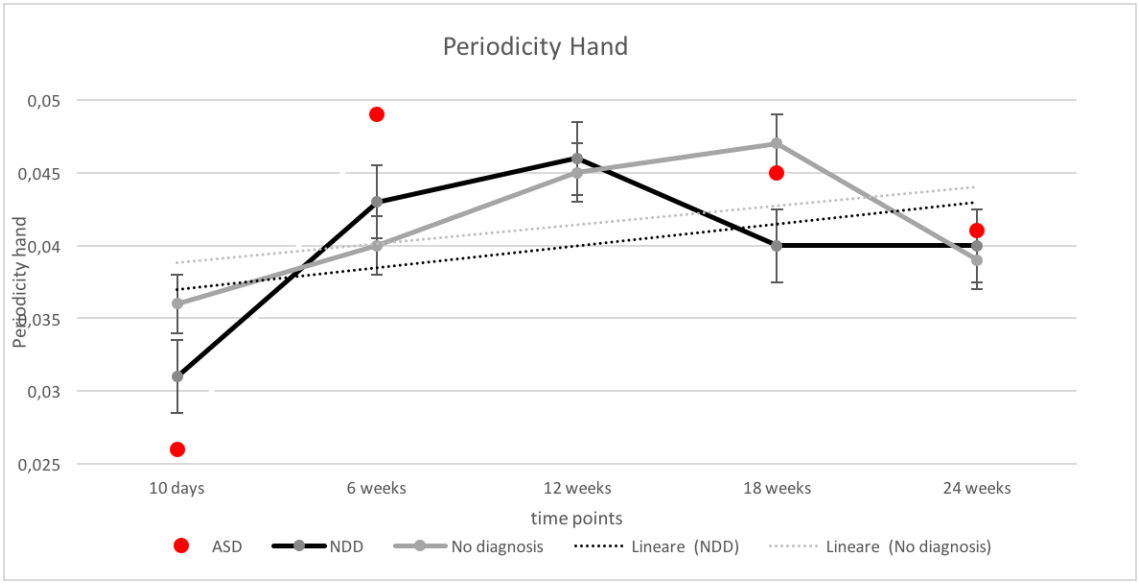

Figure 12 Periodicity of hand. Bars are standard errors

As for the category of '*Periodicity of foot*', HR_ASD infants showed a periodicity of foot higher than HR_ No diagnosis group at 6,18 weeks of testing (Figure 13).

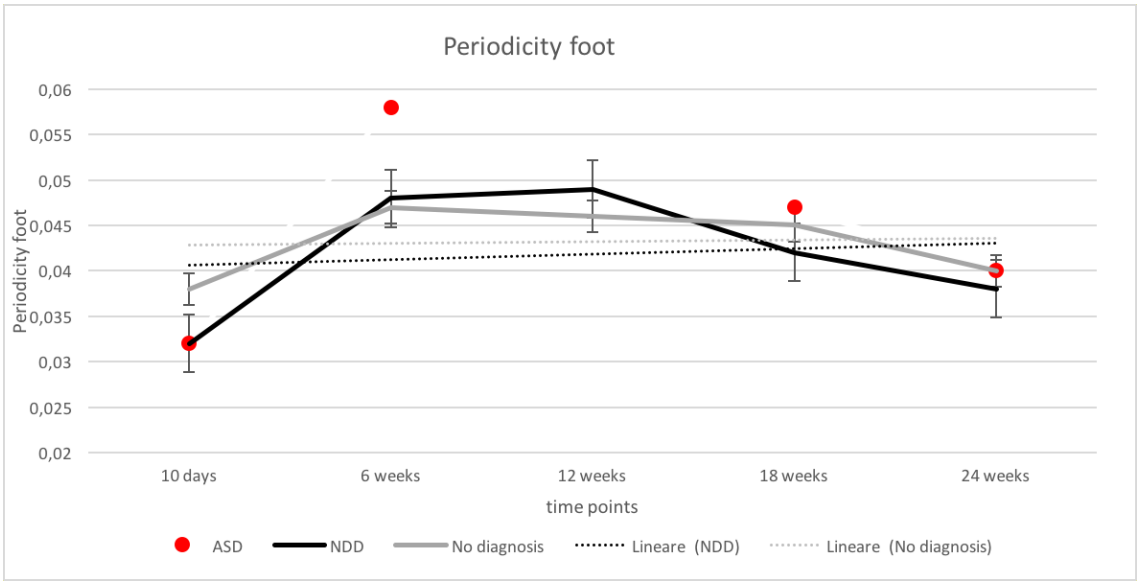

Figure 13 Periodicity of foot. Bars are standard errors

As for the category 'Cross correlation of hand', HR_ASD infants showed a cross correlation of hand lower than HR_ No diagnosis group at 18-24 weeks (Figure 14).

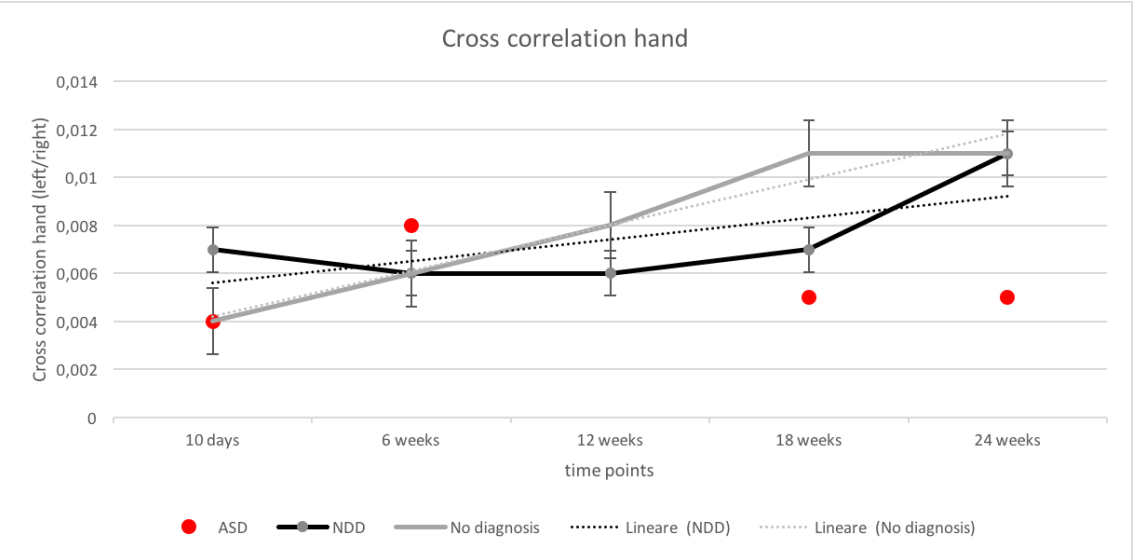

Figure 14 Cross correlation hand. Bars are standard errors

As for the 'Cross correlation of foot' category, HR_ASD infants showed a lower score than the HR_ No diagnosis group at 6, 24 weeks (Figure 15).

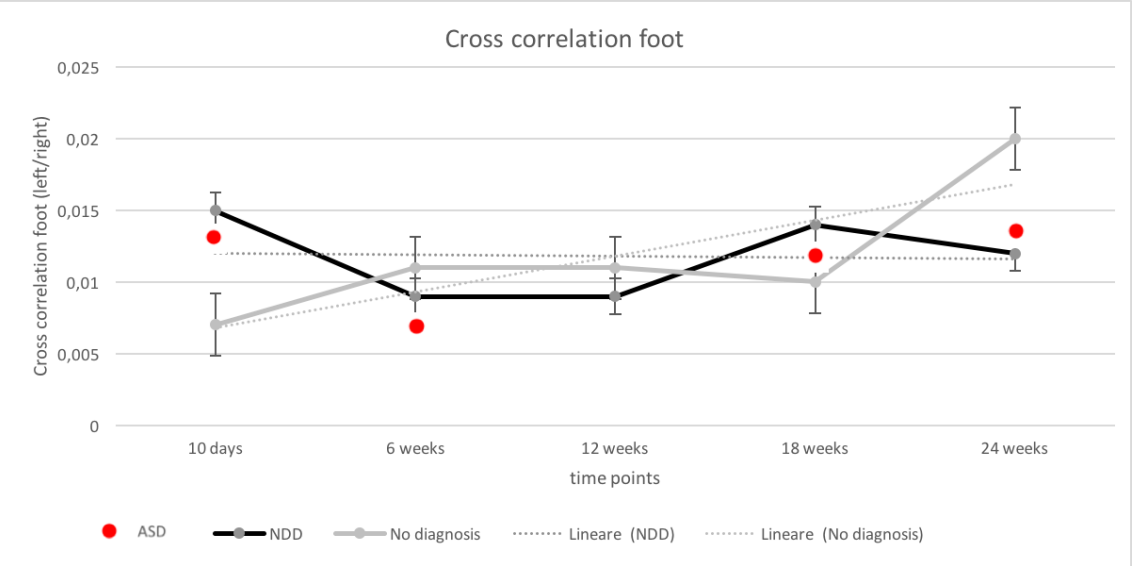

Figure 15 Cross correlation foot. Bars are standard errors

Discussion

The Italian Network for early detection of autism spectrum disorder (NIDA) involve the largest pediatric hospitals and clinical-research centers of the Italian territory and recruit LR and HR infants from birth to 36 months. The child psychiatric units enroll high-risk pregnant mothers or baby siblings when assessing the ASD proband. Difficulties in catching mothers/siblings at the right time and the tendency of couples with an affected child to stop reproducing, lead to a small sample size in the high-risk group. Moreover, in agreement with the expected recurrence risk of ASD (18.9%) in families with one affected child, our sample includes only three children with ASD and eleven children with NDDs in the high-risk group.

This study aimed to investigate early motor performances of infants at low and high risk for ASD enrolled in the NIDA Network. To these aim, two different experimental strategies have been applied. First, the early motor performances of LR and HR infants have been evaluated by a team of researchers with a specific expertise in the assessment of general movements (advanced GMs course). Second, the motor features have been assessed through MOVIDEA, a new software able to analyze the 2D videos of infant movements by automatically detecting the trajectory of the limbs. Overall, findings suggested that the trajectories of early motor development might be different in HR infants later diagnosed with ASD or with other neurodevelopmental disorders in comparison to those of HR infants without diagnosis and infants with typical development.

According to the Pretchl's method, researchers of the Stella Maris Institute (Smile Infant Lab directed by Prof. Andrea Guzzetta) scored the video-recordings of HR and LR infants providing for each infant the General Movement optimality score (Ferrari et al., 1990) and the Motor optimality score (Einspieler et al., 1997). Observers trained in the gestalt perception of GMs have evaluated the quality of general movements (GMs). The qualitative observation of the spontaneous motor activity in the first five

months of infant' life is one of the most reliable and valid predictors especially of severe neurological impairments.

Findings revealed that the GM optimality score of HR infants later diagnosed with ASD is lower than scores of the other groups, both at 10 days and 6 weeks. Moreover, HR infants later diagnosed with ASD or with other neurodevelopmental disorders showed a different motor developmental trajectory in comparison to infants with typical development (see figure 6). Unfortunately, the small sample size of ASD infants did not allow us to further analyze data using other statistical tests. However, our findings suggest that early motor abnormalities, detected in infants later diagnosed with ASD and NDDs, may be considered a valid predictor of an altered neurodevelopment.

Altogether, our data are in line with previous studies. Phagava and colleagues (2008) reported that the optimality scores of infants later diagnosed with ASD were lower than those of typical developing infants, mainly due to a lack of variable sequences, amplitude, and speed of their writhing GMs. Several studies suggested that motor abnormalities detected in the first year of life may be considered one of the earliest sign of ASD (West, 2018; Esposito, Venuti, Apicella, & Muratori, 2011; Landa & Garrett-Mayer, 2006; Esposito & Venuti, 2008; Phagava et al., 2008; Esposito, Venuti, Maestro, & Muratori, 2009).

In our video-recordings collected in infants between 12 and 18 weeks, HR infants later diagnosed with ASD increased their motor performance reaching the highest mean value of the Motor Optimality Score at 18 weeks. This data seems in contrast with previously published data showing that fidgety movements of infants later diagnosed with ASD are absent (20,8%) and abnormal (29.2%) as compared to healthy infants. However, it is worth noticing that the methodological setting is completely different between the two studies. In fact, Phagava and colleagues (2008) analyzed home-videos generally recorded in the first year of life but collected after diagnosis and not recorded in a longitudinal and standardized manner as in our experimental setting. Non-homogeneous material, such as home videos recorded by parents, has many limitations. For example, the videotaped events varied from one child to another and the age was not always known. Another limitation is that parents may choose to videotape their children when they are at their best and not necessarily during adverse conditions when abnormal behaviors or signs of autism may be more evident.

Due to the fact that it is requested a specific and deep expertise to analyze the qualitative nature of GMs, the implementation, generalizability and overall utility of the method have been questioned (Adde et al., 2007; 2009). The Gestalt perception technique requires experience, and clinicians working alone will be at risk of drifting away from the general movements assessment standards over time. Starting from these considerations, the ISS has established a scientific collaboration with Ab.Acus, one of the most important Italian companies of the information technology sector, to develop the software MOVIDEA. Our hypothesis is that the computer-based analysis of movements may support the quantitative analysis of spontaneous movements and its implementation in clinical and research settings.

Preliminary results from MOVIDEA suggested that it is possible to analyze developmental trajectories of several infant motor features. Unfortunately, the software is not fully automatic and requires the manual marking of arms/limbs from the experimenter. Thus, analysis of each three-minute-video-recording requires about two hours of work.

Our pilot study performed on 23 infants (11 HR_No diagnosis, 10 HR_NDD, 2 HR_ASD) detected some differences in specific motor features of ASD and NDD infants as compared to No_diagnosis HR infants. According to the literature (Esposito et AL., 2009; Esposito & Venuti, 2008), we found a delay in developing the cross-correlation between arms across time of testing. Indeed, results seems to suggest that, conversely from No_diagnosis HR infants, HR infants later diagnosed with ASD did not gradually increase the cross-correlation between arms (especially hands) and appears less coordinated. This finding is in line with data showing early motor asymmetries (either static and dynamic) and unsupported gait in infants and toddlers later diagnosed with ASD either tested at 5 months (supine position) and at 12 months (in the right position) (Esposito et al., 2009; Esposito & Venuti, 2008). According to our data, the observation of asymmetry in infants with ASD might start already in the first months of life and it supports the hypothesis of an underdevelopment of motor system in autism.

Several methodological limitations should be discussed since the features extracted by MOVIDEA still need to be verified, implemented and validated. The Ab.Acus Bioengineers and the ISS motor therapist are still assessing the accuracy of the extracted features. Pilot data presented in this PhD thesis should be considered preliminary since

the very low number of videos coded. However, it should be noted that the features extracted by MOVIDEA are correlated with the qualitative and quantitative analysis performed by the GMs experts. In fact, according to the GMs analysis performed on the same videos, the MOVIDEA software detected more periodic movement in infants later diagnosed with ASD than infants with TD at 6 weeks.

Overall, findings from this experimental study highlight the importance of a longitudinal assessment of motor development in infants at high risk for ASD since it could be useful to detect a derailed developmental motor trajectory as early as in the first weeks of life. Moreover, further video-analyses should be carried out by the MOVIDEA software to increase the potential value of an objective and reliable tool to identify early motor deficits in infants at risk for neurodevelopmental disorders.

3.2 Experiment 2

Analysis of fetal movements in pregnancies at low and high risk for ASD

Introduction

The present study was performed within the Work-Package 2 of the European project *"Brainview– fetal ultrasound screening for neurodevelopmental disorders in normal and high risk pregnancies"*, coordinated by ISS. First step of this experimental activity was to review literature on the analysis of fetal movements and their potential role as early markers of ASD.

The standard operative procedures for ultrasound (US) examination including the methodology and the timing to perform US recording have been elaborated thanks to the collaboration of the gynecologist of the "Ultrasound Diagnostic Centre Eco.B.I.", Dr Laura Iaconianni and of the child psychiatrist Prof. Andrea Guzzetta (Stella Maris Institute). Dr Laura Iaconianni is an expert gynecologist certified by the Fetal Medicine Foundation (https://fetalmedicine.org/lists/map/certified/NT) and Prof. Guzzetta is member of the Senior Licensed Tutors of the General Movement trust (http://general-movements-trust.info/48/licenced-tutors)

3.2.1 Fetal movements and their relevance in the research field of ASD

Neural activity and genetic programs interact to specify the composition and organization of neural circuits during all stages of development. Even at extremely early stages, well before synapses form, neurons and neuronal precursors exhibit spontaneous electrical and chemical activity. These early forms of activity, which often occur on a cell-by-cell basis and are not typically correlated across cells, influence developmental events such as neuronal differentiation, establishment of neurotransmitter phenotype, and neuronal migration.

Spontaneous activity of motoneurons seems to begin at the same time as their differentiation. Indeed, when motor neurons are exploring and innervating the skeletal muscles, the onset of rhythmic bursts of spontaneously generated action potentials induce motor activity (Fagard, Esseily, Jacquey, O'Regan, & Somogyi, 2018). This motor activity increase the concentration of calcium in the neurons, influencing gene expression (Feller, 1999; Kirkby, Sack, Firl, & Feller, 2013), and more in general, neuronal activity sustains the development of neuronal networks (Fagard, Esseily, Jacquey, O'Regan, & Somogyi, 2018; Milh et al., 2007).

Spontaneous startles, general movements (GMs), isolated movements and twitches represent the earliest motor behaviors of fetuses. Initially, the fetal motility consisting of small and simple sideways bending (SB) of the head and/or rump starts at 7 weeks. Between 7 and 8,5 gestational weeks, movements occur still slow, small, and in one direction, but the duration increases from 1 second to few seconds. Moreover, arms or legs become active.

Fig

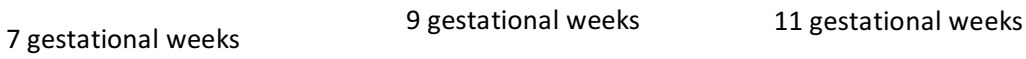

Figure 16 The emergence of fetal movements (modified by J. Perinat. Med. 33 (2005) 406-414)

Around 7–8 gestational weeks of age, the fetus performed occasional startles. In the beginning, startles are often followed by GMs (i.e., movements in which all parts of the body participate and during which movement direction, amplitude and speed varies). During GMs, all possible combinations of degrees of freedom in the various body joints are explored. GMs may be considered the example of motor behavior during the phase of primary variability (Hadders-Algra, 2018). The first GMs, which appear at about eight gestational weeks (Kurjak et al., 2008; de Vries, Visser, & Prechtl, 1985) are always preceded by a startle (Piontelli, 2010). The onset of GMs at 9-10 gestational weeks is characterized by variation in joining body parts and amplitude, speed, and direction during more extended periods of time. Between 9 and 13 gestational weeks, simple and stereotyped SBs and GMs may coexist. At the 9th gestational week, the incidence of SBs decreases and that of GMs increases (Lüchinger et al., 2008).

Even if different hypothesis have been suggested (de Vries, Visser, & Prechtl, 1985), it is possible that the massive displacements due to startles trigger a chain of counter-reactive movements able to facilitate the initiation of GMs (Piontelli, 2010). Lüchinger and colleagues (2008) supposed that initial simple fetal motility is generated by spinal and brainstem circuitries and the onset of GMs (complex and variable) correlates with the emergence of supraspinal modulation of this spinal and brainstem activity.

After the 17th gestational week, GMs do not necessarily follow a startle and

appear spontaneously. The isolated movements emerge soon after GMs became more frequently than GMs by the 14th gestational week (Kuriak et al., 2008).

Fig

Figure 17 The emergence of specific fetal movement patterns with time

The onset of isolated movements is simultaneous for arms and legs (Kurjak et al., 2008) but arm movements are more frequent than leg movements, at least in 14- to 18-gestational-week fetuses (Kuno et al., 2001). The incidence of isolated arm movements increases gradually from 8 through 19 gestational weeks whereas this does not occur for isolated leg movements (de Vries et al., 1985). Twitches are a kind of spontaneous motor activity produced during active sleep. Brief contractions of muscles trigger quick extensions or flexions of a limb or the neck. The onset of twitches is approximately at the age of 10–12 gestational weeks, and from 15–16 gestational weeks they increase up. In general, the frequency of fetal movements increases until a plateau is reached and decreases from 16 gestational weeks onward (Fagard, Esseily, Jacquey, O'Regan, & Somogyi, 2018). The periods of calm (without GMs, isolated movements of all sorts including limb movements, trunk movements, head movements, mouth movements (jaw opening, yawning), hiccups, facial movements, etc.) are very short until 20 gestational weeks (de Vries et al., 1985).

The first movements of the fetus, general or isolated, seem to be spontaneous and randomly distributed across space around it. These kinds of movements are called "motor babbling" and allow the fetus to explore the space around it, to explore its body and its environment and to explore the consequences of its movements on its body and

on its environment (Fagard et al., 2018).

The fetal movements may be spontaneous or triggered by sensations (i.e. due to the mother's movements or to internal sensations). As reported by Fagard and colleagues (2018) mainly two kinds of movements occur: reflexive and non-reflexive movements. Reflexive reactions to touch have been observed at 7–8 weeks and they appear as spontaneous motor behaviors in the region around the mouth. Indeed, after stroking the perioral area, fetuses present contraction of the neck muscles on the side opposite the stimulation, making the surface touched move away from the stimulator (Fagard, Esseily, Jacquey, O'Regan, & Somogyi, 2018). Studies on twins between 11 and 13 weeks revealed that a twin fetus strongly reacts when touched by the other twin (Piontelli, 2010).

With the development of the sensory systems, the non-reflexive responses to stimulations emerge. Indeed, when the fetuses are exposed to sounds, light, and touch, they can orient the motor response away or towards the source (Lecanuet et al., 1989). It has been reported that fetuses (21-23 weeks) respond to the maternal touch of the abdomen or vibroacoustic probes by an increase of arm, head and mouth movements (Marx & Nagy, 2015) and by changes in the fetal heart rate.

However, the first movements of the fetus seem to be spontaneous allowing the fetus to explore the space around it. Spontaneous, self-produced, motor behavior with its associated sensorimotor experience plays a pivotal role in motor development (Hadders-Algra, 2018).

In this regard, some constraints influence the fetal movements since characteristics of the articulations and state of development of the nervous system are different between fetuses and through the gestation. The fetuses can move arms and legs if there is enough space and enough amniotic fluid around the fetus and these variables assume relevance especially at the end of pregnancy when the area is reducing as the fetus grows. However, the decrease in the amount of movements during pregnancy is believed to be due, not only to the restriction in available space but also to the maturation of nervous system also expressed by the emergence of cortical inhibitory influences. Motor babbling may result in accidental contacts with the body or with the uterine environment. It has been suggested that these unintentional contacts appear to create a memory of consequences. Thus, the fetuses are thought to be able to present

a repertoire of ‘‘preferred’’ movements.

Since the motor performance requires that the fetus know the connections between motoneurons and muscles, it has been suggested that a sort of sensorimotor mapping emerge during the fetal stage. Spontaneous movements, twitches, and GMs contribute to the emerging sensorimotor mapping (Blumberg et al., 2013; Piontelli, 2010). Also, the isolated movements may be able to contribute since occurring touching induces double tactile stimulation: stimulation of the active touching part (hand, leg, tongue) and passive stimulation of the touched region (Fagard et al., 2018).

Therefore, even before the brain starts to receive significant sensory input from the outside world, spontaneous movements provide sensory stimuli. The fetuses seem to prefer those parts that are richly innervated. The isolated movements causing face contacts start at 10-12 weeks and increase. It is relevant to note that the trigeminal is an essential source of tactile and proprioceptive sensations (Kuriak et al., 2008). It has been supposed that arm movements increase toward the mouth because they are both highly innervated (Fanagard et al., 2018; Piontelli, 2010).

At 16–18 weeks, the fetus starts touching its eyelids, closed until 23–24 weeks. It should be noted that rubbing the eyelids may generate flashes of light in the fetus. Other self-touch behaviors observed in utero include scratching the temples with the fingers, which, even without nails, may elicit sensations. The skull is rarely scraped since sensory fibers very little innervate it, except for occiput and the nape. Fetuses also may touch their feet, which are well innervated. Conversely, the abdomen or the thorax that are less sensitive are rarely touched (Fanagard et al., 2018).

From 15 weeks post menstrual age starts the thumb sucking (Hadders-Algra, 2018). This may imply that goal directed activity of the upper extremities is already present in the first trimester of gestation and emerges in the absence of visual information. With increasing fetal age, the lower and perioral parts of the face are more often touched, at the expense of a decrease of movements directed to the upper parts of the face (Reissland et al., 2014). Moreover, this redistribution of hand activity is accompanied by a differentiated velocity profile: movements directed to the upper part, or rather to the eye, reach their target with a slower speed than those directed to the mouth region. The latter suggests that movement velocity is adapted to some extent to the delicacy of the target (Zoia et al., 2013).

GMs and isolated movements are important for the development of the motor machinery of muscles, tendons, ligaments, cartilages, spindles, and bones (Müller, 2003) and for the development of sensorimotor circuits and sensorimotor mapping (Milh et al., 2007).

Abnormal fetal GMs have been observed in fetuses at risk for preterm birth (Rosier-van Dunné et al., 2010) or in pregnancies complicated by a severe reduction in amniotic fluid (Bekedam et al., 1985; Sival et al., 1990). A standardized scoring system for fetal movements based on prenatal assessment by 3D/4D ultrasonography (Stanojevic et al., 2011), the Kurjak's Antenatal Neurodevelopmental Test (KANET, Kurjak et al., 2008), has been applied in high-risk pregnancies to early detect neurological disorders that clearly appear in perinatal and postnatal periods (Abo-Yaqoub et al., 2012; Athanasiadis et al., 2013; Honemeyer et al., 2013; Kurjak et al., 2010; Lebit & Vladareanu, 2011; Neto & Ramos, 2016; Neto & Kurjak, 2015; Predojevic, 2014; Talic et al., 2011). To date, abnormal fetal neurobehaviors detected through the KANET test have been identified in fetuses with chromosomal abnormalities (Miskovic et al., 2010), cerebral ventriculomegaly (Talic et al., 2011), intrauterine growth restriction (Vladareanu et al., 2012) and abnormal fetal circulatory system (Predojevi et al., 2014).

Fig

Figure 18 Kurjak's Antenatal Neurodevelopmental Test

Several studies documented that the fetuses are sensitive to the communicative input of the mother (Kisilevsky et al. 2009; Voegtline et al., 2013) and change their behavior accordingly (Marx & Nagy, 2015). Through 2D ultrasonography at 25 weeks of gestation, Ferrari et al. (2016) found that fetuses are sensitive only to specific maternal vocalizations and respond to them by performing congruent mouth movements. The authors suggested that fetal congruent response could be an early sign of mirroring behaviors that could become functional in the postnatal period (Ferrari et al., 2016).

It has been supposed that the emergence of social behavior could be dated at the prenatal stage (Castiello et al., 2010). Castiello and co-authors (2010) explored, through 4D investigation of twin pregnancies, whether the propensity to socially interact is already present before birth. The authors reported that 'social actions' are already performed in the second trimester of gestation as twin fetuses plan and execute movements specifically aimed at the co-twin. Twins exhibited with more accuracy movements towards the eye or mouth areas of their twin sibling rather than self-directed. Moreover, starting from the 22nd week of gestation, fetal movements should be directed to specific targets suggesting an early motor planning process already operating during the prenatal period (Zoia et al., 2007). In this regard, two studies showed that fetuses anticipate their movement toward the mouth by opening the mouth before the hand arrives (Myowa-Yamakoshi and Takeshita, 2006; Reissland et al., 2014).

Recently, Fulceri and colleagues (2018) reviewed over 3000 articles to summarize data on antenatal US parameters that might be considered early indices for social impairments later in life. However, only four studies were specifically aimed to investigate prenatal measures in the ASD population: a) two studies retrospectively examined fetal US records in children with ASD (Abel et al., 2013; Hobbs et al., 2007); b) another one prospectively applied the US techniques to investigate fetal measurements of children later diagnosed with ASD (Whitehouse et al., 2011); c) Hellmuth et al. (2017) explored the predictive value of fetal nuchal thickness for later neurodevelopmental outcomes, mainly focusing on ASD risk, in a large sample of children. The remaining reported studies were not explicitly focused on the ASD population but reported outcome measures associated with ASD or its core symptomatology. Overall, the fetal

measures that could be useful in determining the early presence of ASD or other neurodevelopmental disorders were biometric parameters, uteroplacental/fetal Doppler US measurements, fetal nuchal thickness and the width of the fetal lateral ventricular atrium. Although some US antenatal measurements have been reported to be of some interest in the ASD research field, data appeared to be still limited, controversial and not specific. In detail, the head circumference may be a relevant measure to assess in fetuses at risk since the presence of macrocephaly or brain volume overgrowth have been repeatedly described in children with ASD (Courchesne et al., 2003; Hazlett et al., 2017; Sacco et al., 2015).

The deviation in fetal growth developmental trajectory in children diagnosed with ASD (Abel et al., 2013) needs to be confirmed and the association between fetal weight growth trajectories with neurodevelopment needs to be further investigated (Harvey et al., 1982; Henrichs et al., 2010; Walker et al., 2007). The uteroplacental/fetal Doppler US measurement provide crucial information about placenta functioning and fetal oxygenation (Akolekar et al., 2015; Khalil & Thilaganathan, 2017; Polavarapu et al., 2018). In fact, several studies suggest that intrauterine growth restriction may influence the long-term developmental outcome (Chen et al., 2016). To date, data relating antenatal uteroplacental/fetal blood flow mechanisms to postnatal social development appear to be extremely limited. The nuchal translucency is commonly performed as part of the first-trimester screening for Down's syndrome (Bakker et al., 2014). The fetal nuchal thickness has been found increased in fetuses who later develop ASD and this relationship has been detected in fetuses without prenatal or postnatal genetic diagnosis or screened for structural malformation. Finally, also the enlargement of the lateral ventricles is a structural brain abnormality reported in several unhealthy conditions during childhood, including neurodevelopmental disorders (Gilmore et al., 2008).

Although no focused studies have been published yet, retrospective studies on neonatal GMs in children who later developed ASD appear to be encouraging (Phagava et al., 2008; Zappella et al., 2015). The similarity between movement patterns before and after birth supports the assessment of GMs also at the fetal stage providing information about the development of the central nervous system.

To investigate the possibility to record and assess fetal movements, we defined the standard operative procedures for collecting US in 2D/3D at first (from 11 weeks to 13weeks +5 days) and at the second trimester (from 20 weeks to 22 weeks +5 days). Moreover, with the collaboration of an expert gynecologist, Laura Iaconianni, we developed a detailed protocol to record (including the methodological setting, timing and length of recording) and analyze spontaneous movements and biometric data.

Methods

Participants were 12 pregnant women between 11th and 22nd weeks of gestation. Ten low-risk pregnant women (LR group) were enrolled according to the follow criteria: 1. being a healthy pregnant woman without a child with a neurodevelopmental disorder; 2. pregnancies between the 11th and 38th gestational week.

Only two high-risk participants (HR group) were enrolled according to follow criteria: 1. being a healthy pregnant woman of a child with ASD; 2. pregnancies the 11th and 38th gestational week.

Exclusion criteria for both groups were: Drugs abuse; Severe impairment of cardiac, pulmonary, renal, hepatic, endocrine or hematological nature; Genetic diseases, Chronic infectious or malignant neoplasms; Diagnosis of acquired immunodeficiency syndrome or HIV seroconversion; Confirmed diagnosis of psychiatric diseases; Clinical involvement of other neurological systems (sensory, extrapyramidal, oculomotor, cerebellar, vegetative).

Low risk participants were identified by gynecologists collaborating with Dr. Laura Iaconianni. High risk participants were identified by [……] and participating at the NIDA Network.

[……].

Each participant received a DVD with the US recording and a bodysuit (Figure 19). General data of pregnant women recruited by the project are summarized in table 5.

Fig.9

Figure 19 Gadgets for pregnant mothers provided by the NIDA Network

Table 5. General data of pregnant women

Tab.

Standard Operative Procedures

The standard operative procedures (SOP) for conducting fetal ultrasound recording and assessing biometric and movement's features have been defined with the collaboration and the support of the gynecologist Dr. Laura Iaconianni and Prof. Andrea Guzzetta. The methodology and the timing to perform US recording has been widely discussed together with the advantages and limits of the US examination according to gestational age, also from the technical point of view.

The following actions were applied for obstetric ultrasound recording in the first and in the second trimester:

⇒ Around 30' minutes before the recording, we asked to pregnant women to drink a fruit juice to elicit fetal movements.

⇒ Participants were in a semi- recumbent position.

First trimester - Trans-abdominal ultrasound examination includes:

1. 2D unstructured fetal ultrasound recording performed according to gynecologist routine. Ultrasound probe must be moved freely.
2. Five minutes of 2D structured fetal ultrasound recording. Ultrasound probe view must include the entire fetus. Frontal approach should be preferred. The probe must be maintained in static position for 5 minutes.
3. Five minutes of 4D structured fetal ultrasound recording. Ultrasound probe view must include the entire fetus. Frontal approach should be preferred. The probe must be maintained in static position for 5 minutes.

Second trimester - Trans-abdominal ultrasound examination includes:

1. Five minutes of 2D structured fetal ultrasound recording. Ultrasound probe view must focus on the upper torso of the body (especially the neck and the shoulders). The probe must be maintained in static position for 5 minutes.
2. Five minutes of 4D structured fetal ultrasound recording. Ultrasound probe view must include or focus on only the upper torso of the body (especially the neck and the shoulders). The probe must be maintained in static position for 5 minutes.

3. 2D unstructured fetal ultrasound recording. It must be performed according to gynecologist routine. Ultrasound probe should be moved freely.

In the third trimester, the Cardiotocographic trace was performed to record fetal movements and uterine contractions.

Data analysis

The coding of fetal movements has been performed through the software Observer XT Version 14, NOLDUS. Thanks to the collaboration with Dr. Angela Caruso, and under the supervision of Dr. Maria Luisa Scattoni, I have elaborated the design of the coding scheme applied to prenatal recording. In detail, the following movements have been observed and analyzed in terms of frequency (number of events) and duration:

VIEW	
	Entire
	Partial
LOST VIEW	

MOVEMENTS	
	Complex movements
	Startle (jumping movement)
	Moving arm to head (not clear the end-point of movements)
	Moving arm to eyes
	Moving arm to mouth
	Touching eyes
	Touching head
	Touching face
	Touching chin
	Sucking hand
	Moving the hand away from the head
	Movement of the hand towards/away from the mouth
	Ante-flexion of the head
	Retro-flexion of the head
	Moving legs
	Moving superior arms
	Moving mouth

Fig

Figure 20 Probe view during US examination (a)partial view; b) entire view)

Fig

Figure 21 Fetal movements (a) moving mouth; b) moving arm to mouth)

Fig

Figure 22 Fetal movements (moving arm to head (not clear the end of movement)

Fig

Figure 23 Touching head

Fig

Figure 24 Touching eyes

Fig

Figure 25 Startle/jumping movement (2D and 4D US examination)

Fig

Figure 26 Complex movement

Fig

Figure 27 Complex movement

Results

Fetal biometry

In the following table, fetal biometry measures recorded across gestation are reported.

Table 6 Fetal biometry across gestation

Tab

In the following graph, the longitudinal development of biometric data has been reported. Measures collected in the 2 fetuses at risk for ASD are indicated in red.

Fig

Figure 28 Longitudinal developmental of biometry in the sample

Fetal movements

Fetal movements detected are summarized in table 5. Each video recording has been evaluated to identify:

1. video-frames in which visibility was not sufficient to clearly understand the behaviors of fetuses. Those frames were labelled “lost view”. The “lost view” frames occurred when the probe was moved by the gynecologist (for example to clearly focus the view on the fetuses or when the quality of signal was not optimal).
2. video-frames in which fetal movements were observed. Those frames were labelled “movements”.

Each video-frame labelled as “movements” has been further evaluated using Observer to assign the observed movements to one of the category previously defined.
Table 5 presents data recorded in each trimester and according to the ultrasound technologies applied. Data from LR and HR fetuses are collapsed.

Table 7 Fetal movements detected

	First trimester			**Second trimester**		
	2D and 4D	Only 2D	Only 4D	2D and 4D	Only 2D	Only 4D
LOST VIEW	11%	10%	12%	29%	20%	37%
SUFFICIENT VIEW	89%	90%	88%	71%	80%	63%
Fetus viewed enterely*	83%	90%	72%	19%	40%	-
Fetus viewed partially*	17%	10%	28%	74%	60%	100%
RESTING STATE	85%	87%	83%	75%	82%	68%
MOVEMENT	15%	13%	17%	25%	18%	32%

*ENTERILY OR PARTIAL is a mutual exclusive condition relating to the entirely or partial view of fetuses. The values are calculated on the full lasting of video recording

Evaluability of video recording

The highest percentage of "lost view" occurred in the second trimester during 4D video recording (37%), whereas the lowest percentage of "lost view" occurred in the first trimester during 2D video recording (10%). In detail, the video recordings collected in the second trimester of gestation are characterized by the most relevant loss of frames (20 % for 2D ultrasound video recording and 37% for 4D ultrasound video recording) whereas the video recordings of the first trimester are characterized by the lowest relevant loss of frames (10 % for 2D ultrasound video recording and 12% for 4D ultrasound video recording). In figure 29, the mean value (%) of frames labelled as "Lost view" for each trimester are presented (LR and HR fetuses are collapsed).

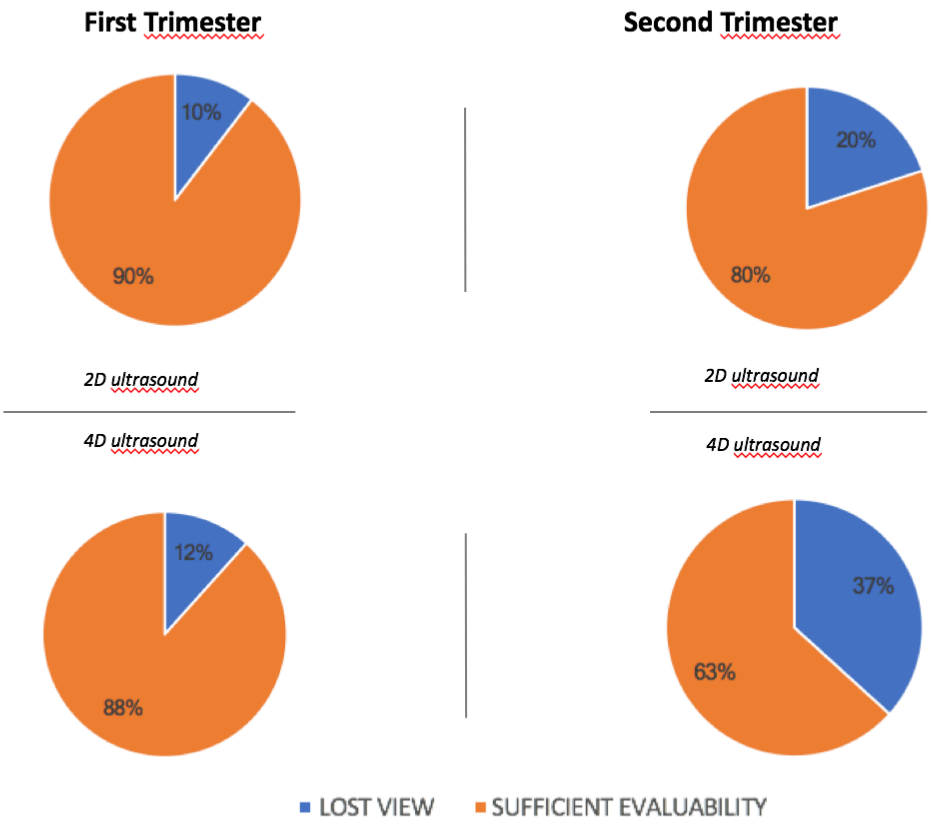

Figure 29"Lost view" frames during video recording of first trimester

Percentage of fetal movements

The highest percentage of "movements" occurred in the second trimester during 4D video recording (32%) whereas the lowest percentage of "movements" occurred in the first trimester during 2D video recording (13%). In detail, the video recordings of the second trimester of gestation are characterized by the most relevant percentage of sequences of movements (18 % for 2D ultrasound video recording and 32% for 4D ultrasound video recording) whereas the video recordings of the first trimester are characterized by the lowest percentage of sequences of movements (13 % for 2D ultrasound video recording and 17% for 4D ultrasound video recording).

In figure 30, the mean value (%) of frames labelled as "movements" for each trimester are presented (LR and HR fetuses are collapsed). Each mean value has been calculated excluding the "lost view" frames from the total duration of the video-recording.

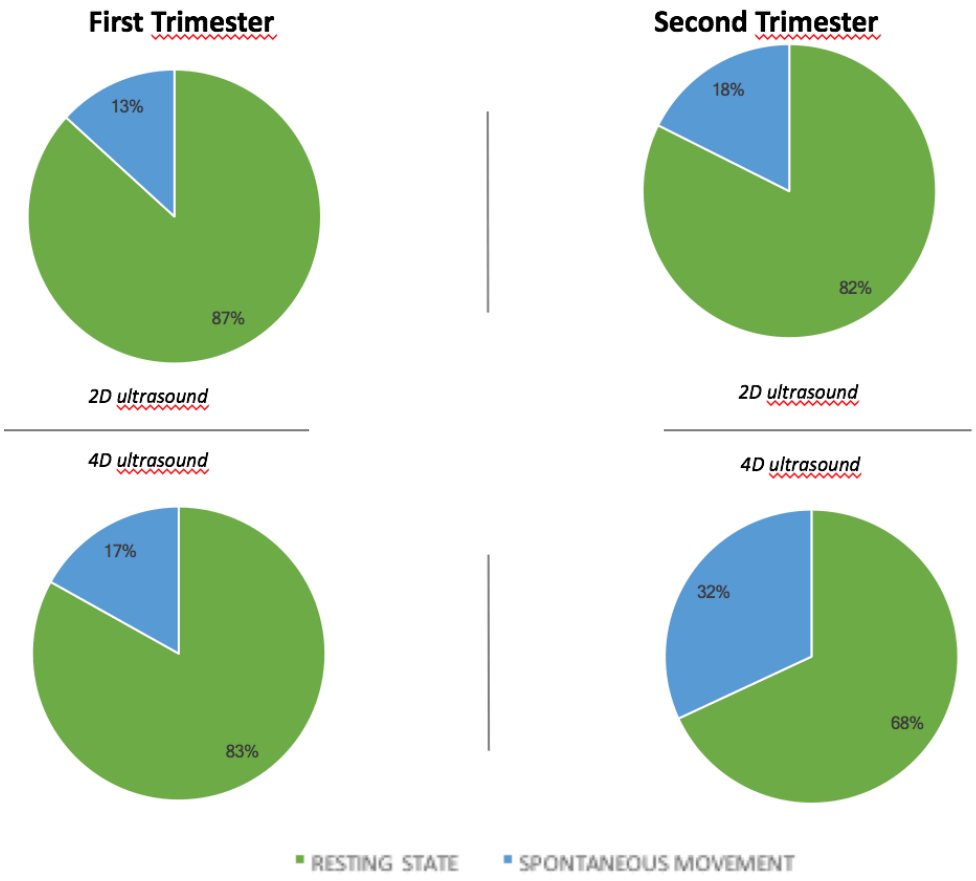

Figure 30 Movements during evaluable video recording

Types of fetal movements across gestation

Each sequence of frames labelled as "movements" has been further evaluated to assign by Observer the observed movements to one of the category previously defined. Data are presented in table 8. In the figure 31, the mean value (%) of frames labelled as "categorized movements" for each trimester are presented (LR and HR fetuses are collapsed). Each mean value has been calculated considering the total duration of movement period of each fetus.

Table 8 Fetal movements across gestation

	First trimester		**Second trimester**	
	Only 2D	Only 4D	Only 2D	Only 4D
RESTING STATE	87%	83%	82%	68%
MOVEMENT	13%	17%	18%	32%
Not classified	5%	2%	9%	5%
Touching eyes	-	-	-	1%
Touching head	-	-	-	5%
Touching face	-	-	-	-
Touching chin	-	-	-	-
Sucking hand	1%	-	2%	-
Complex movements	1%	12%	1%	20%
Startle (jump movement)	4%	1%	2%	-
Moving arm to head*	-	1%	-	1%
Moving arm to eyes	-	-	-	-
Moving arm to mouth	-	-	1%	-
Movement of the hand towards/away from the mouth	-	-	-	-
Ante-flexion of the head	-	-	-	-
Moving the hand away from the head	-	-	-	-
Retro-flexion of the head	1%	-	1%	-
Moving legs	1%	-	2%	-
Moving mouth	2%	-	2%	-
Moving superior arms	-	1%	1%	-

*(not clear the end-point of movements)

There is an increasing number of complex movements across gestation along with a gradually reducing number of startles. The fetal movements have been detected both

in 2D and in 4D ultrasound recordings but are more visible in 4D (see figure 30). It is worth noticing that the 2D approach allows the coding of movements performed in the sagittal plane whereas the 4D approach allows the coding of complex movements. When the fetus was moving but the movement (more often general movement) was not clearly identified we categorized it as 'Not classified' movements.

Fig

Figure 31 Movements across gestation

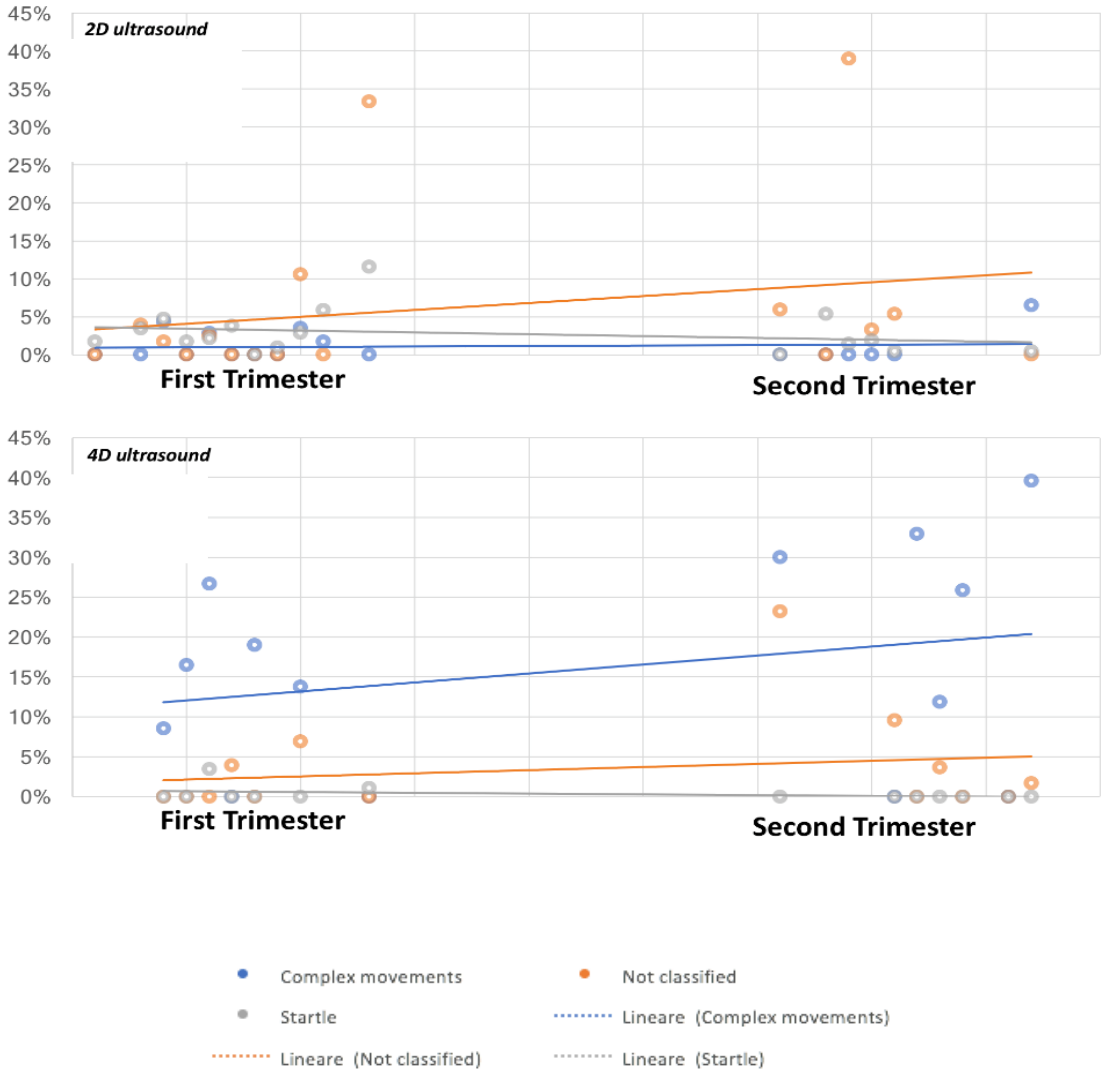

Figure 32 Longitudinal development of movements (complex movements, startle/jumping, not classified) across gestation

Discussion

The ISS coordinates the research activities of the ESR6 in the European project *"Brainview– fetal ultrasound screening for neurodevelopmental disorders in normal and high-risk pregnancies"*. Prof. Guzzetta, of the SMILE Infant Lab of the Stella Maris Institute, collaborated at the project by supervising Dr. Fulceri in developing the standard operative procedures to detect antenatal motor abnormalities in infants at risk for ASD.

Main aim of the Brainview research activity was to define a structured approach to evaluate antenatal movements of fetuses at LR and HR for ASD and to investigate whether HR fetuses presented antenatal motor abnormalities that might be correlated to postnatal social impairments. The similarity between movements patterns before and after delivery suggests that, the assessment of GMs could be performed also at the fetal stage providing important information about the development of the central nervous system (Rosier-van Dunné et al., 2010).

The Standard Operative Procedures have been defined taking into account the difficulties of recruiting pregnant women for research purposes, the requested long duration of recording to detect general movements and the relevance of investigating the fetal motor development (Abel et al., 2013, Harvey et al., 1982; Henrichs et al., 2010; Walker et al., 2007; Kanet et al., 2008; Phagava et al., 2008; Rosier-van Dunné et al., 2010; Zappella et al., 2015; Einspieler et al., 2014). To be potentially applied in the everyday context of the public health system, we fixed the length of recording to not more than 15 minutes. Previously published protocols recorded US for at least 20-30 minutes up to 1 hour (Honemeyer et al., 2013; Neto et al., 2015; Athanasiadis et al., 2013; Parma, Brasselet, Zoia, Bulgheroni & Castiello, 2017).

Our protocol consist of 10 minutes of video-recording of fetal movements performed together with the standard biometric examination executed at the first (from 11 weeks to 13 weeks +5 days) and at the second trimester (from 20 weeks to 22 weeks +5 days). The probe view during the ultrasound examination varied according to the gestational period (i.e., depending on the size of the fetus). We selected both the 2D and 4D examinations to assess different kind of movements (Abo-Yaquob et al., 2014;

Talic et al., 2011). In addition, based on information collected by our systematic review (Fulceri et al., 2018), we included in the SOPs also the collection of biometric data.

Starting from July 2007, the SOPs have been applied to the US examinations of recruited pregnant women at Eco B.I. center. The rate of the enrollment has been approximately of one woman every one-two months, and the recruitment-area has been limited to Rome and its surroundings for both the LR and HR pregnant women. Unfortunately, we encountered several difficulties in enrolling HR pregnant women since generally families with one child with ASD do not have a second child. Moreover, the child psychiatry units recruit them and this requires that, the day of the clinical evaluation of the ASD child, the child psychiatrists/psychologists recognize that the woman is pregnant (the first trimester).

Overall, the SOPs defined within the present project could be easily applied in the standard clinical setting (gynecological examination) for the simultaneous collection of motor, physiological and biometric parameters. However, all recordings required the presence of both the gynecologist and the researcher involved in the off-line analysis of data to optimize and define the position of the ultrasound sensor for the correct visualization of the fetus.

Based on the small number of participants, only a descriptive analysis has been feasible. Indeed, pregnant women at high risk for ASD (i. e., mother of a child with a diagnosis of ASD) participated at only one of the recordings. Thus, a comparison between data collected in HR with LR fetuses was not possible. However, the analysis showed that fetal movements were observed both in the first and in the second trimester, increasing with gestational age.

During the first trimester, the movements predominantly observed are the “startles” (i.e., fast movements of the body causing a body lifting as a jump) and occurring in the sagittal plane. Startles have been observed especially through the 2D recording. Other movements observed during the first trimester were the “complex movements” (i.e., involving different body segments including internal rotation) (see figure 26 and figure 27). The 4D approach resulted more suitable to visualize and assess the complex movements both in the first and in the second trimester. In the second trimester, the “startle” movements disappeared, and other kinds of movement emerged (see figure 32). However, the assessment of the movements in the second

trimester was limited by an increasing of “lost view” sequences according to the fetal size and the need to move the probe to ensure the vision.

In conclusion, findings from this pilot study suggest that the SOPs elaborated may be useful to collect longitudinal data on fetuses at LR and HR for ASD. Both dynamic measurements and biometry should be added to data collected during the standard gynecological examination since fetal size and growth trajectories are considered indicators of an adequate fetal health.

To the best of our knowledge, this is on the first studies on the reproducibility assessment of fetal movement counting using 4D ultrasound. However, the data and their interpretation in the present study should be taken with some degree of caution because of the small number of subjects studied. Further studies involving a larger sample size are needed to assess the reproducibility of fetal movement analysis using 4D ultrasound and to investigate antenatal neurodevelopment of infants at risk for ASD. Thus, even if the number of participants prevents us from any consideration regarding the comparison between groups, the current findings suggest that the antenatal ultrasound examination according to this SOPs may be a feasible way forward to investigate motor developmental trajectories in infants at LR and HR of neurodevelopmental disorder.

Conclusions

It is quite well established the presence of motor disturbances in children with ASD. However, data on early motor developmental disorders in infants and toddlers with ASD are still poorly explored. Some studies observed differences in the motor milestones, the presence of asymmetries and early repetitive behaviors, but data in this field are very mixed and not all studies have been replicated.

Given the importance of further exploring the early motor trajectories in infants with ASD, this study had the overall purpose to collect longitudinal data on motor development of infants at high risk for ASD. The novelty of the present work is the focus on the identification of early motor development patterns instead of specific motor performances. This approach is extremely valuable for the early detection of autistic signs and the consequent early interventions and access to services and care.

The present work has several strengths and gave light to novel findings. First, data from the first experimental study supported the importance of carefully exploring the developmental trajectories of the spontaneous movements in the first 5-6 months of life of infants at high-risk for ASD. The possibility to explore the early motor developmental trajectory is extremely informative because may be predictive of later social competencies such as joint attention capacity, sharing skills, gestures and body posture. In this prospective, early motor trajectory exploration is a relevant candidate for early detection of social impairments in populations that show deficits in these domains such as Autism Spectrum Disorder.

Second, we developed the MOVIDEA software to study spontaneous movements and possibly applying it in several clinical settings. The MOVIDEA software needs to be validated and automatized in order to further shorten the timing for data analysis of the

videos collected. The present work provided a valuable starting point toward improving of MOVIDEA technology.

Finally, our fetal protocol measuring early motor trajectories is suitable for the future transition to clinical settings as part of the routine-protocol. Despite the paucity of data collected on high risk pregnancies, our fetal protocol was important to individuate the best strategy to collect and analyze data on basal biometrical data, fetal behaviors, complex measures of antenatal neurobehaviors in the first two trimesters of pregnancy, and their correlations with neonatal data. Further studies should seek to replicate the present data using wider samples. The NIDA network will pursuit the incrementation of data collection and will continue to further explore neurobiological mechanisms of autism.

In conclusion, the present work used motor prenatal and postnatal trajectories as bio-markers for the detection of early autistic signs. Given the well-established link between motor development and social competencies, it is possible to use this protocol as screenings in clinical settings to identify children at risk for neurodevelopmental disorders early in life and provide them and their families adequate care, services and interventions.

References

Abel, K. M., Dalman, C., Svensson, A. C., Susser, E., Dal, H., Idring, S., … Magnusson, C. (2013). Deviance in fetal growth and risk of autism spectrum disorder. *The American Journal of Psychiatry*, *170*(4), 391–398. https://doi.org/10.1176/appi.ajp.2012.12040543

Abo-Yaqoub, S., Kurjak, A., Mohammed, A.-B., Shadad, A., & Abdel-Maaboud, M. (2012). The role of 4-D ultrasonography in prenatal assessment of fetal neurobehaviour and prediction of neurological outcome. *The Journal of Maternal-Fetal & Neonatal Medicine: The Official Journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians*, *25*(3), 231–236. https://doi.org/10.3109/14767058.2011.568552

Achenbach, T. M., & Rescorla, L. (2000). Manual for the ASEBA preschool forms and profile. Burlington, VT: ASEBA

Adde, L., Helbostad, J. L., Jensenius, A. R., Taraldsen, G., & Stoen, R. (2009). Using computer-based video analysis in the study of fidgety movements. *Early Hum Dev*, *85*(9), 541–547. https://doi.org/10.1016/j.earlhumdev.2009.05.003

Adde, L., Rygg, M., Lossius, K., Oberg, G. K., & Stoen, R. (2007). General movement assessment: predicting cerebral palsy in clinical practise. *Early Hum Dev*, *83*(1), 13–18. https://doi.org/10.1016/j.earlhumdev.2006.03.005

Akolekar, R., Sarno, L., Wright, A., Wright, D., & Nicolaides, K. H. (2015). Fetal middle cerebral artery and umbilical artery pulsatility index: effects of maternal characteristics and medical history. *Ultrasound in Obstetrics & Gynecology: The Official Journal of the International Society of Ultrasound in Obstetrics and Gynecology*, *45*(4), 402–408. https://doi.org/10.1002/uog.14824

Al-Farsi, Y. M., Waly, M. I., Deth, R. C., Al-Sharbati, M. M., Al-Shafaee, M., Al-Farsi, O., … Ouhtit, A. (2013). Impact of nutrition on serum levels of docosahexaenoic acid among Omani children with autism. *Nutrition (Burbank, Los Angeles County, Calif.)*, *29*(9), 1142–1146. https://doi.org/10.1016/j.nut.2013.03.009

Alkandari, F., Ellahi, A., Aucott, L., Devereux, G., & Turner, S. (2015). Fetal ultrasound measurements and associations with postnatal outcomes in infancy and childhood: a systematic review of an emerging literature. *Journal of Epidemiology and Community Health*, *69*(1), 41–48. https://doi.org/10.1136/jech-2014-204091

Athanasiadis, A. P., Mikos, T., Tambakoudis, G. P., Theodoridis, T. D., Papastergiou, M., Assimakopoulos, E., & Tarlatzis, B. C. (2013). Neurodevelopmental fetal assessment using KANET scoring system in low and high risk pregnancies. *The Journal of Maternal-Fetal & Neonatal Medicine: The Official Journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians*, *26*(4), 363–368. https://doi.org/10.3109/14767058.2012.695824

Äyräs, O., Eronen, M., Tikkanen, M., Rahkola-Soisalo, P., Paavonen, J., & Stefanovic, V. (2015). The significance of gender in fetuses with increased nuchal translucency: pregnancy outcomes and long-term outcomes of children. *Prenatal Diagnosis*, *35*(9), 901–905. https://doi.org/10.1002/pd.4632

Athanasiadou, A., Buitelaar, J. K., Brovedani, P., Chorna, O., Fulceri, F., Guzzetta, A., & Scattoni, M. L. (2019). Early motor signs of attention-deficit hyperactivity disorder: a systematic review. *European Child & Adolescent Psychiatry*. https://doi.org/10.1007/s00787-019-01298-5

Baio, J., Wiggins, L., Christensen, D. L., Maenner, M. J., Daniels, J., Warren, Z., … Dowling, N. F. (2018). 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 (Washington, D.C.: 2002)*, *67*(6), 1–23. https://doi.org/10.15585/mmwr.ss6706a1

Bakker, M., Pajkrt, E., & Bilardo, C. M. (2014). Increased nuchal translucency with normal karyotype and anomaly scan: what next? *Best Practice & Research. Clinical Obstetrics & Gynaecology*, *28*(3), 355–366. https://doi.org/10.1016/j.bpobgyn.2013.10.004

Baranek, G. T. (1999). Autism during infancy: a retrospective video analysis of sensory-motor and social behaviors at 9-12 months of age. *Journal of Autism and Developmental Disorders*, *29*(3), 213–224.

Barber, A. B., Wetherby, A. M., & Chambers, N. W. (2012). Brief report: repetitive behaviors in young children with autism spectrum disorder and developmentally similar peers: a follow up to Watt et al. (2008). *Journal of Autism and Developmental Disorders*, *42*(9), 2006–2012. https://doi.org/10.1007/s10803-011-1434-3

Barger, B. D., Campbell, J. M., & McDonough, J. D. (2013). Prevalence and Onset of Regression within Autism Spectrum Disorders: A Meta-analytic Review. *Journal of Autism and Developmental Disorders*, *43*(4), 817–828. https://doi.org/10.1007/s10803-012-1621-x

Baschat, A. A., Viscardi, R. M., Hussey-Gardner, B., Hashmi, N., & Harman, C. (2009). Infant neurodevelopment following fetal growth restriction: relationship with antepartum surveillance parameters. *Ultrasound in Obstetrics & Gynecology: The Official Journal of the International Society of Ultrasound in Obstetrics and Gynecology*, *33*(1), 44–50. https://doi.org/10.1002/uog.6286

Bedford, R., Pickles, A., & Lord, C. (2016). Early gross motor skills predict the subsequent development of language in children with autism spectrum disorder. *Autism Res*, *9*(9), 993–1001. https://doi.org/10.1002/aur.1587

Bekedam, D. J., Visser, G. H., de Vries, J. J., & Prechtl, H. F. (1985). Motor behaviour in the growth retarded fetus. *Early Human Development*, *12*(2), 155–165.

Billeci, L., Narzisi, A., Campatelli, G., Crifaci, G., Calderoni, S., Gagliano, A., … group, A. (2016). Disentangling the initiation from the response in joint attention: an eye-tracking study in toddlers with autism spectrum disorders. *Translational Psychiatry*, *6*, e808. https://doi.org/10.1038/tp.2016.75

Billeci, L., Narzisi, A., Campatelli, G., Crifaci, G., Calderoni, S., Gagliano, A., … Muratori, F. (2016). Disentangling the initiation from the response in joint attention: an eye-tracking study in toddlers with autism spectrum disorders. *Transl Psychiatry*, *6*, e808. https://doi.org/10.1038/tp.2016.75

Billeci, L., Narzisi, A., Tonacci, A., Sbriscia-Fioretti, B., Serasini, L., Fulceri, F., … Muratori, F. (2017). An integrated EEG and eye-tracking approach for the study of responding and initiating joint attention in Autism Spectrum Disorders. *Sci Rep*, *7*(1), 13560. https://doi.org/10.1038/s41598-017-13053-4

Billeci, L., Narzisi, A., Tonacci, A., Sbriscia-Fioretti, B., Serasini, L., Fulceri, F., … Muratori, F. (2017). An integrated EEG and eye-tracking approach for the study of responding and initiating joint attention in Autism Spectrum Disorders. *Scientific Reports*, *7*(1), 13560. https://doi.org/10.1038/s41598-017-13053-4

Billeci, L., Tonacci, A., Narzisi, A., Manigrasso, Z., Varanini, M., Fulceri, F., … Muratori, F. (2018). Heart Rate Variability During a Joint Attention Task in Toddlers With Autism Spectrum Disorders. *Front Physiol*, *9*, 467. https://doi.org/10.3389/fphys.2018.00467

Biran-Gol, Y., Malinger, G., Cohen, H., Davidovitch, M., Lev, D., Lerman-Sagie, T., & Schweiger, A. (2010). Developmental outcome of isolated fetal macrocephaly. *Ultrasound in Obstetrics & Gynecology: The Official Journal of the International Society of Ultrasound in Obstetrics and Gynecology*, *36*(2), 147–153. https://doi.org/10.1002/uog.7585

Bishop, S. L., Hus, V., Duncan, A., Huerta, M., Gotham, K., Pickles, A., … Lord, C. (2013). Subcategories of Restricted and Repetitive Behaviors in Children with Autism Spectrum Disorders. *Journal of Autism and Developmental Disorders*, *43*(6), 1287–1297. https://doi.org/10.1007/s10803-012-1671-0

Blumberg, M. S., Marques, H. G., & Iida, F. (2013). Twitching in sensorimotor development from sleeping rats to robots. *Current Biology: CB*, *23*(12), R532-537. https://doi.org/10.1016/j.cub.2013.04.075

Bodfish, J. W., Symons, F. J., Parker, D. E., & Lewis, M. H. (2000). Varieties of repetitive behavior in autism: Comparisons to mental retardation. *Journal of Autism and Developmental Disorders*, 30, 237–243.

Bölte, S., Marschik, P. B., Falck-Ytter, T., Charman, T., Roeyers, H., & Elsabbagh, M. (2013). Infants at risk for autism: a European perspective on current status, challenges and opportunities. *European Child & Adolescent Psychiatry*, *22*(6), 341–348. https://doi.org/10.1007/s00787-012-0368-4

Boria, S., Fabbri-Destro, M., Cattaneo, L., Sparaci, L., Sinigaglia, C., Santelli, E., … Rizzolatti, G. (2009). Intention understanding in autism. *PloS One*, *4*(5), e5596. https://doi.org/10.1371/journal.pone.0005596

Brewer, R., Biotti, F., Catmur, C., Press, C., Happe, F., Cook, R., & Bird, G. (2016). Can Neurotypical Individuals Read Autistic Facial Expressions? Atypical Production of

Emotional Facial Expressions in Autism Spectrum Disorders. *Autism Res*, *9*(2), 262–271. https://doi.org/10.1002/aur.1508

Brian, J., Bryson, S. E., Garon, N., Roberts, W., Smith, I. M., Szatmari, P., & Zwaigenbaum, L. (2008). Clinical assessment of autism in high-risk 18-month-olds. *Autism: The International Journal of Research and Practice*, *12*(5), 433–456. https://doi.org/10.1177/1362361308094500

Brisson, J., Warreyn, P., Serres, J., Foussier, S., & Adrien-Louis, J. (2012). Motor anticipation failure in infants with autism: a retrospective analysis of feeding situations. *Autism: The International Journal of Research and Practice*, *16*(4), 420–429. https://doi.org/10.1177/1362361311423385

Brownell, C. A., Ramani, G. B., & Zerwas, S. (2006). Becoming a social partner with peers: cooperation and social understanding in one- and two-year-olds. *Child Dev*, *77*(4), 803–821. https://doi.org/10.1111/j.1467-8624.2006.00904.x

Bryson, S. E., Zwaigenbaum, L., Brian, J., Roberts, W., Szatmari, P., Rombough, V., & McDermott, C. (2007). A prospective case series of high-risk infants who developed autism. *Journal of Autism and Developmental Disorders*, *37*(1), 12–24. https://doi.org/10.1007/s10803-006-0328-2

Bryson, S., Garon, N., McMullen, T., Brian, J., Zwaigenbaum, L., Armstrong, V., … Szatmari, P. (2018). Impaired disengagement of attention and its relationship to emotional distress in infants at high-risk for autism spectrum disorder. *Journal of Clinical and Experimental Neuropsychology*, *40*(5), 487–501. https://doi.org/10.1080/13803395.2017.1372368

Buie, T., Campbell, D. B., Fuchs, G. J., Furuta, G. T., Levy, J., Vandewater, J., … Winter, H. (2010). Evaluation, diagnosis, and treatment of gastrointestinal disorders in individuals with ASDs: a consensus report. *Pediatrics*, *125 Suppl 1*, S1-18. https://doi.org/10.1542/peds.2009-1878C

Buscema, M., Grossi, E., Montanini, L., and Street, M. E. (2015). Data mining of determinants of intrauterine growth retardation revisited using novel algorithms generating semantic maps and prototypical discriminating variable profiles. PLoS One 10:e0126020. doi: 10.1371/journal.pone.012 6020

Calderoni, S., Santocchi, E., Del Bianco, T., Brunori, E., Caponi, L., Paolicchi, A., … Muratori, F. (2016). Serological screening for Celiac Disease in 382 pre-schoolers

with Autism Spectrum Disorder. *Ital J Pediatr*, *42*(1), 98. https://doi.org/10.1186/s13052-016-0308-x

Calderoni, S., Santocchi, E., Del Bianco, T., Brunori, E., Caponi, L., Paolicchi, A., … Muratori, F. (2016). Serological screening for Celiac Disease in 382 pre-schoolers with Autism Spectrum Disorder. *Italian Journal of Pediatrics*, *42*(1), 98. https://doi.org/10.1186/s13052-016-0308-x

Campione, G. C., Piazza, C., Villa, L., & Molteni, M. (2016). Three-Dimensional Kinematic Analysis of Prehension Movements in Young Children with Autism Spectrum Disorder: New Insights on Motor Impairment. *Journal of Autism and Developmental Disorders*, *46*(6), 1985–1999. https://doi.org/10.1007/s10803-016-2732-6

Cannell, J. J., & Grant, W. B. (2013). What is the role of vitamin D in autism? *Dermato-Endocrinology*, *5*(1), 199–204. https://doi.org/10.4161/derm.24356

Carpenter Rich, E., Loo, S. K., Yang, M., Dang, J., & Smalley, S. L. (2009). Social functioning difficulties in ADHD: association with PDD risk. *Clin Child Psychol Psychiatry*, *14*(3), 329–344. https://doi.org/10.1177/1359104508100890

Carr, E. G., & Owen-Deschryver, J. S. (2007). Physical illness, pain, and problem behavior in minimally verbal people with developmental disabilities. *Journal of Autism and Developmental Disorders*, *37*(3), 413–424. https://doi.org/10.1007/s10803-006-0176-0

Castiello, U., Becchio, C., Zoia, S., Nelini, C., Sartori, L., Blason, L., … Gallese, V. (2010). Wired to be social: the ontogeny of human interaction. *PLoS One*, *5*(10), e13199. https://doi.org/10.1371/journal.pone.0013199

Castiello, U., Becchio, C., Zoia, S., Nelini, C., Sartori, L., Blason, L., … Gallese, V. (2010). Wired to be social: the ontogeny of human interaction. *PloS One*, *5*(10), e13199. https://doi.org/10.1371/journal.pone.0013199

Chaidez, V., Hansen, R. L., & Hertz-Picciotto, I. (2014). Gastrointestinal problems in children with autism, developmental delays or typical development. *Journal of Autism and Developmental Disorders*, *44*(5), 1117–1127. https://doi.org/10.1007/s10803-013-1973-x

Charman, T. (2014). Early identification and intervention in autism spectrum disorders: some progress but not as much as we hoped. *International Journal of Speech-*

Language Pathology, *16*(1), 15–18. https://doi.org/10.3109/17549507.2013.859732

Charman, T., & Baird, G. (2002). Practitioner review: Diagnosis of autism spectrum disorder in 2- and 3-year-old children. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *43*(3), 289–305.

Chaste, P., & Leboyer, M. (2012). Autism risk factors: genes, environment, and gene-environment interactions. *Dialogues in Clinical Neuroscience*, *14*(3), 281–292.

Chen, J., Chen, P., Bo, T., & Luo, K. (2016). Cognitive and Behavioral Outcomes of Intrauterine Growth Restriction School-Age Children. *Pediatrics*, *137*(4), e20153868. https://doi.org/10.1542/peds.2015-3868

Choi, B., Leech, K. A., Tager-Flusberg, H., & Nelson, C. A. (2018). Development of fine motor skills is associated with expressive language outcomes in infants at high and low risk for autism spectrum disorder. *Journal of Neurodevelopmental Disorders*, *10*(1), 14. https://doi.org/10.1186/s11689-018-9231-3

Colombi, C., Liebal, K., Tomasello, M., Young, G., Warneken, F., & Rogers, S. J. (2009). Examining correlates of cooperation in autism: Imitation, joint attention, and understanding intentions. *Autism*, *13*(2), 143–163. https://doi.org/10.1177/1362361308098514

Cook, J. (2016). From movement kinematics to social cognition: the case of autism. *Philos Trans R Soc Lond B Biol Sci*, *371*(1693). https://doi.org/10.1098/rstb.2015.0372

Courchesne, E., Carper, R., & Akshoomoff, N. (2003). Evidence of brain overgrowth in the first year of life in autism. *JAMA*, *290*(3), 337–344. https://doi.org/10.1001/jama.290.3.337

Coury, D., Jones, N. E., Klatka, K., Winklosky, B., Perrin, J.M. (2009) Healthcare for children with autism: the Autism Treatment Network. Curr Opin Pediatr. Dec;21(6):828-32. doi: 10.1097/MOP.0b013e328331eaaa.

Croen, L. A., Grether, J. K., Yoshida, C. K., Odouli, R., & Hendrick, V. (2011). Antidepressant use during pregnancy and childhood autism spectrum disorders. *Archives of General Psychiatry*, *68*(11), 1104–1112. https://doi.org/10.1001/archgenpsychiatry.2011.73

Cuijpers, R. H., van Schie, H. T., Koppen, M., Erlhagen, W., & Bekkering, H. (2006). Goals and means in action observation: a computational approach. *Neural Netw*, *19*(3), 311–322. https://doi.org/10.1016/j.neunet.2006.02.004

Damasio, H., Maurer, R. G., Damasio, A. R., & Chui, H. C. (1980). Computerized tomographic scan findings in patients with autistic behavior. *Archives of Neurology*, *37*(8), 504–510.

David, F. J., Baranek, G. T., Giuliani, C. A., Mercer, V. S., Poe, M. D., & Thorpe, D. E. (2009). A pilot study: coordination of precision grip in children and adolescents with high functioning autism. *Pediatric Physical Therapy: The Official Publication of the Section on Pediatrics of the American Physical Therapy Association*, *21*(2), 205–211. https://doi.org/10.1097/PEP.0b013e3181a3afc2

David, F. J., Baranek, G. T., Wiesen, C., Miao, A. F., & Thorpe, D. E. (2012). Coordination of precision grip in 2-6 years-old children with autism spectrum disorders compared to children developing typically and children with developmental disabilities. *Frontiers in Integrative Neuroscience*, *6*, 122. https://doi.org/10.3389/fnint.2012.00122

de Vries, J. I., Visser, G. H., & Prechtl, H. F. (1985). The emergence of fetal behaviour. II. Quantitative aspects. *Early Human Development*, *12*(2), 99–120.

Dowd, A. M., McGinley, J. L., Taffe, J. R., & Rinehart, N. J. (2012). Do planning and visual integration difficulties underpin motor dysfunction in autism? A kinematic study of young children with autism. *Journal of Autism and Developmental Disorders*, *42*(8), 1539–1548. https://doi.org/10.1007/s10803-011-1385-8

Dowell, L. R., Mahone, E. M., & Mostofsky, S. H. (2009). Associations of postural knowledge and basic motor skill with dyspraxia in autism: implication for abnormalities in distributed connectivity and motor learning. *Neuropsychology*, *23*(5), 563–570. https://doi.org/10.1037/a0015640

Downey, R., & Rapport, M. J. (2012). Motor activity in children with autism: a review of current literature. *Pediatr Phys Ther*, *24*(1), 2–20. https://doi.org/10.1097/PEP.0b013e31823db95f

Downey, R., & Rapport, M. J. K. (2012a). Motor activity in children with autism: a review of current literature. *Pediatric Physical Therapy: The Official Publication of the*

Section on Pediatrics of the American Physical Therapy Association, *24*(1), 2–20. https://doi.org/10.1097/PEP.0b013e31823db95f

Downey, R., & Rapport, M. J. K. (2012b). Motor activity in children with autism: a review of current literature. *Pediatric Physical Therapy: The Official Publication of the Section on Pediatrics of the American Physical Therapy Association*, *24*(1), 2–20. https://doi.org/10.1097/PEP.0b013e31823db95f

Dror, R., Malinger, G., Ben-Sira, L., Lev, D., Pick, C. G., & Lerman-Sagie, T. (2009). Developmental outcome of children with enlargement of the cisterna magna identified in utero. *Journal of Child Neurology*, *24*(12), 1486–1492. https://doi.org/10.1177/0883073808331358

Duby, J. C., Disabilities, C. on C. with, Lipkin, P. H., Disabilities, C. on C. with, Macias, M. M., Pediatrics, S. on D. and B., … Capers, M. (2018). Identifying infants and young children with developmental disorders in the medical home: An algorithm for developmental surveillance and screening. *Pediatrics*, *118*(1), 405–420. https://doi.org/10.1542/peds.2006-1231

Dziuk, M. A., Gidley Larson, J. C., Apostu, A., Mahone, E. M., Denckla, M. B., & Mostofsky, S. H. (2007). Dyspraxia in autism: association with motor, social, and communicative deficits. *Dev Med Child Neurol*, *49*(10), 734–739. https://doi.org/10.1111/j.1469-8749.2007.00734.x

Egaña-Ugrinovic, G., Sanz-Cortés, M., Couve-Pérez, C., Figueras, F., & Gratacós, E. (2014). Corpus callosum differences assessed by fetal MRI in late-onset intrauterine growth restriction and its association with neurobehavior. *Prenatal Diagnosis*, *34*(9), 843–849. https://doi.org/10.1002/pd.4381

Eggleston, J. D., Harry, J. R., Hickman, R. A., & Dufek, J. S. (2017). Analysis of gait symmetry during over-ground walking in children with autism spectrum disorder. *Gait & Posture*, *55*, 162–166. https://doi.org/10.1016/j.gaitpost.2017.04.026

Einspieler C, et al. (1997). The qualitative assessment of general movements in preterm, term and young infants--review of the methodology. - PubMed - NCBI. Retrieved from https://www-ncbi-nlm-nih-gov.bibliosan.clas.cineca.it/pubmed/?term=Einspieler%2CC.%2CPrechtl%2CH.F.R.%2CBos%2CA.F.%2CFerrari%2CF.%2Cand+Cioni%2CG.Prechtl%E2%80%99s+method+on+the+qualitative+assessment+of+general+movements+in+preterm%2C+t

erm+and+young+infants.+2004%3B+Clin.+Dev.+Med%3B+167%3A+1%E2%80%9391.

Einspieler, C., Bos, A. F., Libertus, M. E., & Marschik, P. B. (2016). The General Movement Assessment Helps Us to Identify Preterm Infants at Risk for Cognitive Dysfunction. *Front Psychol*, *7*, 406. https://doi.org/10.3389/fpsyg.2016.00406

Einspieler, C., & Prechtl, H. F. (2005). Prechtl's assessment of general movements: a diagnostic tool for the functional assessment of the young nervous system. *Ment Retard Dev Disabil Res Rev*, *11*(1), 61–67. https://doi.org/10.1002/mrdd.20051

Einspieler, C., Sigafoos, J., Bölte, S., Bratl-Pokorny, K. D., Landa, R., & Marschik, P. B. (2014). Highlighting the first 5 months of life: General movements in infants later diagnosed with autism spectrum disorder or Rett Syndrome. *Res Autism Spectr Disord*, *8*(3), 286–291. https://doi.org/10.1016/j.rasd.2013.12.013

Eixarch, E., Meler, E., Iraola, A., Illa, M., Crispi, F., Hernandez-Andrade, E., … Figueras, F. (2008). Neurodevelopmental outcome in 2-year-old infants who were small-for-gestational age term fetuses with cerebral blood flow redistribution. *Ultrasound in Obstetrics & Gynecology: The Official Journal of the International Society of Ultrasound in Obstetrics and Gynecology*, *32*(7), 894–899. https://doi.org/10.1002/uog.6249

Eliasen, M., Tolstrup, J. S., Nybo Andersen, A.-M., Grønbaek, M., Olsen, J., & Strandberg-Larsen, K. (2010). Prenatal alcohol exposure and autistic spectrum disorders--a population-based prospective study of 80,552 children and their mothers. *International Journal of Epidemiology*, *39*(4), 1074–1081. https://doi.org/10.1093/ije/dyq056

Elison, J. T., Paterson, S. J., Wolff, J. J., Reznick, J. S., Sasson, N. J., Gu, H., … Network, I. (2013). White matter microstructure and atypical visual orienting in 7-month-olds at risk for autism. *The American Journal of Psychiatry*, *170*(8), 899–908. https://doi.org/10.1176/appi.ajp.2012.12091150

Epstein, J. N., Langberg, J. M., Rosen, P. J., Graham, A., Narad, M. E., Antonini, T. N., … Altaye, M. (2011). Evidence for higher reaction time variability for children with ADHD on a range of cognitive tasks including reward and event rate manipulations. *Neuropsychology*, *25*(4), 427–441. https://doi.org/10.1037/a0022155

Esposito, G., & Venuti, P. (2008). Analysis of toddlers' gait after six months of independent walking to identify autism: a preliminary study. *Perceptual and Motor Skills*, *106*(1), 259–269. https://doi.org/10.2466/pms.106.1.259-269

Esposito, G., Venuti, P., Apicella, F., & Muratori, F. (2011). Analysis of unsupported gait in toddlers with autism. *Brain & Development*, *33*(5), 367–373. https://doi.org/10.1016/j.braindev.2010.07.006

Esposito, G., Venuti, P., Maestro, S., & Muratori, F. (2009). An exploration of symmetry in early autism spectrum disorders: analysis of lying. *Brain & Development*, *31*(2), 131–138. https://doi.org/10.1016/j.braindev.2008.04.005

Fabbri-Destro, M., Cattaneo, L., Boria, S., & Rizzolatti, G. (2009). Planning actions in autism. *Experimental Brain Research*, *192*(3), 521–525. https://doi.org/10.1007/s00221-008-1578-3

Fagard J, et al. (2019). Fetal Origin of Sensorimotor Behavior. - PubMed - NCBI. Retrieved from https://www-ncbi-nlm-nih-gov.bibliosan.clas.cineca.it/pubmed/29875649

Fakhoury, M. (2015). Autistic spectrum disorders: A review of clinical features, theories and diagnosis. *International Journal of Developmental Neuroscience*, *43*, 70–77. https://doi.org/10.1016/j.ijdevneu.2015.04.003

Falck-Ytter, T., Gredeback, G., & von Hofsten, C. (2006). Infants predict other people's action goals. *Nat Neurosci*, *9*(7), 878–879. https://doi.org/10.1038/nn1729

Falip, C., Blanc, N., Maes, E., Zaccaria, I., Oury, J. F., Sebag, G., & Garel, C. (2007). Postnatal clinical and imaging follow-up of infants with prenatal isolated mild ventriculomegaly: a series of 101 cases. *Pediatric Radiology*, *37*(10), 981–989. https://doi.org/10.1007/s00247-007-0582-2

Fatemi, S. H., Aldinger, K. A., Ashwood, P., Bauman, M. L., Blaha, C. D., Blatt, G. J., … Welsh, J. P. (2012). Consensus paper: pathological role of the cerebellum in autism. *Cerebellum (London, England)*, *11*(3), 777–807. https://doi.org/10.1007/s12311-012-0355-9

Ferrari, F., Cioni, G., Einspieler, C., Roversi, M. F., Bos, A. F., Paolicelli, P. B., … Prechtl, H. F. (2002). Cramped synchronized general movements in preterm infants as an early marker for cerebral palsy. *Arch Pediatr Adolesc Med*, *156*(5), 460–467.

Ferrari, F., Cioni, G., Einspieler, C., Roversi, M. F., Bos, A. F., Paolicelli, P. B., … Prechtl, H. F. R. (2019). Cramped Synchronized General Movements in Preterm Infants as an

Early Marker for Cerebral Palsy. *Archives of Pediatrics & Adolescent Medicine*, *156*(5), 460–467. https://doi.org/10.1001/archpedi.156.5.460

Ferrari, G. A., Nicolini, Y., Demuru, E., Tosato, C., Hussain, M., Scesa, E., … Ferrari, P. F. (2016). Ultrasonographic Investigation of Human Fetus Responses to Maternal Communicative and Non-communicative Stimuli. *Frontiers in Psychology*, *7*, 354. https://doi.org/10.3389/fpsyg.2016.00354

Figueras, F., Eixarch, E., Meler, E., Iraola, A., Figueras, J., Puerto, B., & Gratacos, E. (2008). Small-for-gestational-age fetuses with normal umbilical artery Doppler have suboptimal perinatal and neurodevelopmental outcome. *European Journal of Obstetrics, Gynecology, and Reproductive Biology*, *136*(1), 34–38. https://doi.org/10.1016/j.ejogrb.2007.02.016

Figueras, F., & Gardosi, J. (2011). Intrauterine growth restriction: new concepts in antenatal surveillance, diagnosis, and management. *American Journal of Obstetrics and Gynecology*, *204*(4), 288–300. https://doi.org/10.1016/j.ajog.2010.08.055

Fitzpatrick, P., Diorio, R., Richardson, M. J., & Schmidt, R. C. (2013). Dynamical methods for evaluating the time-dependent unfolding of social coordination in children with autism. *Front Integr Neurosci*, *7*, 21. https://doi.org/10.3389/fnint.2013.00021

Flanagan, J. E., Landa, R., Bhat, A., & Bauman, M. (2012). Head lag in infants at risk for autism: a preliminary study. *The American Journal of Occupational Therapy: Official Publication of the American Occupational Therapy Association*, *66*(5), 577–585. https://doi.org/10.5014/ajot.2012.004192

Folio MR, Fewell RR (2000). Peabody developmental motor scales examiner's manual (2nd ed.). pro-Ed, Austin.

Fombonne, E. (2003). Epidemiological surveys of autism and other pervasive developmental disorders: an update. *J Autism Dev Disord*, *33*(4), 365–382.

Forti, S., Valli, A., Perego, P., Nobile, M., Crippa, A., & Molteni, M. (2011). Motor planning and control in autism. A kinematic analysis of preschool children. *Research in Autism Spectrum Disorders*, *5*(2), 834–842. https://doi.org/10.1016/j.rasd.2010.09.013

Fournier, K. A., Hass, C. J., Naik, S. K., Lodha, N., & Cauraugh, J. H. (2010). Motor coordination in autism spectrum disorders: a synthesis and meta-analysis. *Journal of Autism and Developmental Disorders*, *40*(10), 1227–1240. https://doi.org/10.1007/s10803-010-0981-3

Fulceri, F., Guzzetta, A., Athanasiadou, A., Iaconianni, L., & Scattoni, M. L. (2018). Antenatal ultrasound value in risk calculation for Autism Spectrum Disorder: A systematic review to support future research. *Neuroscience and Biobehavioral Reviews*, *92*, 83–92. https://doi.org/10.1016/j.neubiorev.2018.05.016

Fulceri, F., Morelli, M., Santocchi, E., Cena, H., Del Bianco, T., Narzisi, A., … Muratori, F. (2016). Gastrointestinal symptoms and behavioral problems in preschoolers with Autism Spectrum Disorder. *Dig Liver Dis*, *48*(3), 248–254. https://doi.org/10.1016/j.dld.2015.11.026

Fulceri, F., Narzisi, A., Apicella, F., Balboni, G., Baldini, S., Brocchini, J., … Calderoni, S. (2016). Application of the Repetitive Behavior Scale-Revised--Italian version--in preschoolers with autism spectrum disorder. *Res Dev Disabil*, *48*, 43–52. https://doi.org/10.1016/j.ridd.2015.10.015

Fulceri, F., Tonacci, A., Lucaferro, A., Apicella, F., Narzisi, A., Vincenti, G., … Contaldo, A. (2018). Interpersonal motor coordination during joint actions in children with and without autism spectrum disorder: The role of motor information. *Res Dev Disabil*, *80*, 13–23. https://doi.org/10.1016/j.ridd.2018.05.018

Fulceri F., Contaldo A., Parrini I., Sara C., Narzisi A., Tancredi R., Apicella F., Muratori F. (2015). Locomotion and grasping impairment in preschoolers with autism spectrum disorder. *Clinical Neuropsychiatry* 12(4):94-100

Fulceri F., Grossi E., Contaldo A., Narzisi A., Apicella F., Parrini I., Tancredi R., Calderoni S., Muratori F. Motor Skills as Moderators of Core Symptoms in Autism Spectrum Disorders: Preliminary Data from an Exploratory Analysis with Artificial Neural Networks. Frontiers in Physiology 09 January 2019 | https://doi.org/10.3389/fpsyg.2018.02683

Gallese, V., Rochat, M. J., & Berchio, C. (2013). The mirror mechanism and its potential role in autism spectrum disorder. *Developmental Medicine and Child Neurology*, *55*(1), 15–22. https://doi.org/10.1111/j.1469-8749.2012.04398.x

Gamliel, M., Ebstein, R., Yirmiya, N., & Mankuta, D. (2012). Minor fetal sonographic findings in autism spectrum disorder. *Obstetrical & Gynecological Survey*, *67*(3), 176–186. https://doi.org/10.1097/OGX.0b013e31824bb5d6

Gardener, H., Spiegelman, D., & Buka, S. L. (2011). Perinatal and neonatal risk factors for autism: a comprehensive meta-analysis. *Pediatrics*, *128*(2), 344–355. https://doi.org/10.1542/peds.2010-1036

Garrido, D., Petrova, D., Watson, L. R., Garcia-Retamero, R., & Carballo, G. (2017). Language and motor skills in siblings of children with autism spectrum disorder: A meta-analytic review. *Autism Res*, *10*(11), 1737–1750. https://doi.org/10.1002/aur.1829

Gazzola, V., & Keysers, C. (2009). The observation and execution of actions share motor and somatosensory voxels in all tested subjects: single-subject analyses of unsmoothed fMRI data. *Cerebral Cortex (New York, N.Y.: 1991)*, *19*(6), 1239–1255. https://doi.org/10.1093/cercor/bhn181

Gernsbacher, M. A., Sauer, E. A., Geye, H. M., Schweigert, E. K., & Hill Goldsmith, H. (2008). Infant and toddler oral- and manual-motor skills predict later speech fluency in autism. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *49*(1), 43–50. https://doi.org/10.1111/j.1469-7610.2007.01820.x

Ghanouni, P., Memari, A. H., Shayestehfar, M., Moshayedi, P., Gharibzadeh, S., & Ziaee, V. (2015). Biological Motion Perception Is Affected by Age and Cognitive Style in Children Aged 8–15. *Neurology Research International*, *2015*. https://doi.org/10.1155/2015/594042

Gillberg, C., Ehlers, S., Schaumann, H., Jakobsson, G., Dahlgren, S. O., Lindblom, R., … Blidner, E. (1990). Autism under age 3 years: a clinical study of 28 cases referred for autistic symptoms in infancy. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *31*(6), 921–934.

Gillberg, C., & Kadesjo, B. (2003). Why bother about clumsiness? The implications of having developmental coordination disorder (DCD). *Neural Plast*, *10*(1–2), 59–68. https://doi.org/10.1155/np.2003.59

Gilmore, J. H., Smith, L. C., Wolfe, H. M., Hertzberg, B. S., Smith, J. K., Chescheir, N. C., … Gerig, G. (2008). Prenatal mild ventriculomegaly predicts abnormal development

of the neonatal brain. *Biological Psychiatry*, *64*(12), 1069–1076. https://doi.org/10.1016/j.biopsych.2008.07.031

Gilmore, J. H., van Tol, J. J., Lewis Streicher, H., Williamson, K., Cohen, S. B., Greenwood, R. S., … Chescheir, N. C. (2001). Outcome in children with fetal mild ventriculomegaly: a case series. *Schizophrenia Research*, *48*(2–3), 219–226.

Glazebrook, C. M., Elliott, D., & Lyons, J. (2006). A kinematic analysis of how young adults with and without autism plan and control goal-directed movements. *Motor Control*, *10*(3), 244–264.

Glazebrook, C. M., Elliott, D., & Szatmari, P. (2008). How do individuals with autism plan their movements? *Journal of Autism and Developmental Disorders*, *38*(1), 114–126. https://doi.org/10.1007/s10803-007-0369-1

Gonzalez, D. A., Glazebrook, C. M., Studenka, B. E., & Lyons, J. (2013). Motor interactions with another person: do individuals with Autism Spectrum Disorder plan ahead? *Front Integr Neurosci*, *7*, 23. https://doi.org/10.3389/fnint.2013.00023

Gowen, E., & Hamilton, A. (2013a). Motor abilities in autism: a review using a computational context. *Journal of Autism and Developmental Disorders*, *43*(2), 323–344. https://doi.org/10.1007/s10803-012-1574-0

Gowen, E., & Hamilton, A. (2013b). Motor Abilities in Autism: A Review Using a Computational Context. *Journal of Autism and Developmental Disorders*, *43*(2), 323–344. https://doi.org/10.1007/s10803-012-1574-0

Green, D., Charman, T., Pickles, A., Chandler, S., Loucas, T., Simonoff, E., & Baird, G. (2009). Impairment in movement skills of children with autistic spectrum disorders. *Developmental Medicine and Child Neurology*, *51*(4), 311–316. https://doi.org/10.1111/j.1469-8749.2008.03242.x

Greffou, S., Bertone, A., Hahler, E.-M., Hanssens, J.-M., Mottron, L., & Faubert, J. (2012). Postural hypo-reactivity in autism is contingent on development and visual environment: a fully immersive virtual reality study. *Journal of Autism and Developmental Disorders*, *42*(6), 961–970. https://doi.org/10.1007/s10803-011-1326-6

Groen, W., Teluij, M., Buitelaar, J., & Tendolkar, I. (2010). Amygdala and hippocampus enlargement during adolescence in autism. *Journal of the American Academy of*

Child and Adolescent Psychiatry, *49*(6), 552–560. https://doi.org/10.1016/j.jaac.2009.12.023

Gross, A. L., Stuart, E. A., & Faherty, A. (2013). Developmental trajectories in children with and without autism spectrum disorders: the first 3 years. *Child Development*, *84*(2), 429–442. https://doi.org/10.1111/j.1467-8624.2012.01870.x

Grzadzinski, R., Di Martino, A., Brady, E., Mairena, M. A., O'Neale, M., Petkova, E., … Castellanos, F. X. (2011). Examining autistic traits in children with ADHD: does the autism spectrum extend to ADHD? *J Autism Dev Disord*, *41*(9), 1178–1191. https://doi.org/10.1007/s10803-010-1135-3

Hadders-Algra, M. (2007). Putative neural substrate of normal and abnormal general movements. *Neurosci Biobehav Rev*, *31*(8), 1181–1190. https://doi.org/10.1016/j.neubiorev.2007.04.009

Hadders-Algra, M., Bouwstra, H., & Groen, S. E. (2009). Quality of general movements and psychiatric morbidity at 9 to 12 years. *Early Hum Dev*, *85*(1), 1–6. https://doi.org/10.1016/j.earlhumdev.2008.05.005

Hadders-Algra, M. (2018), Neural substrate and clinical significance of general movements: an update. *Dev Med Child Neurol*, 60: 39-46. doi:10.1111/dmcn.13540

Hadders-Algra, M. (2018), Early human motor development: From variation to the ability to vary and adapt. *Neuroscience and Biobehavioral Reviews*, Jul;90:411-427. doi: 10.1016/j.neubiorev.2018.05.009. Epub 2018 May 9.

Hallett, M., Lebiedowska, M. K., Thomas, S. L., Stanhope, S. J., Denckla, M. B., & Rumsey, J. (1993). Locomotion of autistic adults. *Archives of Neurology*, 50(12), 1304–1308.

Hamer EG, et al. (2016). Specific characteristics of abnormal general movements are associated with functional outcome at school age. - PubMed - NCBI. Retrieved from https://www-ncbi-nlm-nih-gov.bibliosan.clas.cineca.it/pubmed/26896696

Happé, F., Ronald, A., & Plomin, R. (2006). Time to give up on a single explanation for autism. *Nature Neuroscience*, *9*(10), 1218–1220. https://doi.org/10.1038/nn1770

Harrop, C., McConachie, H., Emsley, R., Leadbitter, K., Green, J., & Consortium, P. (2014). Restricted and repetitive behaviors in autism spectrum disorders and typical development: cross-sectional and longitudinal comparisons. *Journal of Autism and*

Developmental Disorders, *44*(5), 1207–1219. https://doi.org/10.1007/s10803-013-1986-5

Hazlett, H. C., Gu, H., Munsell, B. C., Kim, S. H., Styner, M., Wolff, J. J., … Statistical, A. (2017). Early brain development in infants at high risk for autism spectrum disorder. *Nature*, *542*(7641), 348–351. https://doi.org/10.1038/nature21369

Heathcock, J. C., Tanner, K., Robson, D., Young, R., & Lane, A. E. (2015). Retrospective Analysis of Motor Development in Infants at High and Low Risk for Autism Spectrum Disorder. *American Journal of Occupational Therapy*, *69*(5), p1–p9. https://doi.org/10.5014/ajot.2015.017525

Hedgecock, J. B., Dannemiller, L. A., Shui, A. M., Rapport, M. J., & Katz, T. (2018). Associations of Gross Motor Delay, Behavior, and Quality of Life in Young Children With Autism Spectrum Disorder. *Phys Ther*, *98*(4), 251–259. https://doi.org/10.1093/ptj/pzy006

Hellmuth, S. G., Pedersen, L. H., Miltoft, C. B., Petersen, O. B., Kjaergaard, S., Ekelund, C., & Tabor, A. (2017). Increased nuchal translucency thickness and risk of neurodevelopmental disorders. *Ultrasound in Obstetrics & Gynecology: The Official Journal of the International Society of Ultrasound in Obstetrics and Gynecology*, *49*(5), 592–598. https://doi.org/10.1002/uog.15961

Henderson SE, Sugden DA, Barnett AL. Movement assessment battery for children-2 second edition [Movement ABC-2]. London, UK: The Psychological Corporation, 2007.

Henrichs, J., Schenk, J. J., Barendregt, C. S., Schmidt, H. G., Steegers, E. A., Hofman, A., … Tiemeier, H. (2010). Fetal growth from mid- to late pregnancy is associated with infant development: the Generation R Study. *Developmental Medicine and Child Neurology*, *52*(7), 644–651. https://doi.org/10.1111/j.1469-8749.2009.03513.x

Hiller, R. M., Young, R. L., & Weber, N. (2016). Sex differences in pre-diagnosis concerns for children later diagnosed with autism spectrum disorder. *Autism*, *20*(1), 75–84. https://doi.org/10.1177/1362361314568899

Hilton, C. L., Zhang, Y., Whilte, M. R., Klohr, C. L., & Constantino, J. (2012). Motor impairment in sibling pairs concordant and discordant for autism spectrum disorders. *Autism: The International Journal of Research and Practice*, *16*(4), 430–441. https://doi.org/10.1177/1362361311423018

Hitzert, M. M., Roze, E., Van Braeckel, K. N., & Bos, A. F. (2014). Motor development in 3-month-old healthy term-born infants is associated with cognitive and behavioural outcomes at early school age. *Dev Med Child Neurol*, *56*(9), 869–876. https://doi.org/10.1111/dmcn.12468

Hobbs, K., Kennedy, A., Dubray, M., Bigler, E. D., Petersen, P. B., McMahon, W., & Lainhart, J. E. (2007). A retrospective fetal ultrasound study of brain size in autism. *Biological Psychiatry*, *62*(9), 1048–1055. https://doi.org/10.1016/j.biopsych.2007.03.020

Honemeyer, U., Talic, A., Therwat, A., Paulose, L., & Patidar, R. (2013). The clinical value of KANET in studying fetal neurobehavior in normal and at-risk pregnancies. *Journal of Perinatal Medicine*, *41*(2), 187–197. https://doi.org/10.1515/jpm-2011-0251

Horak, F. B. (2006). Postural orientation and equilibrium: what do we need to know about neural control of balance to prevent falls? *Age and Ageing*, *35 Suppl 2*, ii7-ii11. https://doi.org/10.1093/ageing/afl077

Hughes, C. (1996). Brief report: planning problems in autism at the level of motor control. *Journal of Autism and Developmental Disorders*, *26*(1), 99–107.

Hunter, D. J. (2005). Gene-environment interactions in human diseases. *Nature Reviews. Genetics*, *6*(4), 287–298. https://doi.org/10.1038/nrg1578

Identifying Infants and Young Children With Developmental Disorders in the Medical Home: An Algorithm for Developmental Surveillance and Screening. (2006). *Pediatrics*, *118*(1), 405. https://doi.org/10.1542/peds.2006-1231

Iverson, J. M., & Wozniak, R. H. (2007). Variation in vocal-motor development in infant siblings of children with autism. *Journal of Autism and Developmental Disorders*, *37*(1), 158–170. https://doi.org/10.1007/s10803-006-0339-z

Iwanaga, R., Kawasaki, C., & Tsuchida, R. (2000). Brief report: Comparison of sensory-motor and cognitive function between autism and Asperger syndrome in preschool children. *Journal of Autism and Developmental Disorders*, *30*(2), 169–174.

Jasmin, E., Couture, M., McKinley, P., Reid, G., Fombonne, E., & Gisel, E. (2009a). Sensori-motor and daily living skills of preschool children with autism spectrum disorders.

Journal of Autism and Developmental Disorders, *39*(2), 231–241. https://doi.org/10.1007/s10803-008-0617-z

Jasmin, E., Couture, M., McKinley, P., Reid, G., Fombonne, E., & Gisel, E. (2009b). Sensori-motor and daily living skills of preschool children with autism spectrum disorders. *Journal of Autism and Developmental Disorders*, *39*(2), 231–241. https://doi.org/10.1007/s10803-008-0617-z

Jia, F., Wang, B., Shan, L., Xu, Z., Staal, W. G., & Du, L. (2015). Core symptoms of autism improved after vitamin D supplementation. *Pediatrics*, *135*(1), e196-198. https://doi.org/10.1542/peds.2014-2121

Jones, E. J. H., Gliga, T., Bedford, R., Charman, T., & Johnson, M. H. (2014). Developmental pathways to autism: A review of prospective studies of infants at risk. *Neuroscience & Biobehavioral Reviews*, *39*, 1–33. https://doi.org/10.1016/j.neubiorev.2013.12.001

Jones, W., Carr, K., & Klin, A. (2008). Absence of preferential looking to the eyes of approaching adults predicts level of social disability in 2-year-old toddlers with autism spectrum disorder. *Archives of General Psychiatry*, *65*(8), 946–954. https://doi.org/10.1001/archpsyc.65.8.946

Joseph, L., Thurm, A., Farmer, C., & Shumway, S. (2013). Repetitive Behavior and Restricted Interests in Young Children with Autism: Comparisons with Controls and Stability Over 2 Years. *Autism Research*, *6*(6), 584–595. https://doi.org/10.1002/aur.1316

Karasik, L. B., Tamis-Lemonda, C. S., & Adolph, K. E. (2014). Crawling and walking infants elicit different verbal responses from mothers. *Developmental Science*, *17*(3), 388–395. https://doi.org/10.1111/desc.12129

Kennedy, J., Brown, T., & Chien, C.-W. (2012). Motor skill assessment of children: is there an association between performance-based, child-report, and parent-report measures of children's motor skills? *Phys. Occup. Ther. Pediatr.*, *32*(2), 196–209. https://doi.org/10.3109/01942638.2011.631101

Kern JK, et al. (2015). Are ASD and ADHD a Continuum? A Comparison of Pathophysiological Similarities Between the Disorders. - PubMed - NCBI. Retrieved from https://www-ncbi-nlm-nih-gov.bibliosan.clas.cineca.it/pubmed/23074304

Keysers, C., & Gazzola, V. (2009). Expanding the mirror: vicarious activity for actions, emotions, and sensations. *Current Opinion in Neurobiology*, *19*(6), 666–671. https://doi.org/10.1016/j.conb.2009.10.006

Khalil, A., & Thilaganathan, B. (2017). Role of uteroplacental and fetal Doppler in identifying fetal growth restriction at term. *Best Practice & Research. Clinical Obstetrics & Gynaecology*, *38*, 38–47. https://doi.org/10.1016/j.bpobgyn.2016.09.003

Kilner, J. M., & Frith, C. D. (2007). A possible role for primary motor cortex during action observation. *Proc Natl Acad Sci U S A*, *104*(21), 8683–8684. https://doi.org/10.1073/pnas.0702937104

Kim, H. U. (2008). Development of early language and motor skills in preschool children with autism. *Percept Mot Skills*, *107*(2), 403–406. https://doi.org/10.2466/pms.107.2.403-406

Kim, S. H., & Lord, C. (2010). Restricted and repetitive behaviors in toddlers and preschoolers with autism spectrum disorders based on the Autism Diagnostic Observation Schedule (ADOS). *Autism Research: Official Journal of the International Society for Autism Research*, *3*(4), 162–173. https://doi.org/10.1002/aur.142

Kindregan, D., Gallagher, L., & Gormley, J. (2015). Gait deviations in children with autism spectrum disorders: a review. *Autism Research and Treatment*, *2015*, 741480. https://doi.org/10.1155/2015/741480

Kisilevsky, B. S., Hains, S. M. J., Brown, C. A., Lee, C. T., Cowperthwaite, B., Stutzman, S. S., … Wang, Z. (2009). Fetal sensitivity to properties of maternal speech and language. *Infant Behavior & Development*, *32*(1), 59–71. https://doi.org/10.1016/j.infbeh.2008.10.002

Klukowski, M., Wasilewska, J., Lebensztejn, D. (2015) Sleep and gastrointestinal disturbances in autism spectrum disorder in children. *Dev Period Med*. 2015 Apr-Jun;19(2):157-61.

Knoblich, G., & Sebanz, N. (2008). Evolving intentions for social interaction: from entrainment to joint action. *Philos Trans R Soc Lond B Biol Sci*, *363*(1499), 2021–2031. https://doi.org/10.1098/rstb.2008.0006

Kohen-Raz, R., Volkmar, F. R., & Cohen, D. J. (1992). Postural control in children with autism. *Journal of Autism and Developmental Disorders*, *22*(3), 419–432.

Kopp, S., Beckung, E., & Gillberg, C. (2010). Developmental coordination disorder and other motor control problems in girls with autism spectrum disorder and/or attention-deficit/hyperactivity disorder. *Research in Developmental Disabilities*, *31*(2), 350–361. https://doi.org/10.1016/j.ridd.2009.09.017

Kovaniemi, S., Alakortes, J., Carter, A. S., Yliherva, A., Bloigu, R., Joskitt, L. O., … Ebeling, H. E. (2018). How are social-emotional and behavioral competences and problems at age 1 year associated with infant motor development? A general population study. *Infant Behavior & Development*, *51*, 1–14. https://doi.org/10.1016/j.infbeh.2018.02.007

Kuno, A., Akiyama, M., Yamashiro, C., Tanaka, H., Yanagihara, T., & Hata, T. (2001). Three-dimensional sonographic assessment of fetal behavior in the early second trimester of pregnancy. *Journal of Ultrasound in Medicine: Official Journal of the American Institute of Ultrasound in Medicine*, *20*(12), 1271–1275.

Kurjak, A., Abo-Yaqoub, S., Stanojevic, M., Yigiter, A. B., Vasilj, O., Lebit, D., … Kadic, A. S. (2010). The potential of 4D sonography in the assessment of fetal neurobehavior--multicentric study in high-risk pregnancies. *Journal of Perinatal Medicine*, *38*(1), 77–82. https://doi.org/10.1515/JPM.2010.012

Kurjak, A., Stanojević, M., Predojević, M., Laušin, I., & Salihagić-Kadić, A. (2012). Neurobehavior in fetal life. *Seminars in Fetal & Neonatal Medicine*, *17*(6), 319–323. https://doi.org/10.1016/j.siny.2012.06.005

Kurjak, A., Tikvica, A., Stanojevic, M., Miskovic, B., Ahmed, B., Azumendi, G., & Di Renzo, G. C. (2008). The assessment of fetal neurobehavior by three-dimensional and four-dimensional ultrasound. *The Journal of Maternal-Fetal & Neonatal Medicine: The Official Journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians*, *21*(10), 675–684. https://doi.org/10.1080/14767050802212166

Kutuk, M. S., Ozgun, M. T., Uludag, S., Dolanbay, M., Poyrazoglu, H. G., & Tas, M. (2013). Postnatal outcome of isolated, nonprogressive, mild borderline fetal ventriculomegaly. *Child's Nervous System: ChNS: Official Journal of the*

International Society for Pediatric Neurosurgery, *29*(5), 803–808. https://doi.org/10.1007/s00381-013-2020-0

Lai, M. C., Baron-Cohen, S., & Buxbaum, J. D. (2015). Understanding autism in the light of sex/gender. *Mol Autism*, *6*, 24. https://doi.org/10.1186/s13229-015-0021-4

Landa, R., & Garrett-Mayer, E. (2006). Development in infants with autism spectrum disorders: a prospective study. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *47*(6), 629–638. https://doi.org/10.1111/j.1469-7610.2006.01531.x

Landa, R. J., Gross, A. L., Stuart, E. A., & Bauman, M. (2012). Latent class analysis of early developmental trajectory in baby siblings of children with autism. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *53*(9), 986–996. https://doi.org/10.1111/j.1469-7610.2012.02558.x

LeBarton, E. S., & Iverson, J. M. (2013). Fine motor skill predicts expressive language in infant siblings of children with autism. *Developmental Science*, *16*(6), 815–827. https://doi.org/10.1111/desc.12069

Lebit, D. F.-D., & Vladareanu, P. D. R. (2011). The Role of 4D Ultrasound in the Assessment of Fetal Behaviour. *Maedica*, *6*(2), 120–127.

Lecanuet, J. P., Granier-Deferre, C., & Busnel, M. C. (1989). Differential fetal auditory reactiveness as a function of stimulus characteristics and state. *Seminars in Perinatology*, *13*(5), 421–429.

Leekam, S. R., Prior, M. R., & Uljarevic, M. (2011). Restricted and repetitive behaviors in autism spectrum disorders: a review of research in the last decade. *Psychological Bulletin*, *137*(4), 562–593. https://doi.org/10.1037/a0023341

Lemcke, S., Juul, S., Parner, E. T., Lauritsen, M. B., & Thorsen, P. (2013a). Early signs of autism in toddlers: a follow-up study in the Danish National Birth Cohort. *Journal of Autism and Developmental Disorders*, *43*(10), 2366–2375. https://doi.org/10.1007/s10803-013-1785-z

Lemcke, S., Juul, S., Parner, E. T., Lauritsen, M. B., & Thorsen, P. (2013b). Early signs of autism in toddlers: a follow-up study in the Danish National Birth Cohort. *Journal of Autism and Developmental Disorders*, *43*(10), 2366–2375. https://doi.org/10.1007/s10803-013-1785-z

Leonard, H. C., Elsabbagh, M., Hill, E. L., & Basis, team. (2014). Early and persistent motor delay in infants at-risk of developing autism spectrum disorder: A prospective study. *European Journal of Developmental Psychology*, *11*, 18–35.

Libertus, K., & Landa, R. J. (2013). The Early Motor Questionnaire (EMQ): a parental report measure of early motor development. *Infant Behav. Dev.*, *36*(4), 833–842. https://doi.org/10.1016/j.infbeh.2013.09.007

Libertus, K., & Needham, A. (2011). Reaching experience increases face preference in 3-month-old infants. *Dev Sci*, *14*(6), 1355–1364. https://doi.org/10.1111/j.1467-7687.2011.01084.x

Libertus, K., Sheperd, K. A., Ross, S. W., & Landa, R. J. (2014). Limited fine motor and grasping skills in 6-month-old infants at high risk for autism. *Child Development*, *85*(6), 2218–2231. https://doi.org/10.1111/cdev.12262

Libertus, K., & Violi, D. A. (2016). Sit to Talk: Relation between Motor Skills and Language Development in Infancy. *Frontiers in Psychology*, *7*, 475. https://doi.org/10.3389/fpsyg.2016.00475

Liebal, K., Colombi, C., Rogers, S. J., Warneken, F., & Tomasello, M. (2008). Helping and cooperation in children with autism. *J Autism Dev Disord*, *38*(2), 224–238. https://doi.org/10.1007/s10803-007-0381-5

Lim, Y. H., Partridge, K., Girdler, S., & Morris, S. L. (2017). Standing Postural Control in Individuals with Autism Spectrum Disorder: Systematic Review and Meta-analysis. *Journal of Autism and Developmental Disorders*, *47*(7), 2238–2253. https://doi.org/10.1007/s10803-017-3144-y

Linkenauger, S. A., Lerner, M. D., Ramenzoni, V. C., & Proffitt, D. R. (2012). A perceptual-motor deficit predicts social and communicative impairments in individuals with autism spectrum disorders. *Autism Research: Official Journal of the International Society for Autism Research*, *5*(5), 352–362. https://doi.org/10.1002/aur.1248

Liu, T., & Breslin, C. M. (2013). The effect of a picture activity schedule on performance of the MABC-2 for children with autism spectrum disorder. *Research Quarterly for Exercise and Sport*, *84*(2), 206–212. https://doi.org/10.1080/02701367.2013.784725

Lloyd, M., MacDonald, M., & Lord, C. (2013). Motor Skills of Toddlers with Autism Spectrum Disorders. *Autism : The International Journal of Research and Practice*, *17*(2), 133. https://doi.org/10.1177/1362361311402230

Loh, A., Soman, T., Brian, J., Bryson, S. E., Roberts, W., Szatmari, P., … Zwaigenbaum, L. (2007). Stereotyped motor behaviors associated with autism in high-risk infants: a pilot videotape analysis of a sibling sample. *Journal of Autism and Developmental Disorders*, *37*(1), 25–36. https://doi.org/10.1007/s10803-006-0333-5

Lord, C., Risi, S., Lambrecht, L., Cook, E. h., Leventhal, B. L., DiLavore, P. C., Pickles, A., Rutter, M. (2000). The autism diagnostic observation schedule-generic: A standard measure of social and communication deficits associated with the spectrum of autism. *Journal of Autism and Developmental Disorders 30*(3), 205-223.

Lüchinger, A. B., Hadders-Algra, M., van Kan, C. M., & de Vries, J. I. P. (2008). Fetal onset of general movements. *Pediatric Research*, *63*(2), 191–195. https://doi.org/10.1203/PDR.0b013e31815ed03e

Lyall, K., Schmidt, R. J., & Hertz-Picciotto, I. (2014). Maternal lifestyle and environmental risk factors for autism spectrum disorders. *International Journal of Epidemiology*, *43*(2), 443–464. https://doi.org/10.1093/ije/dyt282

MacDonald, M., Lord, C., & Ulrich, D. A. (2013). The relationship of motor skills and social communicative skills in school-aged children with autism spectrum disorder. *Adapted Physical Activity Quarterly: APAQ*, *30*(3), 271–282.

Maenner, M. J., Arneson, C. L., Levy, S. E., Kirby, R. S., Nicholas, J. S., & Durkin, M. S. (2012). Brief report: Association between behavioral features and gastrointestinal problems among children with autism spectrum disorder. *Journal of Autism and Developmental Disorders*, *42*(7), 1520–1525. https://doi.org/10.1007/s10803-011-1379-6

March, M. I., Warsof, S. L., & Chauhan, S. P. (2012). Fetal biometry: relevance in obstetrical practice. *Clinical Obstetrics and Gynecology*, *55*(1), 281–287. https://doi.org/10.1097/GRF.0b013e3182446e9b

Marco, E. J., Khatibi, K., Hill, S. S., Siegel, B., Arroyo, M. S., Dowling, A. F., … Nagarajan, S. S. (2012). Children with autism show reduced somatosensory response: an MEG study. *Autism Research: Official Journal of the International Society for Autism Research*, *5*(5), 340–351. https://doi.org/10.1002/aur.1247

Mari, M., Castiello, U., Marks, D., Marraffa, C., & Prior, M. (2003). The reach-to-grasp movement in children with autism spectrum disorder. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, *358*(1430), 393–403. https://doi.org/10.1098/rstb.2002.1205

Marler, S., Ferguson, B. J., Lee, E. B., Peters, B., Williams, K. C., McDonnell, E., … Veenstra-VanderWeele, J. (2017). Association of Rigid-Compulsive Behavior with Functional Constipation in Autism Spectrum Disorder. *Journal of Autism and Developmental Disorders*, *47*(6), 1673–1681. https://doi.org/10.1007/s10803-017-3084-6

Marx, V., & Nagy, E. (2015). Fetal Behavioural Responses to Maternal Voice and Touch. *PloS One*, *10*(6), e0129118. https://doi.org/10.1371/journal.pone.0129118

Matson, J. L., Mahan, S., Kozlowski, A. M., & Shoemaker, M. (2010). Developmental milestones in toddlers with autistic disorder, pervasive developmental disorder--not otherwise specified and atypical development. *Developmental Neurorehabilitation*, *13*(4), 239–247. https://doi.org/10.3109/17518423.2010.481299

Matson, J. L., Neal, D., Hess, J. A., Mahan, S., & Fodstad, J. C. (2010). The effect of seizure disorder on symptom presentation in atypically developing children and children with autism spectrum disorders based on the BDI-2. *Developmental Neurorehabilitation*, *13*(5), 310–314. https://doi.org/10.3109/17518421003782192

May, T., McGinley, J., Murphy, A., Hinkley, T., Papadopoulos, N., Williams, K. J., … Rinehart, N. J. (2016). A Multidisciplinary Perspective on Motor Impairment as an Early Behavioural Marker in Children with Autism Spectrum Disorder. *Australian Psychologist*, *51*(4), 296–303. https://doi.org/10.1111/ap.12225

Mazurek, M. O., Vasa, R. A., Kalb, L. G., Kanne, S. M., Rosenberg, D., Keefer, A., … Lowery, L. A. (2013). Anxiety, sensory over-responsivity, and gastrointestinal problems in children with autism spectrum disorders. *Journal of Abnormal Child Psychology*, *41*(1), 165–176. https://doi.org/10.1007/s10802-012-9668-x

McElhanon, B. O., McCracken, C., Karpen, S., & Sharp, W. G. (2014). Gastrointestinal symptoms in autism spectrum disorder: a meta-analysis. *Pediatrics*, *133*(5), 872–883. https://doi.org/10.1542/peds.2013-3995

Meinecke, L., Breitbach-Faller, N., Bartz, C., Damen, R., Rau, G., Disselhorst-Klug C. (2006). Movement analysis in the early detection of newborns at risk for developing spasticity due to infantile cerebral palsy. *Human Movement Science, 25*(2) ; 125-144, ISSN 0167-9457, https://doi.org/10.1016/j.humov.2005.09.012

Meltzoff, A. N., & Moore, M. K. (1983). Newborn infants imitate adult facial gestures. *Child Dev*, *54*(3), 702–709.

Memari, A. H., Ghanouni, P., Shayestehfar, M., & Ghaheri, B. (2014). Postural control impairments in individuals with autism spectrum disorder: a critical review of current literature. *Asian Journal of Sports Medicine*, *5*(3), e22963. https://doi.org/10.5812/asjsm.22963

Meyer, M., Bekkering, H., Paulus, M., & Hunnius, S. (2010). Joint action coordination in 2(1/2)- and 3-year-old children. *Front Hum Neurosci*, *4*, 220. https://doi.org/10.3389/fnhum.2010.00220

Micai, M., Caruso, A., Fatta, L., Fulceri, F. & Scattoni, M.L. (2019). Gender differences in high functioning autism: implications in everyday life and clinical settings. Italian Journal of Gender-Specific Medicine *in press*

Milh, M., Kaminska, A., Huon, C., Lapillonne, A., Ben-Ari, Y., & Khazipov, R. (2007). Rapid cortical oscillations and early motor activity in premature human neonate. *Cerebral Cortex (New York, N.Y.: 1991)*, *17*(7), 1582–1594. https://doi.org/10.1093/cercor/bhl069

Miller, M., Chukoskie, L., Zinni, M., Townsend, J., & Trauner, D. (2014). Dyspraxia, motor function and visual-motor integration in autism. *Behav Brain Res*, *269*, 95–102. https://doi.org/10.1016/j.bbr.2014.04.011

Ming, X., Brimacombe, M., & Wagner, G. C. (2007). Prevalence of motor impairment in autism spectrum disorders. *Brain & Development*, *29*(9), 565–570. https://doi.org/10.1016/j.braindev.2007.03.002

Minshew, N. J., Sung, K., Jones, B. L., & Furman, J. M. (2004). Underdevelopment of the postural control system in autism. *Neurology*, *63*(11), 2056–2061.

Mirenda, P., Smith, I. M., Vaillancourt, T., Georgiades, S., Duku, E., Szatmari, P., … Team, T. P. in A. S. D. S. (2010). Validating the Repetitive Behavior Scale-Revised in Young Children with Autism Spectrum Disorder. *Journal of Autism and Developmental Disorders*, *40*(12), 1521–1530. https://doi.org/10.1007/s10803-010-1012-0

Miskovic, B., Vasilj, O., Stanojevic, M., Ivanković, D., Kerner, M., & Tikvica, A. (2010). The comparison of fetal behavior in high risk and normal pregnancies assessed by four dimensional ultrasound. *The Journal of Maternal-Fetal & Neonatal Medicine: The Official Journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians*, *23*(12), 1461–1467. https://doi.org/10.3109/14767051003678200

Mitchell, S. R., Reiss, A. L., Tatusko, D. H., Ikuta, I., Kazmerski, D. B., Botti, J.-A. C., … Kates, W. R. (2009). Neuroanatomic alterations and social and communication deficits in monozygotic twins discordant for autism disorder. *The American Journal of Psychiatry*, *166*(8), 917–925. https://doi.org/10.1176/appi.ajp.2009.08101538

Molloy, C. A., Dietrich, K. N., & Bhattacharya, A. (2003). Postural stability in children with autism spectrum disorder. *Journal of Autism and Developmental Disorders*, *33*(6), 643–652.

Moseley, R. L., & Pulvermüller, F. (2018). What can autism teach us about the role of sensorimotor systems in higher cognition? New clues from studies on language, action semantics, and abstract emotional concept processing. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior*, *100*, 149–190. https://doi.org/10.1016/j.cortex.2017.11.019

Mostofsky, S. H., & Ewen, J. B. (2011). Altered connectivity and action model formation in autism is autism. *The Neuroscientist: A Review Journal Bringing Neurobiology, Neurology and Psychiatry*, *17*(4), 437–448. https://doi.org/10.1177/1073858410392381

Mullen, E. M. (1995). Mullen Scales of Early Learning (AGS ed.). Circle Pines, MN: American Guidance Service Inc.

Müller, G. B. (2003). Embryonic motility: environmental influences and evolutionary innovation. *Evolution & Development*, *5*(1), 56–60.

Mulligan, S., & White, B. P. (2012). Sensory and motor behaviors of infant siblings of children with and without autism. *The American Journal of Occupational Therapy: Official Publication of the American Occupational Therapy Association*, *66*(5), 556–566. https://doi.org/10.5014/ajot.2012.004077

Mundy, P., & Crowson, M. (1997). Joint attention and early social communication: implications for research on intervention with autism. *Journal of Autism and Developmental Disorders*, *27*(6), 653–676.

Mundy, P., & Jarrold, W. (2010). Infant joint attention, neural networks and social cognition. *Neural Networks: The Official Journal of the International Neural Network Society*, *23*(8–9), 985–997. https://doi.org/10.1016/j.neunet.2010.08.009

Muresan, D., Popa, R., Stamatian, F., & Rotar, I. C. (2015). The use of modern ultrasound tridimensional techniques for the evaluation of fetal cerebral midline structures-a practical approach. *Medical Ultrasonography*, *17*(2), 235–240.

Narzisi A, et al. (2018). Prevalence of Autism Spectrum Disorder in a large Italian catchment area: a school-based population study within the ASDEU project. - PubMed - NCBI. Retrieved from https://www-ncbi-nlm-nih-gov.bibliosan.clas.cineca.it/pubmed/30187843

Nayate, A., Bradshaw, J. L., & Rinehart, N. J. (2005). Autism and Asperger's disorder: are they movement disorders involving the cerebellum and/or basal ganglia? *Brain Research Bulletin*, *67*(4), 327–334. https://doi.org/10.1016/j.brainresbull.2005.07.011

Nayate, A., Tonge, B. J., Bradshaw, J. L., McGinley, J. L., Iansek, R., & Rinehart, N. J. (2012). Differentiation of high-functioning autism and Asperger's disorder based on neuromotor behaviour. *Journal of Autism and Developmental Disorders*, *42*(5), 707–717. https://doi.org/10.1007/s10803-011-1299-5

Nazarali, N., Glazebrook, C. M., & Elliott, D. (2009). Movement planning and reprogramming in individuals with autism. *Journal of Autism and Developmental Disorders*, *39*(10), 1401–1411. https://doi.org/10.1007/s10803-009-0756-x

Neto, R. M., & Ramos, J. G. L. (2016). 3D power Doppler ultrasound in early diagnosis of preeclampsia. *Pregnancy Hypertension*, *6*(1), 10–16. https://doi.org/10.1016/j.preghy.2015.11.003

Newborg J. Battelle developmental inventory-second edition. Riverside, Itasca, IL 2005

Nickel, L. R., Thatcher, A. R., Keller, F., Wozniak, R. H., & Iverson, J. M. (2013a). Posture Development in Infants at Heightened vs. Low Risk for Autism Spectrum Disorders.

Infancy: The Official Journal of the International Society on Infant Studies, *18*(5), 639–661. https://doi.org/10.1111/infa.12025

Nickel, L. R., Thatcher, A. R., Keller, F., Wozniak, R. H., & Iverson, J. M. (2013b). Posture Development in Infants at Heightened vs. Low Risk for Autism Spectrum Disorders. *Infancy: The Official Journal of the International Society on Infant Studies*, *18*(5), 639–661. https://doi.org/10.1111/infa.12025

Nijmeijer, J. S., Hoekstra, P. J., Minderaa, R. B., Buitelaar, J. K., Altink, M. E., Buschgens, C. J., … Hartman, C. A. (2009). PDD symptoms in ADHD, an independent familial trait? *J Abnorm Child Psychol*, *37*(3), 443–453. https://doi.org/10.1007/s10802-008-9282-0

Nikolov, R. N., Bearss, K. E., Lettinga, J., Erickson, C., Rodowski, M., Aman, M. G., … Scahill, L. (2009). Gastrointestinal symptoms in a sample of children with pervasive developmental disorders. *Journal of Autism and Developmental Disorders*, *39*(3), 405–413. https://doi.org/10.1007/s10803-008-0637-8

Nobile, M., Perego, P., Piccinini, L., Mani, E., Rossi, A., Bellina, M., & Molteni, M. (2011a). Further evidence of complex motor dysfunction in drug naive children with autism using automatic motion analysis of gait. *Autism: The International Journal of Research and Practice*, *15*(3), 263–283. https://doi.org/10.1177/1362361309356929

Nobile, M., Perego, P., Piccinini, L., Mani, E., Rossi, A., Bellina, M., & Molteni, M. (2011b). Further evidence of complex motor dysfunction in drug naive children with autism using automatic motion analysis of gait. *Autism: The International Journal of Research and Practice*, *15*(3), 263–283. https://doi.org/10.1177/1362361309356929

O'Gorman. (2018). Fetal biometry to assess the size and growth of the fetus. Retrieved from https://doi.org/10.1016/j.bpobgyn.2018.02.005

Ohuma, E. O., Njim, T., & Sharps, M. C. (2018). Current Issues in the Development of Foetal Growth References and Standards. https://doi.org/10.1007/s40471-018-0168-6

Osterling, J. A., Dawson, G., & Munson, J. A. (2002). Early recognition of 1-year-old infants with autism spectrum disorder versus mental retardation. *Development and Psychopathology*, *14*(2), 239–251.

Ouahba, J., Luton, D., Vuillard, E., Garel, C., Gressens, P., Blanc, N., … Oury, J. F. (2006). Prenatal isolated mild ventriculomegaly: outcome in 167 cases. *BJOG: An International Journal of Obstetrics and Gynaecology*, *113*(9), 1072–1079. https://doi.org/10.1111/j.1471-0528.2006.01050.x

Ozonoff, S., Iosif, A.-M., Baguio, F., Cook, I. C., Hill, M. M., Hutman, T., … Young, G. S. (2010). A Prospective Study of the Emergence of Early Behavioral Signs of Autism. *Journal of the American Academy of Child and Adolescent Psychiatry*, *49*(3), 256-66-2.

Ozonoff, S., Macari, S., Young, G. S., Goldring, S., Thompson, M., & Rogers, S. J. (2008). Atypical object exploration at 12 months of age is associated with autism in a prospective sample. *Autism: The International Journal of Research and Practice*, *12*(5), 457–472. https://doi.org/10.1177/1362361308096402

Ozonoff, S., Young, G. S., Belding, A., Hill, M., Hill, A., Hutman, T., … Iosif, A.-M. (2014). The broader autism phenotype in infancy: when does it emerge? *Journal of the American Academy of Child and Adolescent Psychiatry*, *53*(4), 398–407.e2. https://doi.org/10.1016/j.jaac.2013.12.020

Ozonoff, S., Young, G. S., Carter, A., Messinger, D., Yirmiya, N., Zwaigenbaum, L., … Stone, W. L. (2011). Recurrence risk for autism spectrum disorders: a Baby Siblings Research Consortium study. *Pediatrics*, *128*(3), e488-495. https://doi.org/10.1542/peds.2010-2825

Ozonoff, S., Young, G. S., Goldring, S., Greiss-Hess, L., Herrera, A. M., Steele, J., … Rogers, S. J. (2008). Gross motor development, movement abnormalities, and early identification of autism. *Journal of Autism and Developmental Disorders*, *38*(4), 644–656. https://doi.org/10.1007/s10803-007-0430-0

Palchik, A. B., Einspieler, C., Evstafeyeva, I. V., Talisa, V. B., & Marschik, P. B. (2013). Intra-uterine exposure to maternal opiate abuse and HIV: the impact on the developing nervous system. *Early Hum Dev*, *89*(4), 229–235. https://doi.org/10.1016/j.earlhumdev.2013.02.004

Palmer, N., Beam, A., Agniel, D., Eran, A., Manrai, A., Spettell, C., … Kohane, I. (2017). Association of Sex With Recurrence of Autism Spectrum Disorder Among Siblings. In *JAMA Pediatr* (Vol. 171, pp. 1107–1112). https://doi.org/10.1001/jamapediatrics.2017.2832

Paquet, A., Olliac, B., Golse, B., & Vaivre-Douret, L. (2015). Current knowledge on motor disorders in children with autism spectrum disorder (ASD). *Http://Dx.doi.org/10.1080/09297049.2015.1085501*. https://doi.org/10.1080/09297049.2015.1085501

Paquet, A., Olliac, B., Golse, B., & Vaivre-Douret, L. (2016). [Formula: see text]Current knowledge on motor disorders in children with autism spectrum disorder (ASD). *Child Neuropsychology: A Journal on Normal and Abnormal Development in Childhood and Adolescence*, *22*(7), 763–794. https://doi.org/10.1080/09297049.2015.1085501

Parma V., Brasselet, R., Zoia, S., Bulgheroni, M., Castiello, U. (2017). The origin of human handedness and its role in pre-birth motor control. *Scientific Reports* volume 7, Article number: 16804

Phagava, H., Muratori, F., Einspieler, C., Maestro, S., Apicella, F., Guzzetta, A., … Cioni, G. (2008). General movements in infants with autism spectrum disorders. *Georgian Medical News*, (156), 100–105.

Piontelli, A. (2010). *Development of Normal Fetal Movements: The First 25 Weeks of Gestation*. Mailand: Springer-Verlag. Retrieved from http:////www.springer.com/la/book/9788847014015

Polavarapu, S. R., Fitzgerald, G. D., Contag, S., & Hoffman, S. B. (2018). Utility of prenatal Doppler ultrasound to predict neonatal impaired cerebral autoregulation. *Journal of Perinatology: Official Journal of the California Perinatal Association*. https://doi.org/10.1038/s41372-018-0050-x

Predojević, M., Talić, A., Stanojević, M., Kurjak, A., & Salihagić Kadić, A. (2014). Assessment of motoric and hemodynamic parameters in growth restricted fetuses - case study. *The Journal of Maternal-Fetal & Neonatal Medicine: The Official Journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians*, *27*(3), 247–251. https://doi.org/10.3109/14767058.2013.807241

Prosperi, M., Santocchi, E., Balboni, G., Narzisi, A., Bozza, M., Fulceri, F., … Muratori, F. (2017). Behavioral Phenotype of ASD Preschoolers with Gastrointestinal Symptoms or Food Selectivity. *J Autism Dev Disord*, *47*(11), 3574–3588. https://doi.org/10.1007/s10803-017-3271-5

Prosperi, M., Santocchi, E., Balboni, G., Narzisi, A., Bozza, M., Fulceri, F., … Muratori, F. (2017). Behavioral Phenotype of ASD Preschoolers with Gastrointestinal Symptoms or Food Selectivity. *Journal of Autism and Developmental Disorders*, *47*(11), 3574–3588. https://doi.org/10.1007/s10803-017-3271-5

Provost, B., Heimerl, S., & Lopez, B. R. (2007). Levels of gross and fine motor development in young children with autism spectrum disorder. *Physical & Occupational Therapy in Pediatrics*, *27*(3), 21–36.

Purpura, G., Costanzo, V., Chericoni, N., Puopolo, M., Scattoni, M. L., Muratori, F., & Apicella, F. (2017). Bilateral Patterns of Repetitive Movements in 6- to 12-Month-Old Infants with Autism Spectrum Disorders. *Frontiers in Psychology*, *8*, 1168. https://doi.org/10.3389/fpsyg.2017.01168

Purpura, G., Fulceri, F., Puglisi, V., Masoni, P., & Contaldo, A. (2016). Motor coordination impairment in children with autism spectrum disorder: a pilot study using Movement Assessment Battery for Children-2 Checklist. *Minerva Pediatr*. Retrieved from http://dx.doi.org/

Purpura, G., Fulceri, F., Puglisi, V., Masoni, P., & Contaldo, A. (2016). Motor coordination impairment in children with autism spectrum disorder: a pilot study using Movement Assessment Battery for Children-2 Checklist. *Minerva Pediatrica*. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/27733748

Randolph-Gips, M., & Srinivasan, P. (2012). Modeling autism: a systems biology approach. *Journal of Clinical Bioinformatics*, *2*(1), 17. https://doi.org/10.1186/2043-9113-2-17

Rebecca, J. L., Alden, L. G., Elizabeth, A. S., & Faherty, A. (2013). Developmental trajectories in children with and without autism spectrum disorders: the first 3 years. *Child Development*, *84*(2), 429–442. https://doi.org/10.1111/j.1467-8624.2012.01870.x

Reddy, U. M., Filly, R. A., & Copel, J. A. (2008). Prenatal Imaging: Ultrasonography and Magnetic Resonance Imaging. *Obstetrics and Gynecology*, *112*(1), 145. https://doi.org/10.1097/01.AOG.0000318871.95090.d9

Reissland, N., Francis, B., Aydin, E., Mason, J., & Schaal, B. (2014). The development of anticipation in the fetus: a longitudinal account of human fetal mouth movements

in reaction to and anticipation of touch. *Dev Psychobiol*, *56*(5), 955–963. https://doi.org/10.1002/dev.21172

Rinehart, N. J., Tonge, B. J., Bradshaw, J. L., Iansek, R., Enticott, P. G., & McGinley, J. (2006). Gait function in high-functioning autism and Asperger's disorder : evidence for basal-ganglia and cerebellar involvement? *European Child & Adolescent Psychiatry*, *15*(5), 256–264. https://doi.org/10.1007/s00787-006-0530-y

Rinehart, N. J., Tonge, B. J., Iansek, R., McGinley, J., Brereton, A. V., Enticott, P. G., & Bradshaw, J. L. (2006). Gait function in newly diagnosed children with autism: Cerebellar and basal ganglia related motor disorder. *Developmental Medicine and Child Neurology*, *48*(10), 819–824. https://doi.org/10.1017/S0012162206001769

Rosenbaum, D. A., Vaughan, J., Barnes, H. J., & Jorgensen, M. J. (1992). Time course of movement planning: selection of handgrips for object manipulation. *Journal of Experimental Psychology. Learning, Memory, and Cognition*, *18*(5), 1058–1073.

Rosier-van Dunné, F. M. F., van Wezel-Meijler, G., Bakker, M. P. S., Odendaal, H. J., & de Vries, J. I. P. (2010). Fetal general movements and brain sonography in a population at risk for preterm birth. *Early Human Development*, *86*(2), 107–111. https://doi.org/10.1016/j.earlhumdev.2010.01.026

Sacco, R., Gabriele, S., & Persico, A. M. (2015). Head circumference and brain size in autism spectrum disorder: A systematic review and meta-analysis. *Psychiatry Research*, *234*(2), 239–251. https://doi.org/10.1016/j.pscychresns.2015.08.016

Sacrey, L.-A. R., Germani, T., Bryson, S. E., & Zwaigenbaum, L. (2014). Reaching and Grasping in Autism Spectrum Disorder: A Review of Recent Literature. *Frontiers in Neurology*, *5*. https://doi.org/10.3389/fneur.2014.00006

Sacrey, L.-A. R., Zwaigenbaum, L., Bryson, S., Brian, J., Smith, I. M., Roberts, W., … Armstrong, V. (2015). Can parents' concerns predict autism spectrum disorder? A prospective study of high-risk siblings from 6 to 36 months of age. *Journal of the American Academy of Child and Adolescent Psychiatry*, *54*(6), 470–478. https://doi.org/10.1016/j.jaac.2015.03.014

Sadan, S., Malinger, G., Schweiger, A., Lev, D., & Lerman-Sagie, T. (2007). Neuropsychological outcome of children with asymmetric ventricles or unilateral mild ventriculomegaly identified in utero. *BJOG: An International Journal of*

Obstetrics and Gynaecology, *114*(5), 596–602. https://doi.org/10.1111/j.1471-0528.2007.01301.x

Saitoh, O., Karns, C. M., & Courchesne, E. (2001). Development of the hippocampal formation from 2 to 42 years: MRI evidence of smaller area dentata in autism. *Brain: A Journal of Neurology*, *124*(Pt 7), 1317–1324.

Santocchi, E., Guiducci, L., Fulceri, F., Billeci, L., Buzzigoli, E., Apicella, F., … Muratori, F. (2016). Gut to brain interaction in Autism Spectrum Disorders: a randomized controlled trial on the role of probiotics on clinical, biochemical and neurophysiological parameters. *BMC Psychiatry*, *16*, 183. https://doi.org/10.1186/s12888-016-0887-5

Santocchi, E., Guiducci, L., Fulceri, F., Billeci, L., Buzzigoli, E., Apicella, F., … Muratori, F. (2016). Gut to brain interaction in Autism Spectrum Disorders: a randomized controlled trial on the role of probiotics on clinical, biochemical and neurophysiological parameters. *BMC Psychiatry*, *16*, 183. https://doi.org/10.1186/s12888-016-0887-5

Schaevitz, L. R., & Berger-Sweeney, J. E. (2012). Gene-environment interactions and epigenetic pathways in autism: the importance of one-carbon metabolism. *ILAR Journal*, *53*(3–4), 322–340. https://doi.org/10.1093/ilar.53.3-4.322

Scharoun, S. M., & Bryden, P. J. (2016). Anticipatory Planning in Children with Autism Spectrum Disorder: An Assessment of Independent and Joint Action Tasks. *Front Integr Neurosci*, *10*. https://doi.org/10.3389/fnint.2016.00029

Schmitz, C., Martineau, J., Barthélémy, C., & Assaiante, C. (2003). Motor control and children with autism: deficit of anticipatory function? *Neuroscience Letters*, *348*(1), 17–20.

Scott, J. A., Schumann, C. M., Goodlin-Jones, B. L., & Amaral, D. G. (2009). A comprehensive volumetric analysis of the cerebellum in children and adolescents with autism spectrum disorder. *Autism Research: Official Journal of the International Society for Autism Research*, *2*(5), 246–257. https://doi.org/10.1002/aur.97

Sebanz, N., & Knoblich, G. (2009). Prediction in joint action: what, when, and where. *Top Cogn Sci*, *1*(2), 353–367. https://doi.org/10.1111/j.1756-8765.2009.01024.x

Seibert, J. M., Hogan, A. E., & Mundy, P. C. (n.d.). Assessing interactional competencies: The early social-communication scales. *Infant Mental Health Journal*, *3*(4), 244–258. https://doi.org/10.1002/1097-0355(198224)3:4<244::AID-IMHJ2280030406>3.0.CO;2-R

Seifer, R. (2008). Who Should Collect Our Data: Parents or Trained Observers? In *Handbook of Research Methods in Developmental Science* (pp. 15–137). Wiley-Blackwell. Retrieved from https://onlinelibrary.wiley.com/doi/abs/10.1002/9780470756676.ch7

Shetreat-Klein, M., Shinnar, S., & Rapin, I. (2014a). Abnormalities of joint mobility and gait in children with autism spectrum disorders. *Brain & Development*, *36*(2), 91–96. https://doi.org/10.1016/j.braindev.2012.02.005

Shetreat-Klein, M., Shinnar, S., & Rapin, I. (2014b). Abnormalities of joint mobility and gait in children with autism spectrum disorders. *Brain & Development*, *36*(2), 91–96. https://doi.org/10.1016/j.braindev.2012.02.005

Signorelli, M., Tiberti, A., Valseriati, D., Molin, E., Cerri, V., Groli, C., & Bianchi, U. A. (2004). Width of the fetal lateral ventricular atrium between 10 and 12 mm: a simple variation of the norm? *Ultrasound in Obstetrics & Gynecology: The Official Journal of the International Society of Ultrasound in Obstetrics and Gynecology*, *23*(1), 14–18. https://doi.org/10.1002/uog.941

Sinzig, J., Morsch, D., Bruning, N., Schmidt, M. H., & Lehmkuhl, G. (2008). Inhibition, flexibility, working memory and planning in autism spectrum disorders with and without comorbid ADHD-symptoms. *Child and Adolescent Psychiatry and Mental Health*, *2*(1), 4. https://doi.org/10.1186/1753-2000-2-4

Sipes, M., Matson, J. L., & Horovitz, M. (2011). Autism spectrum disorders and motor skills: the effect on socialization as measured by the Baby And Infant Screen For Children with aUtIsm Traits (BISCUIT). *Developmental Neurorehabilitation*, *14*(5), 290–296. https://doi.org/10.3109/17518423.2011.587838

Sival, D. A., Visser, G. H., & Prechtl, H. F. (1990). Does reduction of amniotic fluid affect fetal movements? *Early Human Development*, *23*(3), 233–246.

Soke, G. N., Maenner, M. J., Christensen, D., Kurzius-Spencer, M., & Schieve, L. A. (2018). Prevalence of Co-occurring Medical and Behavioral Conditions/Symptoms Among 4- and 8-Year-Old Children with Autism Spectrum Disorder in Selected Areas of the

United States in 2010. *Journal of Autism and Developmental Disorders*, *48*(8), 2663–2676. https://doi.org/10.1007/s10803-018-3521-1

Sparrow, S.S., Cicchetti, D.V., & Balla, D.A. (2005). Vineland Adaptive Behavior Scales. 2nd ed. Oxford: NCS Pearson, Inc.

Srinivasan, S. M., & Bhat, A. N. (2016). Differences in object sharing between infants at risk for autism and typically developing infants from 9 to 15 months of age. *Infant Behav Dev*, *42*, 128–141. https://doi.org/10.1016/j.infbeh.2015.12.003

Stanojevic, M., Kurjak, A., Salihagić-Kadić, A., Vasilj, O., Miskovic, B., Shaddad, A. N., … Tomasović, S. (2011). Neurobehavioral continuity from fetus to neonate. *Journal of Perinatal Medicine*, *39*(2), 171–177. https://doi.org/10.1515/JPM.2011.004

Stapel, J. C., Hunnius, S., & Bekkering, H. (2012). Online prediction of others' actions: the contribution of the target object, action context and movement kinematics. *Psychol Res*, *76*(4), 434–445. https://doi.org/10.1007/s00426-012-0423-2

Staples, K. L., & Reid, G. (2010). Fundamental movement skills and autism spectrum disorders. *J Autism Dev Disord*, *40*(2), 209–217. https://doi.org/10.1007/s10803-009-0854-9

Stins, J. F., Emck, C., de Vries, E. M., Doop, S., & Beek, P. J. (2015). Attentional and sensory contributions to postural sway in children with autism spectrum disorder. *Gait & Posture*, *42*(2), 199–203. https://doi.org/10.1016/j.gaitpost.2015.05.010

Stoit, A. M. B., Schie, H. T. van, Slaats-Willemse, D. I. E., & Buitelaar, J. K. (2013). Grasping Motor Impairments in Autism: Not Action Planning but Movement Execution is Deficient. *Journal of Autism and Developmental Disorders*, *43*(12), 2793–2806. https://doi.org/10.1007/s10803-013-1825-8

Studholme, C. (2011). Mapping fetal brain development in utero using magnetic resonance imaging: the Big Bang of brain mapping. *Annual Review of Biomedical Engineering*, *13*, 345–368. https://doi.org/10.1146/annurev-bioeng-071910-124654

Talic, A., Kurjak, A., Ahmed, B., Stanojevic, M., Predojevic, M., Kadic, A. S., & Di Renzo, G. C. (2011). The potential of 4D sonography in the assessment of fetal behavior in high-risk pregnancies. *The Journal of Maternal-Fetal & Neonatal Medicine: The Official Journal of the European Association of Perinatal Medicine, the Federation*

of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians, *24*(7), 948–954. https://doi.org/10.3109/14767058.2010.534830

Teitelbaum, O., Benton, T., Shah, P. K., Prince, A., Kelly, J. L., & Teitelbaum, P. (2004). Eshkol-Wachman movement notation in diagnosis: the early detection of Asperger's syndrome. *Proceedings of the National Academy of Sciences of the United States of America*, *101*(32), 11909–11914. https://doi.org/10.1073/pnas.0403919101

Teitelbaum, P., Teitelbaum, O., Nye, J., Fryman, J., & Maurer, R. G. (1998). Movement analysis in infancy may be useful for early diagnosis of autism. *Proceedings of the National Academy of Sciences of the United States of America*, *95*(23), 13982–13987.

Tordjman, S., Somogyi, E., Coulon, N., Kermarrec, S., Cohen, D., Bronsard, G., … Xavier, J. (2014). Gene × Environment interactions in autism spectrum disorders: role of epigenetic mechanisms. *Frontiers in Psychiatry*, *5*, 53. https://doi.org/10.3389/fpsyt.2014.00053

Tran, P. L., Lehti, V., Lampi, K. M., Helenius, H., Suominen, A., Gissler, M., … Sourander, A. (2013). Smoking during pregnancy and risk of autism spectrum disorder in a Finnish National Birth Cohort. *Paediatric and Perinatal Epidemiology*, *27*(3), 266–274. https://doi.org/10.1111/ppe.12043

Travers, B. G., Kana, R. K., Klinger, L. G., Klein, C. L., & Klinger, M. R. (2015). Motor learning in individuals with autism spectrum disorder: activation in superior parietal lobule related to learning and repetitive behaviors. *Autism Research: Official Journal of the International Society for Autism Research*, *8*(1), 38–51. https://doi.org/10.1002/aur.1403

Travers, B. G., Powell, P. S., Klinger, L. G., & Klinger, M. R. (2013a). Motor difficulties in autism spectrum disorder: linking symptom severity and postural stability. *Journal of Autism and Developmental Disorders*, *43*(7), 1568–1583. https://doi.org/10.1007/s10803-012-1702-x

Travers, B. G., Powell, P. S., Klinger, L. G., & Klinger, M. R. (2013b). Motor difficulties in autism spectrum disorder: linking symptom severity and postural stability. *Journal of Autism and Developmental Disorders*, *43*(7), 1568–1583. https://doi.org/10.1007/s10803-012-1702-x

Turner, M. (1999). Annotation: Repetitive Behaviour in Autism: A Review of Psychological Research. *Journal of Child Psychology and Psychiatry*, *40*(6), 839–849. https://doi.org/10.1111/1469-7610.00502

Unwin, L. M., Maybery, M. T., Murphy, A., Lilje, W., Bellesini, M., Hunt, A. M., … Whitehouse, A. J. O. (2016). A Prospective Ultrasound Study of Prenatal Growth in Infant Siblings of Children With Autism. *Autism Research: Official Journal of the International Society for Autism Research*, *9*(2), 210–216. https://doi.org/10.1002/aur.1518

Valicenti-McDermott, M., Hottinger, K., Seijo, R., & Shulman, L. (2012). Age at diagnosis of autism spectrum disorders. *The Journal of Pediatrics*, *161*(3), 554–556. https://doi.org/10.1016/j.jpeds.2012.05.012

Valman, H. B., & Pearson, J. F. (1980). What the fetus feels. *British Medical Journal*, *280*(6209), 233–234.

van Batenburg-Eddes, T., de Groot, L., Steegers, E. A. P., Hofman, A., Jaddoe, V. W. V., Verhulst, F. C., & Tiemeier, H. (2010). Fetal programming of infant neuromotor development: the generation R study. *Pediatric Research*, *67*(2), 132–137. https://doi.org/10.1203/PDR.0b013e3181c2dc76

van den Broek, A. J. M., Kok, J. H., Houtzager, B. A., & Scherjon, S. A. (2010). Behavioural problems at the age of eleven years in preterm-born children with or without fetal brain sparing: a prospective cohort study. *Early Human Development*, *86*(6), 379–384. https://doi.org/10.1016/j.earlhumdev.2010.04.007

van Schie, H. T., & Bekkering, H. (2007). Neural mechanisms underlying immediate and final action goals in object use reflected by slow wave brain potentials. *Brain Research*, *1148*, 183–197. https://doi.org/10.1016/j.brainres.2007.02.085

van Swieten, L. M., van Bergen, E., Williams, J. H. G., Wilson, A. D., Plumb, M. S., Kent, S. W., & Mon-Williams, M. A. (2010). A test of motor (not executive) planning in developmental coordination disorder and autism. *Journal of Experimental Psychology. Human Perception and Performance*, *36*(2), 493–499. https://doi.org/10.1037/a0017177

Vernazza-Martin, S., Martin, N., Vernazza, A., Lepellec-Muller, A., Rufo, M., Massion, J., & Assaiante, C. (2005). Goal directed locomotion and balance control in autistic children. *Journal of Autism and Developmental Disorders*, *35*(1), 91–102.

Vilensky, J. A., Damasio, A. R., & Maurer, R. G. (1981). Gait disturbances in patients with autistic behavior: a preliminary study. *Archives of Neurology*, *38*(10), 646–649.

Voegtline, K. M., Costigan, K. A., Pater, H. A., & DiPietro, J. A. (2013). Near-term fetal response to maternal spoken voice. *Infant Behavior & Development*, *36*(4), 526–533. https://doi.org/10.1016/j.infbeh.2013.05.002

Volk, H. E., Kerin, T., Lurmann, F., Hertz-Picciotto, I., McConnell, R., & Campbell, D. B. (2014). Autism spectrum disorder: interaction of air pollution with the MET receptor tyrosine kinase gene. *Epidemiology (Cambridge, Mass.)*, *25*(1), 44–47. https://doi.org/10.1097/EDE.0000000000000030

Volkmar, F., Chawarska, K., & Klin, A. (2005). Autism in infancy and early childhood. *Annual Review of Psychology*, *56*, 315–336. https://doi.org/10.1146/annurev.psych.56.091103.070159

Watt, N., Wetherby, A. M., Barber, A., & Morgan, L. (2008a). Repetitive and stereotyped behaviors in children with autism spectrum disorders in the second year of life. *Journal of Autism and Developmental Disorders*, *38*(8), 1518–1533. https://doi.org/10.1007/s10803-007-0532-8

Watt, N., Wetherby, A. M., Barber, A., & Morgan, L. (2008b). Repetitive and stereotyped behaviors in children with autism spectrum disorders in the second year of life. *Journal of Autism and Developmental Disorders*, *38*(8), 1518–1533. https://doi.org/10.1007/s10803-007-0532-8

Webb, S. J., Sparks, B.-F., Friedman, S. D., Shaw, D. W. W., Giedd, J., Dawson, G., & Dager, S. R. (2009). Cerebellar vermal volumes and behavioral correlates in children with autism spectrum disorder. *Psychiatry Research*, *172*(1), 61–67. https://doi.org/10.1016/j.pscychresns.2008.06.001

West, K. L. (2018). Infant Motor Development in Autism Spectrum Disorder: A Synthesis and Meta-analysis. *Child Development*. https://doi.org/10.1111/cdev.13086

Wetherby, A. M., Woods, J., Allen, L., Cleary, J., Dickinson, H., & Lord, C. (2004). Early indicators of autism spectrum disorders in the second year of life. *Journal of Autism and Developmental Disorders*, *34*(5), 473–493.

Whitehouse, A. J. O., Hickey, M., Stanley, F. J., Newnham, J. P., & Pennell, C. E. (2011). Brief report: a preliminary study of fetal head circumference growth in autism

spectrum disorder. *Journal of Autism and Developmental Disorders*, *41*(1), 122–129. https://doi.org/10.1007/s10803-010-1019-6

Whitehouse, A. J. O., Zubrick, S. R., Blair, E., Newnham, J. P., & Hickey, M. (2012). Fetal head circumference growth in children with specific language impairment. *Archives of Disease in Childhood*, *97*(1), 49–51. https://doi.org/10.1136/adc.2009.180331

Whyatt, C. P., & Craig, C. M. (2012). Motor skills in children aged 7-10 years, diagnosed with autism spectrum disorder. *Journal of Autism and Developmental Disorders*, *42*(9), 1799–1809. https://doi.org/10.1007/s10803-011-1421-8

Wienerroither, H., Steiner, H., Tomaselli, J., Lobendanz, M., & Thun-Hohenstein, L. (2001). Intrauterine blood flow and long-term intellectual, neurologic, and social development. *Obstetrics and Gynecology*, *97*(3), 449–453.

Wilson, R. B., Enticott, P. G., & Rinehart, N. J. (2018). Motor development and delay: advances in assessment of motor skills in autism spectrum disorders. *Curr Opin Neurol*, *31*(2), 134–139. https://doi.org/10.1097/wco.0000000000000541

Wolff, J. J., Botteron, K. N., Dager, S. R., Elison, J. T., Estes, A. M., Gu, H., … Network, I. (2014). Longitudinal patterns of repetitive behavior in toddlers with autism. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *55*(8), 945–953. https://doi.org/10.1111/jcpp.12207

Wolpert, D. M., & Flanagan, J. R. (2001a). Motor prediction. *Current Biology: CB*, *11*(18), R729-732.

Wolpert, D. M., & Flanagan, J. R. (2001b). Motor prediction. *Current Biology: CB*, *11*(18), R729-732.

Yirmiya, N., & Ozonoff, S. (2007). The very early autism phenotype. *Journal of Autism and Developmental Disorders*, *37*(1), 1–11. https://doi.org/10.1007/s10803-006-0329-1

Young, H., Oreve, M. J., & Speranza, M. (2018). Clinical characteristics and problems diagnosing autism spectrum disorder in girls. *Arch Pediatr*, *25*(6), 399–403. https://doi.org/10.1016/j.arcped.2018.06.008

Yu, C., & Smith, L. B. (2013). Joint attention without gaze following: human infants and their parents coordinate visual attention to objects through eye-hand

coordination. *PLoS One*, *8*(11), e79659. https://doi.org/10.1371/journal.pone.0079659

Yuge, M., Marschik, P. B., Nakajima, Y., Yamori, Y., Kanda, T., Hirota, H., … Einspieler, C. (2011). Movements and postures of infants aged 3 to 5 months: to what extent is their optimality related to perinatal events and to the neurological outcome? *Early Hum Dev*, *87*(3), 231–237. https://doi.org/10.1016/j.earlhumdev.2010.12.046

Zachor D. A., Ilanit T., Esther B. I. (2010). Autism severity and motor abilities correlates of imitation situations in children with autism spectrum disorders. *Research in Autism Spectrum Disorders 4*, 438–443

Zappella, M., Einspieler, C., Bartl-Pokorny, K. D., Krieber, M., Coleman, M., Bölte, S., & Marschik, P. B. (2015). What do home videos tell us about early motor and socio-communicative behaviours in children with autistic features during the second year of life--An exploratory study. *Early Human Development*, *91*(10), 569–575. https://doi.org/10.1016/j.earlhumdev.2015.07.006

Zoia, S., Blason, L., D'Ottavio, G., Biancotto, M., Bulgheroni, M., & Castiello, U. (2013). The development of upper limb movements: from fetal to post-natal life. *PLoS One*, *8*(12), e80876. https://doi.org/10.1371/journal.pone.0080876

Zoia, S., Blason, L., D'Ottavio, G., Bulgheroni, M., Pezzetta, E., Scabar, A., & Castiello, U. (2007). Evidence of early development of action planning in the human foetus: a kinematic study. *Experimental Brain Research*, *176*(2), 217–226. https://doi.org/10.1007/s00221-006-0607-3

Zwaigenbaum, L., Bauman, M. L., Stone, W. L., Yirmiya, N., Estes, A., Hansen, R. L., … Wetherby, A. (2015). Early Identification of Autism Spectrum Disorder: Recommendations for Practice and Research. *Pediatrics*, *136*(Supplement 1), S10–S40. https://doi.org/10.1542/peds.2014-3667C

Zwaigenbaum, L., Bryson, S., Rogers, T., Roberts, W., Brian, J., & Szatmari, P. (2005). Behavioral manifestations of autism in the first year of life. *International Journal of Developmental Neuroscience: The Official Journal of the International Society for Developmental Neuroscience*, *23*(2–3), 143–152. https://doi.org/10.1016/j.ijdevneu.2004.05.001

Zwaigenbaum, L., & Penner, M. (2018). Autism spectrum disorder: advances in diagnosis and evaluation. *BMJ (Clinical Research Ed.)*, *361*, k1674.

Appendix 1

List of publications

Peer-reviewed publications from November 2014

1 Martina Micai, Angela Caruso, Laura Fatta, **Francesca Fulceri**, Maria Luisa Scattoni (2019). Gender differences in high functioning autism: implications in everyday life and clinical settings. Italian Journal of Gender-Specific Medicine *in press*

2 Argyro Athanasiadou, Jan Buitelaar, Paola Brovedani, Olena Chorna, **Francesca Fulceri**, Andrea Guzzetta, Maria Luisa Scattoni (2019). Early motor signs of attention-deficit hyperactivity disorder: a systematic review. *European Child & Adolescent Psychiatry*. https://doi.org/10.1007/s00787-019-01298-5

3 **Francesca Fulceri**, Enzo Grossi, Annarita Contaldo, Antonio Narzisi, Fabio Apicella, Ilaria Parrini, Raffaella Tancredi, Sara Calderoni, Filippo Muratori. Motor Skills as Moderators of Core Symptoms in Autism Spectrum Disorders: Preliminary Data from an Exploratory Analysis with Artificial Neural Networks. Frontiers in Physiology 09 January 2019 | https://doi.org/10.3389/fpsyg.2018.02683

4 **Francesca Fulceri**, Alessandro Tonacci, Lucaferro Andrea, Fabio Apicella, Antonio Narzisi, Giulia Vincenti, Filippo Muratori, Annarita Contaldo: Interpersonal motor coordination during joint actions in children with and without autism spectrum disorder: the role of motor information. Research in Developmental Disabilities 05/2018;

5 **Francesca Fulceri**, Andrea Guzzetta, Argyro Athanasiadou, Laura Iaconianni, Maria Luisa Scattoni: Antenatal ultrasound value in risk calculation for Autism Spectrum Disorder: A systematic review to support future research. Neuroscience & Biobehavioral Reviews 05/2018; DOI: 10.1016/j.neubiorev.2018.05.016

6 Lucia Billeci, Alessandro Tonacci, Antonio Narzisi, Zaira Manigrasso, Maurizio

Varanini, **Francesca Fulceri**, Caterina Lattarulo, Sara Calderoni, Filippo Muratori: Heart Rate Variability During a Joint Attention Task in Toddlers With Autism Spectrum Disorders. Frontiers in Physiology 05/2018; 9:467., DOI:10.3389/fphys.2018.00467

7 Lucia Billeci, Antonio Narzisi, Alessandro Tonacci, Beatrice Sbriscia-Fioretti, Luca Serasini, **Francesca Fulceri**, Fabio Apicella, Federico Sicca, Sara Calderoni, Filippo Muratori: An integrated EEG and eye-tracking approach for the study of responding and initiating joint attention in Autism Spectrum Disorders. Scientific Reports 12/2017; 7(1)., DOI:10.1038/s41598-017-13053-4

8 **Francesca Fulceri**, Scattoni Maria Luisa, Ricceri Laura: Early motor abnormalities in autism spectrum disorders: evidence from preclinical and clinical research. International journal of sport psychology 11/2017; DOI:10.7352/IJSP.2017.

9 Margherita Prosperi, Elisa Santocchi, Giulia Balboni, Antonio Narzisi, Margherita Bozza, **Francesca Fulceri**, Fabio Apicella, Roberta Igliozzi, Angela Cosenza, Raffaella Tancredi, Sara Calderoni, Filippo Muratori: Behavioral Phenotype of ASD Preschoolers with Gastrointestinal Symptoms or Food Selectivity. Journal of Autism and Developmental Disorders 08/2017; 47(6)., DOI:10.1007/s10803-017-3271-5

10 Elisa Santocchi, Letizia Guiducci, **Francesca Fulceri**, Lucia Billeci, Emma Buzzigoli, Fabio Apicella, Sara Calderoni, Enzo Grossi, Maria Aurora Morales, Filippo Muratori: Gut to brain interaction in Autism Spectrum Disorders: A randomized controlled trial on the role of probiotics on clinical, biochemical and neurophysiological parameters. BMC Psychiatry 12/2016; 16(1)., DOI:10.1186/s12888-016-0887-5

11 Sara Calderoni, Elisa Santocchi, Teresa Del Bianco, Elena Brunori, Laura Caponi, Aldo Paolicchi, **Francesca Fulceri**, Margherita Prosperi, Antonio Narzisi, Angela Cosenza, Raffaella Tancredi, Filippo Muratori: Serological screening for Celiac Disease in 382 pre-schoolers with Autism Spectrum Disorder. Italian Journal of Pediatrics 12/2016; 42(1):98., DOI:10.1186/s13052-016-0308-x

12 Giulia Purpura *, **Francesca Fulceri** *, (* Equally Contributing Authors) Vittoria Puglisi, Patrizia Masoni, Annarita Contaldo. Motor coordination impairment in children with autism spectrum disorder: a pilot study using Movement Assessment Battery for Children-2 Checklist. Minerva Peditrica 2016 Oct 12. * Equally Contributing Authors

13 Billeci Lucia, Narzisi Antonio, Campatelli Giulia, Crifaci Giulia, Calderoni Sara, Gagliano Antonella, Calzone Carlo, Colombi Costanza, Pioggia Giovanni, Muratori Filippio and ALERT group (Raso Rossella, Ruta Liliana, Rossi Ilaria, Ballarani Agnese, **Fulceri Francesca**, Darini Alessandra, Maroscia Emilia, Lattarulo Caterina, Tortorella Gaetano, Siracusano Rosamaria, Comminiello Valentina) Disentangling the initiation from the response in joint attention: an eye-tracking study in toddlers with autism spectrum disorders. Transl Psychiatry. 2016 May 17;6: e808

14 **Francesca Fulceri**, Antonio Narzisi, Fabio Apicella, Giulia Balboni, Sara Baldini, Jenny Brocchini, Ilaria Domenici, Sonia Cerullo, Roberta Igliozzi, Angela Cosenza, Raffaella Tancredi, Filippo Muratori, Sara Calderoni: Application of the Repetitive Behavior Scale-Revised – Italian version – in preschoolers with autism spectrum disorder. Research in Developmental Disabilities 01/2016; 48:43-52., DOI: 10.1016/j.ridd.2015.10.015

15 **Francesca Fulceri**, Mariangela Morelli, Elisa Santocchi, Hellas Cena, Teresa Del Bianco, Antonio Narzisi, Sara Calderoni, Filippo Muratori: Gastrointestinal symptoms and behavioral problems in preschoolers with Autism Spectrum Disorder. Digestive and Liver Disease 12/2015; 48(3)., DOI: 10.1016/j.dld.2015.11.026

16 **Francesca Fulceri**, Anna Rita Contaldo, Ilaria Parrini, Sara Calderoni, Antonio Narzisi, Raffaella Tancredi, Fabio Apicella, Filippo Muratori: Locomotion and grasping impairment in preschoolers with Autism Spectrum Disorder. Clinical Neuropsychiatry 10/2015; 12(4):94-100.

Poster/Abstract from november 2014

1 **Francesca Fulceri**, Letizia Gila, Angela Caruso, Tommaso Salvitti, Maria Bulgheroni, Walter Baccinelli, Maria Luisa Scattoni. An Innovative Semi-Automatic Software to Detect Early Motor Signatures in Autism Spectrum Disorder. International Society for Autism Research, Montreal 2019

2 **Francesca Fulceri**, Enzo Grossi, Annarita Contaldo, Antonio Narzisi, Fabio Apicella, Ilaria Parrini, Raffaella Tancredi, Sara Calderoni, Filippo Muratori. "Motor skills as moderators of core symptoms in autism spectrum disorder: insights from the Artificial Networks approach". International Society for Autism Research Rotterdam, 2018

3 **Francesca Fulceri**, Alessandro Tonacci, Fabio Apicella, Antonio Narzisi, Lucia Billeci, Filippo Muratori and Annarita Contaldo "Joint Action Coordination in Children with Autism Spectrum Disorder". International Meeting for Autism Research Salt Lake City, 2015

4 Caruso Angela, **Francesca Fulceri**, Laura Iaconianni, Andrea Guzzetta, Maria Luisa Scattoni: Baby movements in the womb: searching for early markers of autism spectrum disorders. INSAR 2018, Rotterdam; 05/2018

5 Argyro Athanasiadou, Jan Buitelaar, Olena Chorna, **Francesca Fulceri**, Maria Luisa Scattoni, Andrea Guzzetta Early Motor Signs As Biomarkers of Neurodevelopmental Disorders: Applying Recent Findings in Autism to Attention Deficit Hyperactivity Disorder INSAR 2018, Rotterdam; 05/2018

6 Prosperi Margherita, Santocchi Elisa, Narzisi Antonio, **Fulceri Francesca**, Apicella Fabio, Igliozzi Roberta, Cosenza Angela, Tancredi Raffaella, Calderoni Sara, Muratori Filippo. "Gastrointestinal Symptoms, Behavioural Problems and Restricted Repetitive Behaviours in an Italian Sample of ASD Preschoolers. International Meeting for Autism Research San Francisco 2017

7 Narzisi Antonio, Billeci Lucia, Calderoni Sara, Campatelli Giulia, **Fulceri Francesca**, Muratori Filippo. "Visual Pattern as a Secondary 'Biologically-Oriented' Outcome in the Field of Early Intervention of the Autism Spectrum Disorder: Can the Eye-Tracker Provide Useful Suggestions?". International Meeting for Autism Research, San Francisco 2017

8 **Francesca Fulceri**, Mariangela Morelli, Elisa Santocchi, Antonio Narzisi, Sara Calderoni and Filippo Muratori “Gastrointestinal Symptoms and Associated Clinical Features in Preschoolers with Autism Spectrum Disorders”. International Meeting for Autism Research, Salt Lake City 2015

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