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THE ITALIAN NETWORK FOR EARLY DETECTION OF AUTISM SPECTRUM DISORDER: RESEARCH ACTIVITIES AND NATIONAL POLICIES

Angela Caruso, Martina Micai, Letizia Gila, Francesca Fulceri & Maria Luisa Scattoni

Research Coordination and Support Service, Istituto Superiore di Sanità, Rome, Italy

SUMMARY

Background: *Well-structured monitoring system is crucial to identify interventions for children with Neurodevelopmental Disorders (NDD).*

Subjects and methods: *The NIDA Network enrolled more than 760 at risk for NDD and typically developing infants to detect early signs of NDD.*

Results: *The NIDA Network was born in some Italian regions to engage clinical centers in a research project. It is increasingly turning out to be a national monitoring project well integrated in the Italian National Health System policies.*

Conclusions: *The NIDA Network activities are finalized at diagnosis and interventions to improve quality of life of children with NDD and their families.*

Key words: *neurodevelopmental disorders - early recognition - public policies*

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INTRODUCTION

Neurodevelopmental disorders (NDD, including Intellectual Disability, Communication Disorders, Autism Spectrum Disorders, Attention Deficit Hyperactivity Disorder, Specific Learning Disorder, and Motor Disorders) are a relatively heterogeneous set of conditions characterized by impairments of personal, social, and academic functioning (Diagnostic and statistical manual of mental disorders, DSM-5, APA 2013). Despite the early onset in the developmental process, NDD can be diagnosed reliably only between 18 and 24 months of age because the gold standard diagnostic tools are based upon identifying behavioral symptoms, which are most evident starting with this age (Hyman et al. 2020). However, identifying early biomarkers and behavioral measures to determine risk status even before the emergence of clear behavioral symptoms is crucially important to identify a targeted early intervention, even before the disorder has expressed itself to the full. Identifying early signs of NDD allows monitoring of the development and integration of the child within a surveillance program. Thus, early detection and intervention programs improve infants' and parents' outcomes.

This work wants to present the research outcomes and national policies of the Network for early detection of Autism Spectrum Disorders (NIDA Network). The Italian National of Health hosts the NIDA Network of excellence in the pediatric hospitals and clinical research centers of the Italian territory, born to anticipate detection and intervention for people with Autism Spectrum Disorder (ASD). The activities of the NIDA Network served as a foundation for the implementation of infant population's monitoring within the framework of national policies.

SUBJECTS AND METHODS

The NIDA Network enrolls High Risk (HR: siblings of children already diagnosed with ASD, preterm, and small for gestational age infants with a higher risk than the general population to develop ASD) and Low Risk (LR) infants to detect early signs of NDD, including ASD, through the recording and analysis of infant cry and motor patterns at 10 days and 6, 12, 18, and 24 weeks of age. At 6, 12, 18, 24, and 36 months, each infant/toddler receives a comprehensive clinical/diagnostic assessment using standardized tools/tests and structured interviews with parents for checking the presence/absence of an ASD or NDD diagnosis. At the time of clinical evaluation, the clinicians also collect biological samples for each infant/toddler, parents, and siblings to identify early biomarkers of ASD. Whenever specific difficulties are identified, the children are directed towards personalized early care and treatment. This Network makes use of multidisciplinary team made up of child neuropsychiatrists, psychologists, neuro and psychomotricity therapists of developmental age, biostatisticians, neurobiologists, and biomedical engineers. Infant recruitment and data collection are currently ongoing. The Ethics Committee of the Italian Institute of Health approved the study protocol (Approval Number: Pre 469/2016).

RESULTS

The NIDA Network was born in 2012 in the Italian regions of Lombardy, Tuscany, Lazio, and Sicily to engage clinical centers in a research project. In the last years, with the support of public fundings by the Italian Ministry of Health, and the coordination of the Italian National of Health as a part of activities required by ministerial

decrees, the NIDA Network is increasingly turning out to be a national monitoring project well integrated within the Italian National Health System policies.

So far, the NIDA recruitment includes more than 760 infants. This amount of data permitted to conduct research activities focused on the identification of motor, cry, vocal, and early flags for the recognition of ASD (Baccinelli et al. 2020, Caruso et al. 2020, Chericoni et al. 2021, Di Giorgio et al. 2016, 2021, Malatesta et al. 2020, Marchi et al. 2019, Purpura et al. 2017, Riva et al. 2018). In particular, results showed that early motor, language, and social attentional trajectories of HR infants for ASD, who later received a NDD diagnosis, appeared different compared to typically developing infants. Screening instruments, such as the Child Behavior Checklist - CBCL 1½-5 parent report, had difficulty differentiating correctly between HR infants developing ASD and infants who had a typical development at 18 months of age (Chericoni et al. 2021). However, higher scores in CBCL Withdrawn scale correlated positively with the clinician's assessment with the Autism Diagnostic Observation Schedule – 2nd Edition. By applying novel automatic and semi-automatic technological tools, the NIDA research activities identified potential early behavioral precursors of altered development linked to NDD diagnosis (Baccinelli et al. 2020, Caruso et al. 2020, Marchi et al. 2019) (Table 1 describe research outcomes).

Table 1. NIDA Network research outcomes.

Work's title (first author, year)	Main findings
Abnormal visual attention to simple social stimuli in 4-month-old infants at high risk for autism (Di Giorgio et al. 2021)	Significant visual preference for the direct eye-gaze stimulus in infants at-risk for Autism Spectrum Disorder compared to low-risk infants.
A combined study on the use of the Child Behavior Checklist 1½-5 for identifying Autism spectrum disorders at 18 months (Chericoni et al. 2021)	Child Behavior Checklist 1½-5 had difficulty differentiating correctly between high-risk infants developing ASD and infants who had a typical development at 18 months of age. Higher scores in Withdrawn scale correlated positively with the clinician's assessment with the Autism Diagnostic Observation Schedule – 2nd Edition.
Movidea: A software package for automatic video analysis of movements in infants at risk for neurodevelopmental disorders (Baccinelli et al. 2020)	Movidea software allows the operator to track the movement of end-effectors of infants in free moving conditions and extract movement features automatically. Movidea performance did not vary with the operator, and the tracking was stable in home-video recordings.
Early motor development predicts clinical outcomes of siblings at high-risk for autism: Insight from an innovative motion-tracking technology (Caruso et al. 2020)	Early developmental trajectories of specific motor parameters differed in high risk for Autism Spectrum Disorder infants later diagnosed with Neurodevelopmental Disorders compared to typically developing infants.
Received cradling bias during the first year of life: a retrospective study on children with typical and atypical development (Malatesta et al. 2020)	During the second half of the first year of life, dissimilar patterns of cradling preferences. Absence of left-cradling in typical mothers not observed in Autism Spectrum Disorder mothers, who exhibited a significant left-cradling bias in the 6–12 months age group.
Automated pose estimation captures key aspects of General Movements at eight to 17 weeks from conventional videos (Marchi et al. 2019)	More variable arm movements in infants with typical movements.
Distinct ERP profiles for auditory processing in infants at-risk for autism and language impairment (Riva et al. 2018)	At 12-month-old, auditory processing in high risk for Autism Spectrum Disorder (HR-ASD) infants, high risk for language impairment (HR-LI) infants, and controls was characterized via ERP oddball paradigm. Mismatch response latency delayed in HR-ASD and HR-LI compared to controls. Overall larger P3 amplitude compared to controls in HR-ASD compared to controls. Later expressive vocabulary and M-CHAT critical items correlated with ERP measures in all groups.
Bilateral patterns of repetitive movements in 6- to 12-month-old infants with Autism Spectrum Disorders (Purpura et al. 2017)	Higher total scores in bilateral Repetitive Movement Episodes with arms, hands, fingers, and lower limbs in infants with Autism Spectrum Disorders compared to Developmental Delays and typically developing infants.
Difference in visual social predispositions between newborns at low- and high-risk for autism (Di Giorgio et al. 2016)	High-risk and low-risk for Autism Spectrum Disorders newborns differ in visual preferences to social stimuli.

The clinical-diagnostic evaluation protocols of the NIDA Network have been implemented as a system action of all Regions and Autonomous Provinces in the Italian territory aimed at the surveillance of 0-3 years children and the implementation of services dedicated to the diagnosis, care, and treatment of people with ASD. So far, in Italy more than 105 clinical centers have been activated as NIDA sentinel centers, including child neuropsychiatry centers and neonatal intensive care units. All these centers are adopting the NIDA Network clinical protocols.

The NIDA Network was the springboard for The Reading Early Autism Disorders Signs (READS) project on the promoting of early diagnosis and understanding of the multifactorial origin of ASD through the development of software tools for clinical data recording. The READS project foresees the development of an innovative technological platform for the acquisition and analysis of behavioral and physiological biomarkers based on electronic and mechanical systems integrated into a crib for children between 0 to 12 months.

The NIDA Network recruitment and protocols have been implemented also within two European Training Networks. The BRAINVIEW project approached the ultrasound assessment of movements to study well-being and early neurodevelopment of fetuses in LR and HR pregnancies (Athanasiadou et al. 2020, Fulceri et al. 2019). The SAPIENS project used innovative technologies to study the brain and behavioral dynamics during social interactions to determine how individual child and environmental variability can interact and anticipate social developmental trajectories.

The monitoring of NDD has been extended to the general population trough the preparation of checklists that report the main behaviors to be assessed as part of the routinary well-child visits within the first three years of life and the promotion strategies that the pediatrician can propose to parents (and other caregivers) to enhance opportunities and experiences in which certain functions can be promoted (Micai et al. 2020).

The main Italian scientific and professional societies, clinicians, and researchers with well-documented expertise were involved in implementing the NIDA Network clinical protocols and in creating the checklists for the early detection of NDD. In addition, distance learning courses have been promoted for pediatricians, educators, and teachers of nurseries and preschools on people with ASD care.

Implementing a technological platform supports research and project activities within the NIDA Network since it allows anonymous and standardized data collection of the clinical-diagnostic protocols for the surveillance of HR and the general population.

DISCUSSION

The NIDA Network, the largest multi-center and multi-disciplinary network in Italy, aimed to guide observational studies and surveillance programs for the early detection of NDD. It works in collaboration with national and international professionals, scientific organizations, public and academic institutions. The great scientific relevance of the NIDA Network relies on measurements and tools to monitor the central nervous system development and child health in a completely non-invasive way.

The research activities face the complexity and heterogeneity of NDD conditions by exploring behavioral and neurobiological trajectories of HR and LR infants to correlate early developmental anomalies with later diagnostic outcomes and investigate the early indexes of NDD. Moreover, the investigation is aimed to identify diagnostic and screening tools that provide useful information for the detection of infants at risk for NDD as early as possible. The purpose of the Network is to promote early detection of NDD supported by creating of an operational model that has been extended to the whole Italian territory and transferred to other contexts involving the study of the general population. The link between the clinical and diagnostic centers and pediatricians within the NIDA Network ensures constant monitoring, prompt and tailored interventions for all Italian infants and their families. The NIDA Network promotes evidence-based training activities to disseminate and develop specific professional skills on early signs of NDD for teacher and socio-healthcare professionals.

Future directions of the NIDA Network are to empower research and clinical protocols using more sophisticated and non-invasive technologies and include in the monitoring programs also other population at risk for NDD.

CONCLUSIONS

The NIDA Network was born as a research and clinical protocol, then extended to all Italian territory to monitor the population at risk for NDD and the general population. The NIDA Network activities are finalized at the diagnosis and interventions to improve quality of life of children with NDD and their families.

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Contribution of individual authors:

Writing – Original Draft: Angela Caruso & Martina Micai.

Writing – Review & Editing: Francesca Fulceri, Letizia Gila & Maria Luisa Scattoni.

Design of the study, Conceptualization, Funding acquisition, Supervision, and Project administration: Maria Luisa Scattoni.

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Correspondence:

Maria Luisa Scattoni, MD, PhD
Research Coordination and Support Service, Istituto Superiore di Sanità
Viale Regina Elena 299, 00161 - Rome, Italy
E-mail: marialuisa.scattoni@iss.it