

BMJ Open Multistage screening process for neurodevelopmental disorders in siblings of children with autism: the FRATSA protocol study

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ABSTRACT

Introduction The elevated rates of neurodevelopmental disorders (NDDs) among siblings of children with autism spectrum disorder (ASD) raise concerns about their developmental monitoring and development. The main aim of this study is to assess the feasibility and acceptability of a standardised screening process on a large sample of siblings.

Methods and analysis This prospective study will assess the feasibility of a selective and multi-stage screening process for NDD performed on 384 siblings of children with confirmed ASD. Stage 1 will consist of the screening of NDD performed using online parental questionnaires (Social Responsiveness Scale, Identidys scale, DCDQ, parental concerns) through a web platform. In cases of a positive result, the second stage, consisting of a clinical semi-structured interview with a psychologist, will be proposed to the sibling before referral for diagnosis and treatment, if necessary. Approximately 12 months after stage 2, parents will be contacted by telephone to collect the diagnosis established following the referrals and their level of satisfaction concerning the screening process. Based on an expected participation rate of 50%, to estimate this rate with an accuracy of 5%, it is necessary to screen 384 subjects.

Ethics and dissemination The Ethics Committee on the Research of Human Subjects of Paris (Ile de France VII) approved this study in March 2022 (number: 2021-A02241-40). Express consent is required from all participants. Findings from the cohort study will be disseminated by publication of peer-reviewed manuscripts, presentations at scientific meetings and conferences with associated teams.

Trial registration number NCT05512637.

INTRODUCTION

Neurodevelopmental disorders (NDDs), such as autism spectrum disorder (ASD), intellectual developmental disorder, developmental coordination disorder (DCD) and attention deficit/hyperactivity disorder (ADHD), are complex and lifelong conditions that involve some form of disruption of brain maturation

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The main strength of this study is its rigorous assessment of the relevance of an online neurodevelopmental disorder (NDD) screening platform that can be easily used by primary care physicians for targeted screening of high-risk populations.
- ⇒ Second, this study provides a screening tool responding to actual French guidelines that recommend a specific monitoring of siblings of children with autism spectrum disorder.
- ⇒ A limitation is that our screening algorithm targets only the most frequent NDDs.
- ⇒ Resource limitations necessitated confirmation of a negative screening result in a randomly selected subsample of those who screened negative at stage 1.
- ⇒ A third limitation is the lack of inclusion of self-reported measures for older children.

processes. Despite the heterogeneity of their core behavioural symptoms, they share an early onset of deficits in personal and social functioning.¹ Given the functional impact of NDD on developmental trajectories, French guidelines promote early and regular screening in childhood up to the age of 7 years.^{1 2} ASD is one of the most pervasive NDDs,³ characterised by qualitative abnormalities in social communication associated with stereotypic and repetitive behaviours and narrow interests.¹ There is a consensus that early evidence-based interventions are needed to improve the prognosis of NDDs.⁴

Numerous prospective studies have provided evidence that certain populations are at high risk of NDDs, particularly siblings of children with ASD.^{5–10} It has been hypothesised that these siblings show heightened genetic and/or environmental vulnerability for NDDs, as demonstrated by twin studies,^{11 12} with a higher likelihood of having ADHD or

DCD reported among monozygotic twin pairs than for dizygotic pairs.¹³

In recent large studies of siblings of children with ASD, the prevalence of NDDs was estimated to be approximately 36.9% versus 17.4% in a control population¹⁴ and the risk of ASD was between 6% and 25%¹⁵ versus 1% in the general population.⁴ The most common other diagnoses in siblings were learning disorders and DCD (15.7%), ADHD (5%) and ID (2.9%). Further studies found higher-than-average rates of problem behaviours in siblings¹⁶ and specifically internalised (eg, anxiety) or externalised (eg, aggressive) behaviours,¹⁷ the risk being higher when a sibling with ASD had more aberrant behaviours.⁸ In addition, 15%–30% of siblings had behaviours or ‘traits’ of the broader autism phenotype.¹⁸

Given, on the one hand, the discrepancy between the high risk of NDD in siblings and the delay in diagnosing these disorders^{19,20} and, on the other hand, the consensus on the need for early intervention, the French health authority recommends continuous developmental monitoring, regular screening of NDD up to the age of 7 years and the referral of children who are identified.²

Study aims

The main objective of this study is to examine the feasibility of a selective screening process for NDDs for siblings (aged 2–16 years) of children with ASD prior to referral for diagnosis to general practitioners and intervention. Secondary objectives are to investigate: (1) the sensitivity/specificity and positive/negative predictive values (PPV/NPV) of the screening process, (2) the prevalence of each NDD and the prevalence of the broader autism phenotype in siblings and (3) parent’s satisfaction with the multistage process 12 months after screening.

METHODS

Study design

This is a prospective, multi-stage and multicentre feasibility study of a screening process for NDD in siblings of children with ASD. Study is expected to start in March 2023 and to be completed 3 years later, in 2026.

Population and recruitment

The inclusion criteria for eligible participants are 2-year-old to 16-year-old siblings or half-siblings of children with ascertained ASD living in Occitania (a region in the South of France of 5.5 million inhabitants).

The non-inclusion criteria are parents’ or child’s refusal to participate, being an adopted brother or sister, and parents’ inability to read the research questionnaire written in French. If no parents are available to fill questionnaires, legal guardians are acceptable raters.

The participants will be recruited over an 18-month period from tertiary centres or the ELENA cohort.²¹ The ELENA cohort is a French ongoing prospective and multicentre study, in which 876 children age 2–16 years (including 593 (68.15%) from Occitania). Participants

with an ascertained diagnosis of ASD are followed up by trained psychologists over a period of 6 years. Additional medical and interventional data are collected by parent questionnaire completed online. Information about the study is available on two websites (<http://elena-cohorte.org>; <http://www.autisme-ressources-lr.fr/>).

Sample size

The sample size is based on the participation rate of families in the screening programme, which is the main outcome. An expected participation rate of 50% is considered to be acceptable. To estimate this rate with a precision of 5%, it is necessary to screen 384 subjects. In addition, we will conduct a random drawing among screen-negative children over 7 years of age to validate our screening algorithm. It will be necessary to draw 95 children who were negative at the stage 1 screening to achieve an NPV close to 99% with an accuracy of 2% (95% CI).

Patient and public involvement

Members of associations of families of children with autism were involved in the design of the study to review the information notes for families and to verify the acceptability of the protocol. However, participants were not involved in the development of the study design or objectives that were developed by the investigators of the study.

Outcomes

The primary outcome is the rate of participation in screening by eligible families and, among children with a positive screening result, the rate of children who received a specialised diagnosis 12 months after the screening process ended.

Secondary outcomes are the sensitivity/specificity and PPV/NPV of the screening process, the reference diagnosis and rate of broader autism phenotype in siblings, and the parents’ satisfaction with the multistage process.

Screening tools

The Social Responsiveness Scale (SRS-2) preschool age form (2–4 years) and school-age form (from 4.1 to 18 years)²² is a 65-item questionnaire that measures ASD trait severity across five subscales: Social Awareness, Social Cognition, Social Communication, Social Motivation, and Restricted Interests and Repetitive Behaviors. Each question is rated from 1 (not true) to 4 (almost always true) and a total composite score (T-scores) (mean=50, SD=10) is used to assess the severity of symptoms. T-scores ≥ 90 indicate extremely severe social impairment. Total scores of ≤ 59 correspond to the average range, 60–65 a mild degree of impairment, 66–75 a moderate degree of impairment, and 76 or higher, a severe degree of impairment. The internal consistency is 0.95.

*IdentiDys scale*²³ is a screening scale that targets a range of learning disabilities across five developmental domains: attention/hyperactivity/impulsiveness, verbal and written language, motor skills and spatial tracking, and executive

functioning. Each domain is rated from 0 (no difficulty) to 3 (ascertained risk of difficulties). The sensitivity of the scale is <0.05 and fidelity >0.89 .

The *Little Developmental Coordination Disorder Questionnaire-French European* (LDCDQ-FE)^{24 25} and for children over 7 years of age, the *Developmental Coordination Disorder Questionnaire-French European* (DCDQ-FE)²⁶ assess DCD. Scales include 15 items grouped into three domains: control during movement, fine motor function and writing, and global coordination. Each item is rated from 1 ('does not correspond at all to my child') to 5 ('corresponds to my child'), which are summed to obtain a total score. A score ≤ 56 corresponds to a risk of DCD and a score ≥ 56 corresponds to no risk of DCD. Sensitivity is 85% and specificity is 81%. The internal consistency is 0.94.

Only one *parental concerns questionnaire* will be filled in per household by one or both parents (or legal guardians if no parents are available) of each child of the siblings (brother or sister, half-brother or half-sister on the maternal side, half-brother or half-sister on the paternal side).

Note that only parent screening self-questionnaires were used in the absence of screening self-questionnaires available in French for children.

Other collected data

Clinical variables (perinatal medical history, psychiatric comorbidities) and data about schooling and interventions (school degree, learning difficulties, benefiting from specialised interventions) will be also collected for all screened children.

The *parent's satisfaction* with the multistage process will be measured using a Visual Analogue Scale (VAS) from 0 to 10, with 0 being the worst satisfaction and 10 being the highest satisfaction.

The data to be collected are listed in online supplemental table S1.

Screening procedure

The screening process includes two stages (figure 1). Stage 1 consists of the screening of each sibling through online parental questionnaires. These questionnaires targeting the most frequent NDDs will be administered based on the minimum age at which each diagnosis can be made. The thresholds of positivity retained for the questionnaires correspond to the following algorithm: if SRS-2 >59 and/or one of the five domains of *IdentiDys* scale is positive (attention/hyperactivity/impulsiveness: >11.25 , oral language: >6 , written language: >10.5 , motor skills: >4 , executive functioning: >7.25), and/or LDCDQ-FE or DCDQ-FE ≤ 56 , and/or if the parents report at least one concern in a parental concerns questionnaire.

If a child's screening result is positive on at least one of the questionnaires or if the parents describe any concerns, the child will advance to stage 2. Children under 7 years of age and negative at stage 1 will be contacted again every 18 months until they reach 7 years of age for a new

round of online screening. In this negative population, a random sample of 95 children will be selected 6 months after a negative screening result at stage 1. The selected families will have a face-to-face interview with a psychologist by video to confirm the absence of a NDD.

At stage 2, a psychologist will receive children with their parents within 3 months for a clinical semi-structured interview based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria (by teleconsultation) to check for the NDD. In cases of doubt, the psychologist will refer the case to an adjudication committee to confirm the suspicion or decide on the orientation. According to the guidelines of the French National Authority for Health around the diagnosis of NDD, the psychologist will inform the parents of the results of the screening and, in case of a positive screening of their child, will refer the child to a dedicated primary care consultation with the child's regular doctor. This doctor is responsible for referring and coordinating the pathway of children with suspected NDD to the second line specialist for diagnosis and intervention. The psychologist will call the parents 12 months after the clinical interview to collect information concerning the diagnosis established following the specialised referrals, as well as the interventions carried out or in progress, and, finally, their overall satisfaction with the screening.

Data management

Data input, security, storage and processes to promote data quality are ensured by Epiconcept (Voozanoo 4, France), which is a certified health data host (General Data Protection Regulation). Participants' data will be managed and analysed in an anonymous manner. No nominative data will be recorded in the screening questionnaires. Nominative data will be stored in a specific database only accessible to the data manager and given to the psychologist if necessary.

Statistical methods

We will use the 'Standards for Reporting Diagnostic accuracy studies' guidelines for the reporting of diagnostic studies.²⁷ Data will be analysed using SAS V.9.3 (SAS Institute). The variables will be described using means and SD for continuous variables and frequencies and percentages for categorical variables.

In the primary analysis, the rate of participation in screening by eligible families, and the rate of children with a positive screening result who received a reference diagnosis will be estimated with their 95% confidence limits.

In addition, to detail the acceptability of the process, the rate of completion of the parental e-questionnaires, number of missing values for parental e-questionnaire, rate of acceptance to participate in screening stage 2 will be reported. A comparison between the characteristics of non-respondents and respondents to the screening process will be performed to identify possible selection biases.

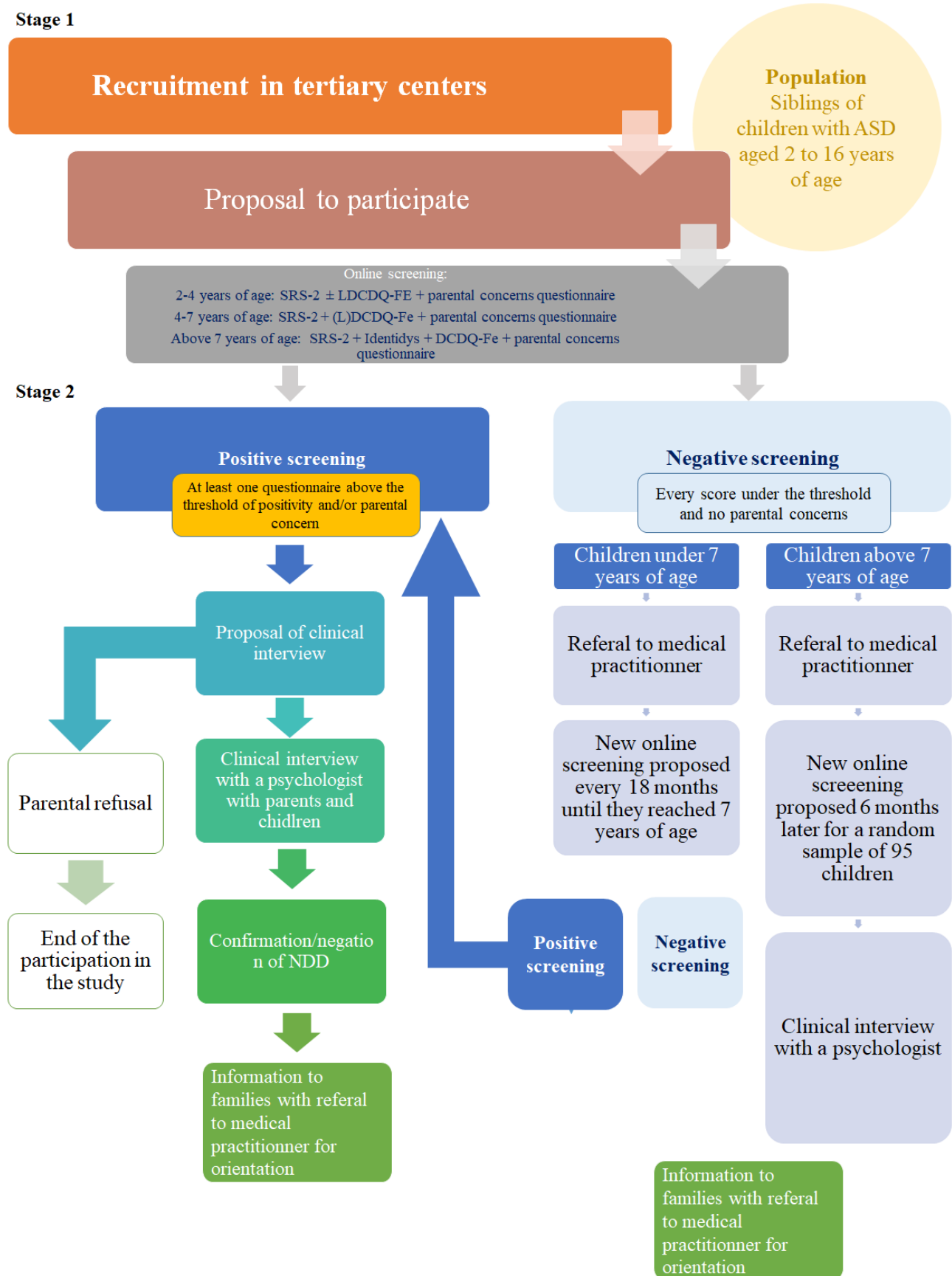


Figure 1 Screening procedure. ASD, autism spectrum disorder; DCDQ-FE, Developmental Coordination Disorder Questionnaire-French European; LDCDQ-FE, Little Developmental Coordination Disorder Questionnaire-French European; NDD, neurodevelopmental disorder; SRS-2, Social Responsiveness Scale.

In secondary analysis, sensitivity, specificity and predictive values of the screening process and the identification of optimal thresholds between index tests. The sensitivity, specificity and predictive values will be calculated, with their 95% confidence limits, globally and for each NDD. A receiver operating characteristic curve (ROC curve) will be generated and the area under the curve determined to evaluate the discriminative power of each scales to diagnose a specific NDD and for the three scales used simultaneously. The area under the ROC curve will provide information in a single numerical value concerning the overall diagnostic accuracy of one or more of the index tests.

The overall prevalence of NDDs and the relative frequency of each NDD will be reported with their 95% confidence limits. Their phenotypic characteristics will be described.

The mean VAS score related to satisfaction with screening will be calculated with their SD as well as the mean time to referral of the screened child and his or her actual management by the care service.

The significance level is conventionally set at 5% for all tests used.

Ethics and dissemination

Research ethics approval

The study protocol is approved by the Human Research Ethics Committee of Ile de France VII (n°2021-A02241-40). Children and their parents/guardians will receive verbal and written information on the study and will provide their consent.

Consent

An information letter will be sent by email or post (if no internet connection) to the eligible families, or in person when families are received in the centres for their children with an ASD diagnosis. Parents will log in to a secure area where they will receive information about the nature of the study, as well as their rights and responsibilities and the potential risks and benefits. Screening will be performed for each child in the sibling group. Parents will be able to indicate their non-objection electronically. If they have any questions, they will be able to contact the coordinating investigator (by e-mail, mail or telephone).

Dissemination policy

Results will be presented at scientific meetings and published in international peer-reviewed journals. Summaries will be provided to the funders of the study, as well as to the patients and their parents/guardians.

DISCUSSION

This study should promote the screening of NDDs in the at-risk population of siblings of children with ASD, as well as make families and health professionals aware of the recurrence of these disorders in the siblings and the need for specific developmental surveillance. In

addition, this screening process will make it possible to improve the coordination of the care pathway for siblings who develop NDDs by promoting links between the specialised structures in charge of screening and those in charge of diagnosis and intervention. If it proves to be effective and meets with the support and satisfaction of the families, this process could be generalised to other families whose children present a high risk of NDDs (eg, family risk and perinatal history, such as prematurity). An important research perspective is to extend this study to mental health disorders in siblings in light of their high risk in siblings.

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