



Promoting emotional and behavioral interventions in ASD treatment: Evidence from EPIGRAM, A naturalistic, prospective and longitudinal study

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ABSTRACT

Background: Prognostic factors from naturalistic treatment studies of children with Autism Spectrum Disorder (ASD) remain largely unknown. We aimed to identify baseline and treatment-related prognostic predictors at 1-year follow-up after Integrative Care Practices (ICPs).

Methods: Eighty-nine preschool children with severe ASD were given ICP combining nine therapeutic workshops based on children's needs. Participants were assessed at baseline and during 12 months follow-up with the Psycho-educational Profile-3-R, Children Autism Rating Scale, Parental Global Impression, and the Autistic Behaviors Scale. We assessed prognostic predictors using multivariable regression models and explored treatment ingredients influencing outcome using Classification and Regression Trees (CART).

Results: Multivariable models showed that being a child from first generation immigrant parents predicted increased maladaptive behaviors, whereas play activities had an opposite effect; severity of ASD symptoms and impaired cognitive functions predicted worse autism severity at follow-up; and lower play activities predicted worse parent impression. Regarding treatment effects, more emotion/behavioral interventions predicted better outcomes, and more communication interventions predicted lower autism severity, whereas more education and cognitive interventions had an opposite effect. CART confirmed that more hours of intervention in the

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emotion/behavioral domain helped classifying cases with better outcomes. More parental support was associated with decreased maladaptive behaviors. Sensorimotor and education interventions also significantly contributed to classifying cases according to outcomes but defined subgroups with opposite prognosis.

Conclusion: Children who exhibited the best prognosis following ICPs had less autism severity, better cognition, and non-immigrant parents at baseline. Emotion/behavior interventions appeared key across all outcomes and should be promoted.

1. Introduction

Autism Spectrum Disorder (ASD) is characterized by persistent deficits in social interaction and communication, alongside restricted, repetitive patterns of behaviors and interests, or hypo/hyper-reactivity to sensory stimuli (American Psychiatric Association, 2013). It represents a heterogeneous neurodevelopmental condition with early onset, which frequently co-occurs with other conditions (Pickles et al., 2020). Early diagnosis and intervention may considerably improve the quality of life of children with ASD and their families, but early identification and treatment are still challenging in public health systems due to the lack of available biomarkers (Narzisi et al., 2014). Children diagnosed with ASD show differences in both social and cognitive aspects, thereby necessitating different interventions tailored to the individual profile (Vivanti et al., 2014). Several interventions have shown promising results in trials focused on early autism intervention, leading to their widespread adoption in clinical practice, e.g., Naturalistic Developmental Behavioral Interventions (NDBI) (Gosling et al., 2022).

Longitudinal studies have shown that the most consistent predictors of higher quality of life include age at diagnosis and intervention (Narzisi et al., 2014), good quality of early assessment, early language development, higher IQ and adaptive behavior scores, lower symptom severity and fewer challenging behaviors at baseline (Farley et al., 2009; Baghdadli et al., 2018), as well as more

Table 1
Characteristics of the children included in the EPIGRAM study at baseline (N = 89).

	All (N = 89)
Socio-demographic Variables	
Gender Male: n(%)	82 (92%)
Age: median [q1-q3]	4[3–5]
Separation from extended family (yes): n(%)	40 (45%)
Serious illness of a parent (yes): n(%)	21 (24%)
Economic difficulties (yes): n(%)	27 (30%)
Separated parents (yes): n(%)	21 (24%)
Clinical characteristics	
Typical (F84-0)/ Atypical Autism (F84-1)	65 (73%)/ 24 (27%)
Absence of language (yes): n(%)	40 (45%)
Eating disturbances (yes): n(%)	69 (78%)
Sleeping disturbances (yes): n(%)	52 (58%)
Child's history	
Acute illness (yes): n(%)	23 (26)
Pregnancy difficulties (yes): n(%)	29 (33)
Childbirth difficulties: median [q1-q3]	0[0,1]
School enrollment at inclusion	
Schooling (yes): n(%)	78 (88%)
With a special needs' aid (yes): n(%)	60 (67%)
Special needs class (yes): n(%)	4 (5)
Delayed in comparison to the grade's level	0[– 0.5-0]
Clinical variables at baseline	
CARS	43.7 (6.5)
PEP-3-R verbal/preverbal cognition: median [q1-q3]	36[14–64]
PEP-3-R expressive language: median [q1-q3]	31[12–52]
PEP-3-R receptive language: median [q1-q3]	30[11–63]
PEP-3-R fine motor skills: median [q1-q3]	32[24–62]
PEP-3 gross motor skills: median [q1-q3]	29[14–48]
PEP-3-R oculo-motor imitation: median [q1-q3]	28[13–59]
PEP-3-R affective expression: median [q1-q3]	45[25–68]
PEP-3-R social reciprocity: median [q1-q3]	41[17–59]
PEP-3-R motor behaviors characteristics: median [q1-q3]	30[12–58]
PEP-3-R verbal behaviors characteristics: median [q1-q3]	15[4–41]
CAT communication: median [q1-q3]	23[11–55]
CAT motor skills: median [q1-q3]	29[15–57]
CAT inappropriate behaviors: median [q1-q3]	11[6–50]
ECA-R global: mean (SD)	62.45 (17.68)
ECA-R relationship impairment: median [q1-q3]	32[25–40]
ECA-R modulatory insufficient: median [q1-q3]	5[4–8]

improvement during the first year of intervention (Moulton et al., 2016). There is also evidence that children's quality of play predicts more positive outcomes (Gray et al., 2012).

However, clinicians often face challenges when applying the aforementioned treatments in routine practice. First, RCTs usually exclude children with comorbid intellectual disability (ID) or challenging behaviors, questioning population representation (Salomone et al., 2016; Hyman et al., 2020). Second, there is insufficient evidence to determine which specific interventions are the most effective for a given child (Vivanti et al., 2014). Third, different treatments are often offered to children with ASD depending on the healthcare system, the financial support available for immigrant and low-income families, and the school system's openness to accommodating children with special educational needs (Salomone et al., 2016). Finally, parental involvement may dramatically vary in routine practice (Zachor and Ben-Itzhak, 2017). Therefore, prognostic predictors in naturalistic contexts are essential in autism treatment to provide individualized, effective interventions that improve outcomes.

Here, we aimed to (1) identify prognostic factors at baseline associated with treatment outcomes at 1-year follow-up after ICP within the framework of the EPIGRAM study; (2) explore which treatment ingredients can predict children's outcome. Based on previous research, we hypothesized migration, severity of autism, cognition and language as baseline predictors of outcomes (Narzisi et al., 2014). In addition, we hypothesized that more education, cognition, parental training and communication interventions were treatment ingredient predictors of better outcomes (Gosling et al., 2022).

2. Methods

2.1. Study design

EPIGRAM is a French prospective, multisite, longitudinal observational study assessing outcomes after ICP in the management of ASD. The experimental protocol was approved on March 24th, 2014 by the local ethics committee, GNEDS (Groupe Nantais d'Éthique) and registered at clinicaltrials.gov under the number NCT02154828.

2.2. Participants

From September 2014 to December 2016, we consecutively recruited 89 children from 19-outpatient centers distributed all over France in order of arrival, where children can access autism care without requiring hospitalization. *Inclusion criteria* were: (1) children between 3 and 6 years old with prior ICD-10 diagnosis of F84.0 or F84.1; (2) interventions delivered in outpatient centers employing ICPs between 2 and 4 half-days per week (8 to 16 h weekly), reflecting routine clinical practice for children with ASD, including therapeutic and educational ASD interventions, ongoing regular assessments, treatment goal updates, and monitoring of developmental progress. Children with non-stabilized comorbidities such as epilepsy and severe somatic or sensory impairment were excluded. Of note, there were no exclusion criteria pertaining to cognitive functions, socioeconomic status (SES), migration, or absence of insurance (Bettencourt et al., 2022). See Table 1 for participants' characteristics.

2.3. ICP manual creation and purpose

ICP interventions were formalized by the Association of Infant and Child Psychiatry of Brittany. The group followed a research methodology recommended by the French National Authority of Health (HAS, 2004), and developed the ICP Manual, constituted with nine multidisciplinary therapeutic interventions. The manual was peer reviewed in 2008 and was later suggested by the HAS as part of the ASD treatment recommendations (Haute Autorité de Santé, 2012; Garret-Gloane et al., 2021).

2.4. ICP Intervention

ICPs are a manualized autism treatment approach that has been proposed in the French context of free access to care in the public outpatient centers. It consists in a set of multidisciplinary, coordinated interventions proposed to children tailored to their individual needs in relation and cooperation with their parents (Bettencourt et al., 2022).

ICP curriculum follows research and clinical guidelines in ASD treatments: being intensive; promoting family inclusion, spontaneous communication and play with peers through group activities; tailoring treatment after careful assessment; favoring natural contexts; supporting positive behaviors rather than tackling challenging behaviors (Vivanti et al., 2020). Additionally, it is based on complementary perspectives: psychopathological, physical, physiological, and associates a plurality of interventions (therapeutic, educational, pedagogical).

The ICP includes nine therapeutic domains, with six developmental interventions proposed in-group settings (sensorimotor, communication, emotion/behavior, socialization, education, cognition). It also includes individual interventions like educational interventions and specific therapies (e.g., speech therapy, occupational therapy, psychotherapy) (Ospina et al., 2018). It also includes school supervision, parental support, and liaison between professionals. All domains are described in detail in the [Supplementary Materials](#).

The manual provides a therapeutic framework to objectivize and personalize the ICP based on children's clinical profile. This can be done through clinical observations, exchanges with the family and other professional, and standardized assessments. The ICP manual was made available to each site during the training phase prior to the beginning of the study (Garret-Gloane et al., 2021). Finally, an observation notebook was employed to monitor prospectively treatment over time. For the current study we included as

treatment variables the exposure to a given therapeutic domain and the mean number of hours received per week over time. Please see the results section for more information.

ICP training phase.

Before the implementation of the study, a comprehensive two-day training phase was conducted, overseen by the main coordinators. This training involved 20 to 30 professionals from the study's outpatient centers, including psychiatrists, psychologists, nurses, and educators experienced in autism care. The primary emphasis during this training phase was to familiarize the professionals with the ICP manual and guide them through clinical assessments of personalized ICP care projects. The objective was to ensure a uniform understanding of the intervention procedures across all professionals, contributing to the consistency and reliability of the study outcomes.

The first in-person session included theoretical principles, methodology presentation, and practical application to two anonymized clinical cases. The second day involved group work, with professionals presenting prepared clinical cases and constructing integrative care projects. The training aimed to enhance skills in clinical observation, data collection and synthesis, collaborative project development, and fostering competence in crafting and regularly reassessing integrative care plans for adjustments. The training used clinical vignettes, active participation, and supervision as pedagogical methods. The anticipated outcomes included synthesizing data, assessing child functioning across domains, involving parents in intervention planning, setting domain-specific objectives, drafting integrative care projects, and the ability to implement and adjust these projects through regular evaluation. The training concluded with a summary by the facilitators, distribution of satisfaction evaluations, post-tests, and practice assessments for remote completion.

Following the training phase, ongoing treatment fidelity was ensured by an external psychologist who paid visits to each center once a month. Her role was to particularly ensure that the administration of the PEP-3 took place under the same conditions, that the recorded videos were readable, and to confirm the correct implementation of the ICP.

Additionally, the data server (supported by the research service server of the University Hospital Center in Nantes) built by the data manager consists of the Electronic Case Report Form (e-CRF) on which all data was recorded through a documentary base with recording grids for the individualized care project, the manual, guides for steps (data entry, parental authorizations), and explanations of standardized tools. All French data protection authority (CNIL) procedures were validated, as well as the ethical verification of data, by a training phase for clinicians, monthly meetings, and regular communication between all investigators and sites' professionals. Finally, an observation notebook was employed to monitor treatment over time and to track and confirm patients' adherence to treatment prescription.

2.5. Study measures and outcomes

At inclusion, diagnosis was confirmed with a Structured Clinical Observation Questionnaire (Garret-Gloane et al., 2021) based on the ADOS-2 and ADI-R items, including communication, social interactions, behaviors and play skills. The observation grid was completed by the psychiatrist after interviewing the parents in the presence of the child. We also assessed socio-demographic variables for each participant, including the immigration status. Immigration status was defined by the presence of at least one parent with immigrant background, referring to a history of parental relocation to France with the intention of settling there. This was done according to previous research (Bettencourt et al., 2022) showing the impact of migration on baseline severity and treatment outcome. Clinical assessments included the following:

- The Psychoeducational Profile, Third Edition-Revised (PEP-3-R, (Schopler et al., 2021)). We focused specifically on the communication domain which includes cognitive verbal/preverbal scores (CVP), expressive language scores (EL) and receptive language scores (RL), but the maladaptive behaviors domain (CATCI), which includes affective expression scores (AE), social reciprocity scores (SR), motor behaviors characteristic (MBC) and verbal behaviors characteristic (CVBC).
- The Autistic Behavior Rating Scale, Edition Revised (ECA-R, (Bonnet-Brilhault et al., 2021))
- Khoms Evaluation of Oral language (ELO, (Khoms, 2001))
- The Childhood Autism Rating Scale (CARS, Schopler et al., 1989)
- The Parental Global Impression (PAR, (Garret-Gloane et al., 2021)). The PAR was developed based on the questionnaire from the Tavistock Clinic and Portman NHS Trust (Anonymous Ref, 2021). It focuses on parental observations concerning their perception of their child's symptoms, their evolution, and also assesses therapeutic alliance. The questionnaire also contains specific questions to assess children's play skills. Parents' rated outcomes were assessed on a 5-point Likert scale (worsening=0 to very satisfactory improvement=4). See [Supplementary Material](#) for additional information on PAR and other clinical assessments.

Each test was administered by independent clinicians at baseline and at 12 months (M12). ECA-R was administered also after 3, 6, and 9 months.

Based on the study protocol, we decided to focus on prediction of three specific outcomes that give a complementary perspective on children's trajectory and response to treatment. First, to grasp maladaptive behaviors, we used the PEP-CATCI as a discrete variable using the thresholds defining severity: none (>89), mild (<89 and >75), moderate (<75 and >25), severe (<25). These behaviors are known to impact children's participation during care and quality of life (Narzisi et al., 2015).

Second, we used the ECA-R to measure symptom severity. The ECA-R is an observational scale designed to assess the main clusters of autistic symptoms based on DSM-5 criteria (Bonnet-Brilhault et al., 2021). Each item is rated on a Likert scale, according to 5 levels from 0 to 4 (0: the behavior is never observed, 1: sometimes, 2: often, 3: very often, 4: always) according to the severity of the various symptoms observed and the frequency of the impaired behavior (Bonnet-Brilhault et al., 2021).

Table 2

Baseline variables associated with better outcome at 12 months.

Baseline	PEP-CATCI improvement					ECA-R improvement					<i>PAR</i>			
	β	SE	OR	t val	p	β	SE	df	t val	p	β	SE	t val	p
CARS total	0.00	0.07	1.00	0.02	0.980	-0.03	0.01	338	-1.96	0.05	0	0.02	-0.12	0.9
ECAR total	0.01	0.03	1.01	0.34	0.731	-0.03	0.01	338	-5.67	< .001	0	0.01	0.59	0.56
Language	0.80	0.69	2.22	1.15	0.250	-0.27	0.2	338	-1.37	0.171	-0.06	0.15	-0.38	0.7
PEP-CVP (cognition)	0.02	0.01	1.02	1.48	0.132	-0.01	0	338	-2.43	0.016	0	0	1.58	0.12
Migration	-1.28	0.58	0.28	-2.21	0.024	0.22	0.2	338	1.1	0.274	-0.09	0.13	-0.65	0.52
Play	0.15	0.07	1.16	1.97	0.044	0	0.03	338	0.02	0.984	0.07	0.02	4	< .001
Worsened/ stable	-2.06	2.56	0.13	-0.80	NA									
Stable/ improved	2.74	2.55	15.56	1.08	NA									

The instrument was validated on a clinical sample with respect to gold standard diagnostic tools (i.e., the ADOS-2). We administered the ECA-R at five time points (baseline, 3 months, 6 months, 9 months, and 12 months).

Finally, we also used the Parental Global Impression questionnaire (PAR) to assess the child's evolution based on the parents' perspectives as a complementary measure (Garret-Gloane et al., 2021). See [Supplementary Materials](#) for detailed information about outcome measures.

2.6. Statistical analysis

Statistical analyses were performed using R 4.1.0, considering two-tailed tests with a level of significance fixed at 5%. Inference relative to quantitative variables involved ANOVA or Kruskal-Wallis rank sum tests, depending on tests assumptions' validity. Similarly, inference relative to qualitative variables involved Chi-squared test or Fisher's exact test. Correlations were performed through Pearson's or Spearman's correlation tests.

The first study question was the effect of baseline predictors on the outcomes. Baseline predictors used in these analyses were CARS total score, ECA-R total score, expressive language score (PEP-EL), cognitive percentile rank (PEP-CVP), immigration status (presence of at least one immigrant parent) and the presence of imaginative/symbolic play assessed during structured clinical observation through an observational grid.

The second study question was the effect of treatment domain intensity on outcome variables. Treatment predictors used in these analyses were time spent in sensorimotor, communication, emotion/behavior, socialization, education, cognition, school inclusion, visits and parental support during the 12-month ICP. The models were fitted using the number of hours per week in each intervention domain, whereas treatment adherence was monitored in clinical contexts as specified by the protocol.

The first strategy was to explain the outcomes using multiple regression models. We used linear regressions for PAR and ordinal logistic regression models (MASS: Venables & Ripley, 2022; and broom packages: (Robinson et al., 2023) for PEP-CATCI (worsened, stable, and improved). Proportional odds assumption was checked with Brant test (brant package: (Schlegel and Steenbergen, 2020). Finally, linear mixed effects regressions specifying the subject as a random intercept (lme4: (Bates et al., 2015); and lmerTest packages: (Kuznetsova et al., 2017) were used for ECA-R, as we had four time points. We report the effect of the interaction of the predictors with time. One model was run per interaction effect tested. In order to control for the effect of baseline variables on treatment outcome, we included pre treatment outcome measures as covariates to disentangle the role of treatment dimensions.

Power analysis for linear regressions (with either 6 or 10 independent predictors) indicated the ability to detect a small-medium effect ($f^2 = 0.09$) with a power of 80% and 5% type I error, that could be expected as effect size for ASD intervention (Sandbank et al., 2020). For ordinal logistic regression, we performed a more conservative estimation of power for a binary logistic regression. The analysis was done with conservative input parameters and indicated that tests performed on standardized continuous variables can detect at least a 3.48 odds-ratio. Power analysis was performed with G*Power (3.1.9.2.).

The second strategy was to classify subjects into groups showing similar outcomes in a data-driven manner, based on their treatment hours. A descriptive approach could provide complementary information and improve clinical interpretations of complex data. Specifically, outcomes were explained using the Classification And Regression Trees (CART) algorithm (rpart:: (Therneau and Atkinson, 2022); and rpartplot packages: (Milborrow, 2022). CART analysis is a Machine Learning (ML) technique used in data exploration and seeks to find the values of the variables of interest that separate the data into groups of children who either had a good outcome or a poor outcome. It may also be used to determine the relative importance of different variables for identifying homogeneous groups in clinical contexts (Breiman et al., 2017). This led to two regression trees (for ECA-R evolution and for parental measurement) and one classification tree (for PEP-CATCI evolution). Since ECA-R score was measured at more than two time points, we estimated each subject's slope of evolution with a linear regression and used the slope as a measure of ECA-R evolution. As CART has a tendency to overfit fine-grained idiosyncrasies in the observed data leading to stable but non-generalizable classifications, it is advisable to curb this algorithmic tendency. As suggested by Hayes, Usami, Jacobucci, and McArdle (Hayes et al., 2015) in order to limit over-fitting, trees were pruned at the optimal number of segmentations, based on cross-validation.

3. Results

3.1. Baseline predictors of 12-Month Outcomes (Table 2)

Being a child from a first generation immigrant negatively predicted PEP-CATCI improvements at 12 months. The quality of play at baseline predicted positive outcomes. Symptom severity (both CARS and ECA-R total scores) and cognition (PEP-CVP score) negatively predicted autism severity (ECA-R scores' increase). Finally, quality of play was the only positive predictor of PAR at 12 months. Correlations between outcomes' variables are given in [Supplementary Materials](#) (figure S1 to S3) Table 2.

3.2. Treatment-related predictors of 12-month outcomes (Table 3)

Emotion/behavior treatment intensity positively predicted PEP-CATCI improvement at 12 months. Specifically, 1 h more of emotion/behavior treatment improved by a factor of 1.08 the odds of belonging to a better prognostic PEP-CATCI category at 12 months. Communication, emotion/behavior, education, and cognition treatment intensity predicted ECA-R at 12 months. Specifically, 1 h more of communication treatment decreased ECA-R score of 0.04 points/months and 1 h more of emotion/behavior treatment decreased ECA-R score of 0.04 points/months which resulted in both cases in a positive evolution. In contrast, 1 h more of education

treatment increased ECA-R score of 0.03 points/months; 1 h more of cognition treatment increased ECA-R score of 0.06 points/months, which resulted in both cases in a worsening trajectory. Finally, emotion/behavior treatment predicted PAR at 12 months. Specifically, 1 h more of emotion/behavior treatment increased PAR of 0.02 points, which resulted in a positive evolution.

Tables 3 and 4 summarizes descriptive statistics about the distribution of weekly hours of intervention in each domain for the participants. Intervention hours are distributed across the different domains based on the individual points of strength and weakness emerged, as well as clinical priorities.

3.3. 12-month maladaptive behavior outcome according to treatment variables through machine learning

The best CART model explaining PEP-CATCI improvement at 12 months was a solution with 3 decision nodes, providing 4 terminal sub-groups (Fig. 1: CATCI_{F1} to CATCI_{F4} from left to right). This model had a 0.65 relative error and a 0.97 cross-validated error (see supplement material S4). The PEP-CATCI classification tree model predicted the improvement of two subgroups (CATCI_{F4} and CATCI_{F3}). Both subgroups received fewer hours related to the sensorimotor domain. CATCI_{F4} received more exposure to the emotion/behavior domain whereas CATCI_{F3} had more parental support.

With regards to the relevance of the CART classification in terms of maladaptive behavior prognosis and improvement processes based on treatment exposure, as shown in Table S3, CATCI_{F4} (n = 13), the most improved subgroup was characterized by mild to moderate maladaptive behavior at baseline and a high proportion of individuals with emerging language, less severe autism and better cognition (PEP-CVP). CATCI_{F3} (n = 13) represented the second improved subgroup in terms of maladaptive behaviors. The cluster showed similar characteristics at baseline than CATCI_{F4} except that they showed moderate to severe maladaptive behavior at baseline. CATCI_{F2} was the largest subgroup (n = 40) with participants that did not change categories in terms of maladaptive behaviors. However, exploring individual scores showed that they were composed of two different types of patients. Some of them had no or mild maladaptive behaviors, moderate autism and better cognition. Other patients had severe maladaptive behavior, severe autism, poor cognition, no language, and did not improve. CATCI_{F1}, the last subgroup (n = 23) included participants that did not improve in terms of maladaptive behavior and had rather similar characteristics than the later CATCI_{F2} subgroup (severe maladaptive behavior, severe autism, poor cognition and no language).

3.4. 12-month autism severity outcome according to treatment variables through machine learning

The best CART model classifying patients according to ECA-R score changes at 12 months was a solution with 3 decision nodes, providing 4 terminal sub-groups (Fig. 2a: ECAR_{F1} to ECAR_{F4} from left to right). This model had a 0.64 relative error and a 0.94 cross-validated error (see supplement material S5). The 2 subgroups that showed improvements in ECAR scores (ECAR_{F1} and ECAR_{F2}) included 20 and 25 patients, respectively, and both received more than 9.5 h of the emotion/behavior domain. Within these 2 subgroups, those in ECAR_{F1} improved the most, and received more exposure to the sensorimotor domain. The two other groups (ECAR_{F3} and ECAR_{F4}) received less exposure with the emotion/behavior domain and were differentiated by exposure to the educational domain. Patients in ECAR_{F4} (N = 20), the group that did not improve, received more exposure with the educational domain than those in ECAR_{F3} (N = 24).

As shown in Table S4, ECAR_{F1}, the subgroup that improved the most in terms of symptom severity, included a high proportion of individuals with severe symptoms and maladaptive behaviors. ECAR_{F2} was a group with moderate maladaptive behaviors, lower symptom severity and higher cognition. Patients in ECAR_{F3} were rather similar to patients from ECAR_{F1} but improved less. They differ on CATCI levels, CARS scores, and in cognition (PEP-CVP) (see Table S4). Finally, patients from ECAR_{F4} included a large proportion of immigrant parents with severe maladaptive behavior and by having children with no language.

3.5. 12-month parental outcome according to treatment variables through machine learning

The tree is shown in Fig. 2b. Again, four subgroups emerged and they all improved despite different amplitudes. This model had a 0.69 relative error and a 1.24 cross-validated error (see supplement material S6). The therapeutic path that was linked to the best improvement (+2.9) (PAR_{F4}) occurred when children received more than 4 h in the behavior/emotion domain and less than 16 h in the education domain. The second best therapeutic path (PAR_{F2}) occurred when children received less than 4 h in the emotion/

Table 3
Average distribution of hours/week per domain.

Characteristic	N = 89 ¹
Sensorimotor	8.43 (7.09)
Motor	9.35 (8.14)
Communication	12.97 (7.46)
Emotion/Behavior	11.38 (9.75)
Socialization	12.20 (9.36)
Education	12.36 (7.66)
Cognition	4.46 (4.31)
School inclusion	1.52 (3.02)
¹ Mean (SD)	

Table 4

Treatment variables associated with improvement at 12 months.

	PEP-CATCI improvement					ECAR improvement					PAR			
	β	SE	OR	stat	p	β	SE	df	t val	p	β	SE	t val	p
Sensorimotor	-0.03	0.04	0.97	-0.68	0.495	-.02	.01	339	-1.11	.266	-.01	.01	-1.24	.22
Motor	0.00	0.03	1.00	-0.04	0.970	-.02	.01	339	-1.27	.203	-.01	.01	-1.06	.29
Communication	0.03	0.04	1.03	0.71	0.481	-.04	.01	339	-3.33	.001	.01	.01	.95	.35
Emotion/ Behavior	0.08	0.03	1.08	2.50	0.008	-.04	.01	339	-4.55	< .001	.02	.01	2.47	.02
Socialization	0.01	0.03	1.01	0.38	0.702	.01	.01	339	1.08	.28	.01	.01	.87	.39
Education	-0.05	0.04	0.95	-1.38	0.160	.03	.01	339	2.03	.043	-.01	.01	-.8	.43
Cognition	0.01	0.06	1.01	0.11	0.908	.06	.02	339	2.8	.005	-.02	.01	-1.36	.18
School inclusion	0.04	0.09	1.04	0.41	0.681	.03	.04	341	0.97	.335	-.01	.02	-.68	0.5
Visit						0.3	.2	339	1.47	.142	-.18	.13	-1.34	.18
Parental support						.09	.17	348	0.51	.611	.02	.1	0.15	.88
Parental support composite	-0.04	0.25	0.96	-0.16	0.876									
Baseline CATCI percentile rank	0.01	0.01	1.01	1.13	0.258									
Worsened/Stable	-2.93	1.21	0.05	-2.43	NA									
Stable/improved	1.76	1.10	5.79	1.60	NA									

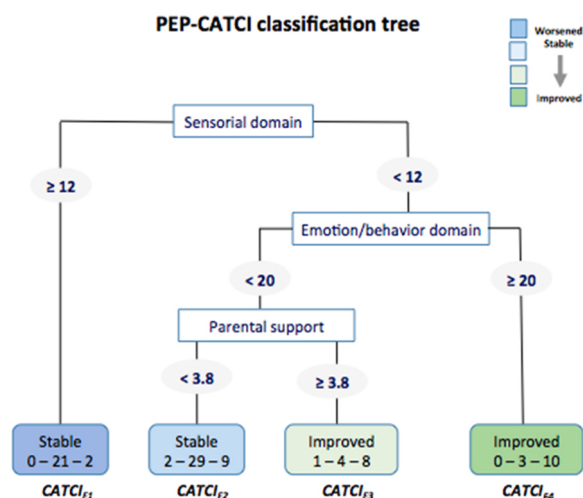


Fig. 1. PEP-CATCI maladaptive behavior at 12-month outcome based on CART classification: tree description. In this analysis, CART classifies subjects with respect to their change in maladaptive behavior (CATCI scores) according to the treatment variables they received. This produces different therapeutic paths with orientation in the tree based on the number of hours of specific treatment exposure. In each leaf, the number on the left is the number of worsened patients. The middle one is the number of stable patients. The right one is the number of improved patients. On top of the numbers are the leaves' predictions. The paths that predicted children's maladaptive behavior improvements were first CATCI_{F4} when the children received less than 12 h in the sensory domain and more than 20 h in the emotion and behavior domain. We can see, on the dark green leaf, that the model predicts that 10 children improved, with a 23% prediction error (Good classification = $(10 / (10 + 3)) \times 100 = 77\%$ | Classification error = $100 - 77 = 23\%$). Second, CATCI_{F3} when the children received less than 12 h in the sensory domain, less than 20 h in the emotion and behavior domain, and more than 3.8 h in the parental support domain. It can also be noticed that the error prediction is high because 5 children out of 13 did not improve, meaning a 27.5% error prediction. A third therapeutic path CATCI_{F2} that predicted the stability of maladaptive behaviors when the children received less than 12 h in the sensory domain, less than 20 h in the emotion and behavior domain, and less than 3.8 h in the parental support domain, with 23.5% of prediction error. The last therapeutic path CATCI_{F1} that also predicted stable maladaptive behaviors was the one where children received more than 12 h in the sensory domain, with a 9% error prediction.

behavior domain, and received less than 6 h in the sensorimotor domain. This group showed an average evolution of 2.8 points for the 10 subjects included. The trajectories that predicted less progress are on the one hand when children received more than 4 h in the emotion/behavior domain, and more than 16 h in the education domain (PAR_{F3}). There was an average evolution of 2.1 points for the 21 subjects included. The last therapeutic path that predicted less progress was when children received less than 4 h in the emotion/behavior domain and more than 6 h in the education domain (PAR_{F1}). There was an average evolution of 2.1 points for the 13 subjects included.

Children who progressed the least (PAR_{F1} and PAR_{F3}) had more severe symptoms, more maladaptive behaviors. PAR_{F3} also had more socio-economic difficulties at baseline. Children who exhibited better outcomes according to parents (PAR_{F2} and PAR_{F4}) had less maladaptive behaviors, less severe symptoms. The PAR_{F4} group also had less socio-economic difficulties at baseline (see [Tables S3 and S4](#)).

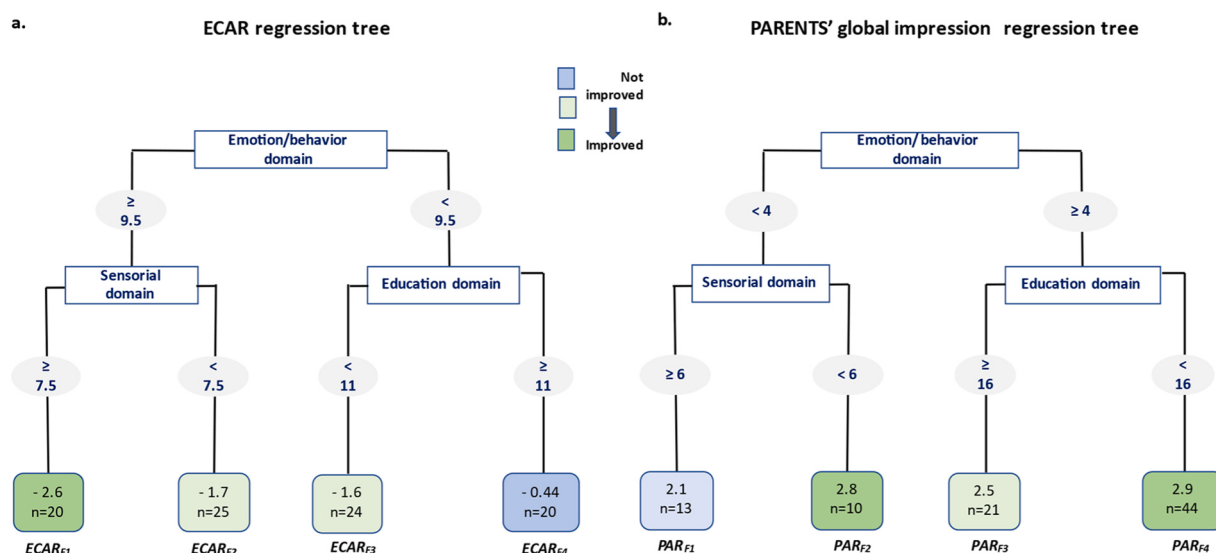


Fig. 2. a. ECA-R autism severity and 2b. parental global impression (PAR) at 12-month outcome based on CART regression classification: tree description. In Fig. 2a, the model shows a classification of the evolution autism severity based on ECA-R scores. The model predicts an average of change according to trajectories in the tree based on hours' of exposure of each domain. The therapeutic path that is linked to the best improvement is when the children received more than 9.5 h in the emotion domain and more than 7.5 h in the sensory domain. The first leaf on the left had an average change of -2.6 points/months of ECA-R score for the 20 subjects included. The second therapeutic path is also linked to some improvement when children were exposed to more than 9.5 h in the emotion/behavior domain and had less than 7.5 h in the sensorimotor domain. There was an average evolution of -1.7 points/months of ECA-R score for the 25 subjects. The trajectories that predicted less progress were, on the one hand, when children were exposed to less than 9.5 h in the emotion/behavior domain and, on the other hand, more than 11 h in the education domain. There was an average evolution of -0.44 points/months of ECA-R score for the 20 subjects. The last therapeutic path that predicted less progress was when children were exposed to less than 9.5 h in the emotion/behavior domain and less than 11 h in the education domain. There was an average evolution of -1.6 points/months of ECA-R score for the 24 subjects. In Fig. 2b, the model shows a classification of the evolution based on parental global impression (PAR scores). As the PAR score represented a quantitative variable, the model predicted an average of change according to trajectories based on hours' of exposure of each domain.

4. Discussion

Children who exhibited the best prognosis following ICP had less autism severity, better cognition and non-immigrant parents at baseline. Analyzing the different therapeutic paths that may be associated with treatment outcomes such as maladaptive behavior, symptom severity, and PAR, we found that emotional/behavioral interventions had a significant impact across all outcomes. In addition, more communication interventions predicted lower symptom severity. However, sensorimotor, education and cognition interventions had bidirectional effects that we discuss in the following sections. However, it is essential to acknowledge the temporal context of our study, as the data spans more than seven years, from September 2014 to December 2016, prior to the global pandemic of 2020. It is pertinent to recognize that circumstances for children, families, and support services may have evolved since the data collection period.

4.1. Baseline predictors of better improvement

High symptom severity and poor cognitive skills at baseline negatively predicted symptom reduction over time. This relationship appeared specific since symptom severity and cognitive skills had no impact on maladaptive behaviors and parent impression. In line with the literature, patients with less severe difficulties at baseline and better cognitive skills had a greater amount of subsequent symptom reduction (Pickles et al., 2020; Baghdadli et al., 2018). Similarly, better cognitive skills at baseline and lower symptom severity were associated with better response trajectories (Farley et al., 2009; Lord, Bishop & Anderson, 2015).

Given our previous report (Bettencourt et al., 2022), we included parents' migration status as a predictor in the regression models, along with SES. Having first-generation immigrant parents was a predictor of increased maladaptive behavior at follow-up. This effect was rather specific, as migration had no impact on symptom severity and PAR. In many studies, first-generation migration and low socioeconomic statuses are negative predictors of ASD outcomes (Delobel-Ayoub et al., 2015; Kawa et al., 2017; Schmengler et al., 2019; Schmengler et al., 2021). Our analysis supported a specific role of migration with respect to maladaptive behaviors, whereas low socioeconomic statuses appeared only in parental impression outcomes via CART (table S4). Since the French healthcare system offers universal health coverage including free access to care with no limitation nor cash advance, this may have helped limit the impact of socioeconomic statuses in our cohort (Verdoux and Tignol, 2003). Migration status may also be related to different micro and macro variables (Hyman et al., 2020), Anonymous Ref, 2022) and we could not disentangle these aspects that require particular attention.

From a clinical standpoint, this result stresses the importance of tailoring the intervention taking into account the cultural context and history of patients, addressing their needs in specific ways (Hyman et al., 2020). Finally, play quality had a positive effect on maladaptive behaviors. This result is in line with a consistent amount of literature that clearly highlights how the presence of some form of early play abilities may have a prognostic value opening to some form of early communicative skills and socialization (Vivanti et al., 2014). The lack of access to play might favor maladaptive behavior promoting so-called deviant communication in some children (Guinchat et al., 2020).

Remarkably, the quality of play appeared to be an important and specific positive predictive factor also for parent impression. This is also in line with research showing the importance of parental inclusion during ASD intervention and with the role of play as a key mediator of parent-infant relationship and promoter of adaptive social and communication routines (Zachor and Ben-Itzhak, 2017). For example, NDBIs received consistent empirical support and stress different key points for ASD intervention with respect to interaction quality, dynamics, and play (Minjarez et al., 2020; Vivanti et al., 2020).

4.1.1. Treatment exposure and outcomes

Receiving more hours of intervention in the emotion/behavior domain had a transversal effect across all the outcome measures and predicted better prognosis. This result supports the importance of focusing on emotional well-being and promoting emotional regulation strategies (Mazefsky et al., 2013). It is probably that when dealing with real life situations, addressing emotional dysregulation and maladaptive behaviors becomes a necessary step towards achieving positive results from other interventions, given that maladaptive behaviors have been linked with unsatisfactory therapeutic outcomes (Salomone et al., 2016; Hyman et al., 2020).

Spending more time in the communication domain predicted a positive impact on ASD severity as previously shown (Bettencourt et al., 2022), but did not influence maladaptive behavior and parent impression. However, spending more time in the education and cognition workshops had a negative effect on symptom severity. This association may be explained by the fact that patients receiving more cognition and education treatments showed the most severe clinical pictures.

4.1.2. CART classification

CART classification confirmed that the number of hours in the emotion/behavior domain is crucial for maladaptive behaviors, autism severity, and parent impression, as it is always the first dimension across all the classification trees. This further supports the need to promote emotional regulation skills in clinical and natural settings (Mazefsky et al., 2013; Hyman et al., 2020), coherently with the regression analysis. Interestingly, individuals with ASD who expressed themselves pointed out that impairments in emotional regulation were important dimensions of their autistic characteristics (Chamak et al., 2008).

Concerning maladaptive behaviors, more hours in the sensorimotor domain helped classifying children with severe symptoms that did not respond to ICP treatment. The children receiving more hours of treatment in this domain showed higher levels of maladaptive behaviors, symptoms severity, and a general absence of language at baseline. Two interpretations may be possible: (1) these profiles may be particularly impaired in terms of sensory processing; (2) sensorimotor workshop is given more frequently to patients with greater severity. Finally, more hours dedicated to parental support also helped classify better outcomes. Likely, when maladaptive behaviors occur they probably affect parents' resilience and interaction with their child (Zachor and Ben-Itzhak, 2017).

Regarding autism severity, in addition to emotional/behavioral interventions and differently with respect to maladaptive behaviors, a greater amount of hours in the sensorimotor domain identified a subgroup of more improved patients. This result suggests that sensorimotor intervention can improve some of the children's autism severity. Finally, the education domain helped classify the subgroup that improved the least. Given the results of some studies highlighting the importance of education (Ospina et al., 2008), this finding may appear paradoxical. However, it is coherent with the aforementioned regression analysis. We can speculate different hypotheses. First, in a real life setting, the most severe patients receive more education treatment as it is a constant demand from families. Second, educational interventions may be too demanding for some children with specific profiles and may lead to a worsening in symptom severity trajectory (Di Renzo et al., 2020).

Finally, regarding parent impression, the analysis found that more hours of emotional/behavioral interventions were associated with better improvements according to parents. The two other nodes that defined the two subgroups with better improvements were children who were exposed to fewer hours of interventions in the education or the sensorimotor domains respectively. Receiving more support in the sensorimotor or education domains was associated with the parental perception of less/not improved cases. This result appears to be consistent with the CART classification according to maladaptive behavior improvement. Further, it is also coherent with the aforementioned prediction analysis. Given the contradictory results for the education and sensorimotor domains, which sometimes predict improvement while other times worsening, it is likely that the association with autism severity and parent impression is complex and/or bidirectional.

5. Limitations

This study comes with some limitations concerning the naturalistic design/setting. Despite manualized treatment and monitoring, some cases lacked sufficient professionals to support each intervention. Additionally, the study included the most severe cases, as it is usually the case for children received in day care hospitals in France (Yianni-Coudurier et al., 2016). It is likely that the lack of prediction of language, contrary to previous studies' results (Hyman et al., 2020) is due to the high proportion of cognitive impairment as language and cognition co-varied greatly, and cognition was the only variable remaining in multivariable models. Cautiousness is warranted before generalizing our results in the whole population with ASD.

As a general limitation the CART models are known to suffer from overfitting, reducing the generalization of results. In this work,

CART models were employed with an explorative and descriptive aim to provide complementary and clinically interpretable information to support and discuss regression and analyze therapeutic trajectories with respect to treatment ingredients, since ML methods can disclose more complex relationships with respect to linear models. Therefore, future works should focus on evaluating this methodology with a more predictive-oriented design. For the purpose of this article, ML was employed with a descriptive approach for data interpretation. The sample size of this study is small for machine learning techniques. Given that, we limited the machine learning analysis to data description. However, the CART methodology has been successfully employed in autism research in clinical contexts with comparable sample sizes (e.g., [Cohen and Flory, 2019](#)).

Finally, even though clinicians underwent prior training of ICP and received monthly supervision from the external psychologist responsible for ensuring practice uniformity, there was no quantitative assessment conducted to measure treatment fidelity, and could not be included in the models. Future research should further investigate the role of treatment adherence from a quantitative standpoint.

6. Conclusion

This study advances our knowledge on baseline and treatment-related predictors of outcome in young children with ASD in a naturalistic setting, including a representative population in terms of socioeconomic status and ethnicity. Children who exhibited the best progression had less autism symptom severity, better cognition and non-immigrant parents at baseline. They also received more emotional/behavioral interventions that appeared key across all outcome variables. Future research should explore how to monitor and adapt ASD interventions over time to understand trajectories associated with the best therapeutic outcomes.

Ethics and consent to participate

The experimental protocol was approved by the local ethics committee, GNEDS (Groupe Nantais d'Éthique) on March 24th, 2014. The study registration can be found on clinicaltrials.gov under the number NCT02154828. All methods were carried out in accordance with the last version of the declaration of Helsinki (Nathanson, 2013). Informed consent was obtained from all subjects and their legal guardians.

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CRedit authorship contribution statement

Giulio Bertamini: Formal analysis, Writing – review & editing. **Morgane P é ré :** Formal analysis. **Hugues Pellerin:** Data curation, Formal analysis. **David Cohen:** Formal analysis, Supervision, Validation, Visualization, Writing – review & editing. **Nicole Garret-Gloanec:** Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Resources, Writing – review & editing. **Samuele Cortese:** Writing – review & editing. **Carlotta Bettencourt:** Formal analysis, Writing – original draft, Writing – review & editing. **Mohamed Chetouani:** Formal analysis. **Gisèle Apter:** Investigation. **Anne-Sophie Pernel:** Investigation. **Lea Ferrand:** Investigation. **Fabienne Roos-Weil:** Conceptualization, Funding acquisition, Investigation, Methodology, Project administration. **Maria Squillante:** Investigation.

Declaration of Competing Interest

None.

Data availability

Data will be made available on request.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.ridd.2024.104688](https://doi.org/10.1016/j.ridd.2024.104688).

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