Pilot Application of the BPSConnect Model: Bio-Psycho-Social Correlation in Children with ASD

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Ethics and Objectives Framework

Ethics Committee Review

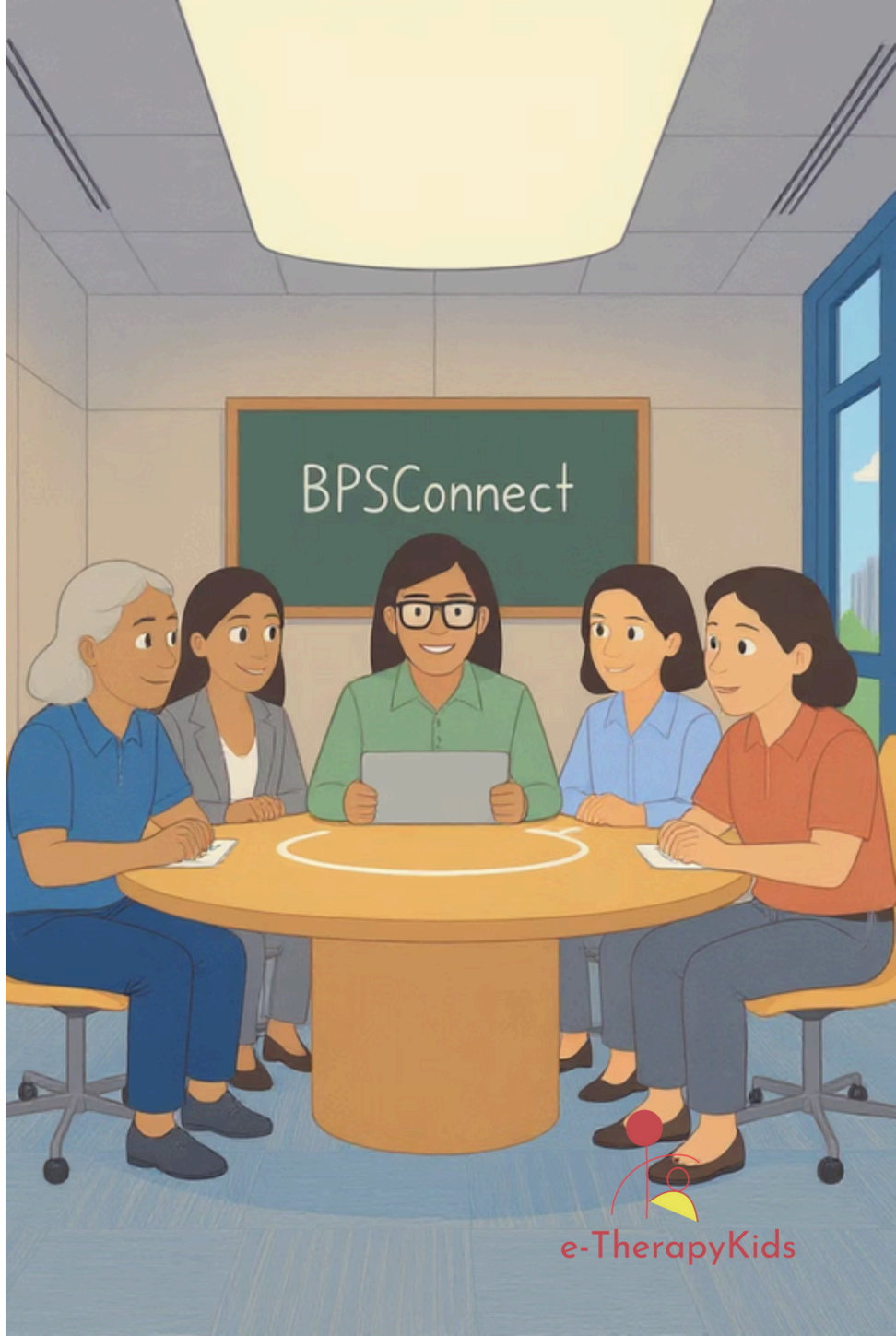
e-TherapyKids Research Ethics Committee (Ref. BPS-TEA/2024-2025-11). Constituted for the project in accordance with the Declaration of Helsinki and EU data protection regulations.

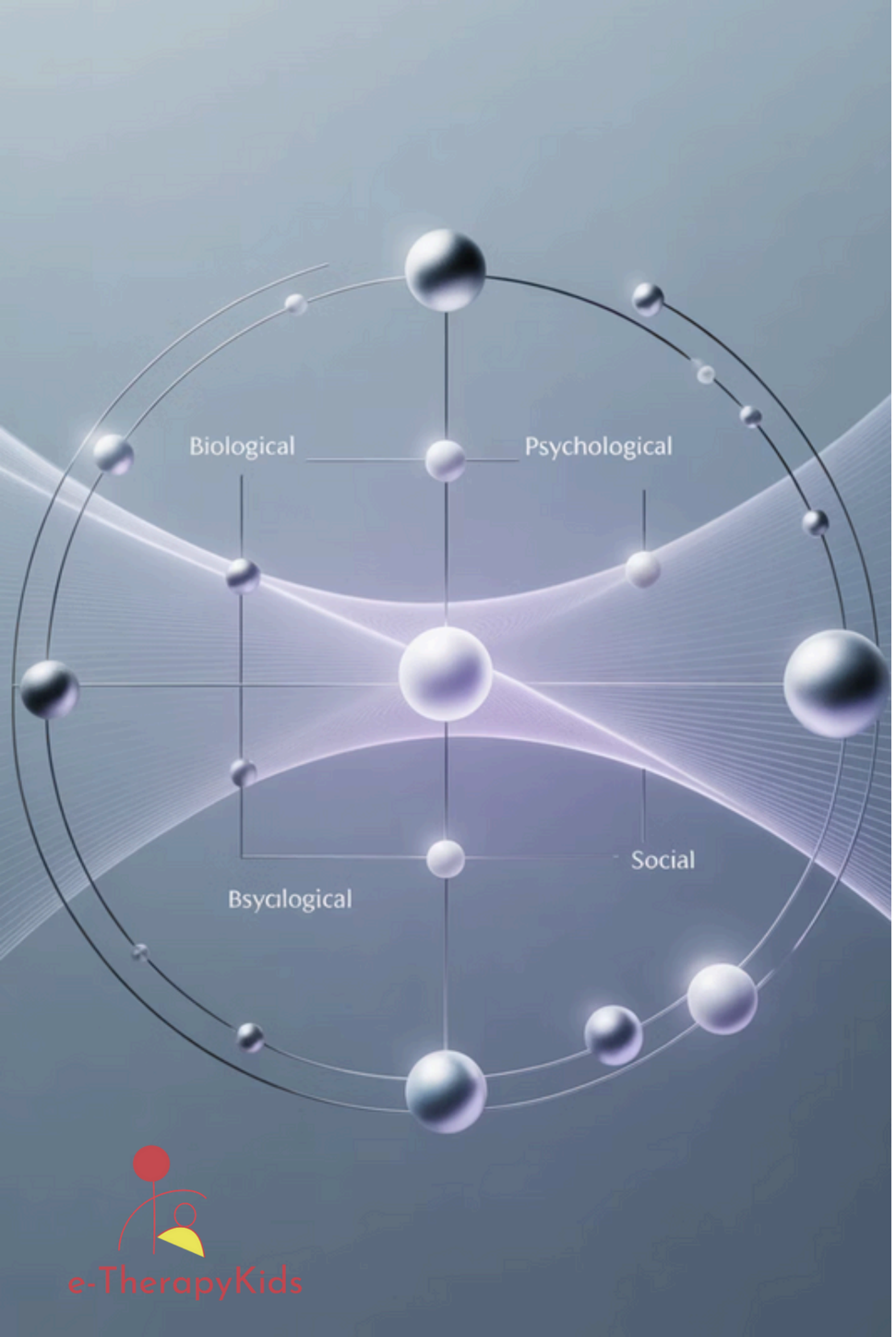
General Objective

To evaluate the feasibility and preliminary clinical utility of the BPSConnect instrument for comprehensive bio-psycho-social screening in ASD, and to identify associations across dimensions.

Specific Objectives

- To determine the applicability of the protocol (completeness, duration)
- To estimate the prevalence of alarm signals per dimension
- To explore correlations between biological variables (including hair epigenetic tests), psychological and social variables, and their relationship with performance and the school environment





Scientific and Clinical Rationale

Biological Factors

Micronutrient deficiencies (vitamin D, iron), functional gastrointestinal dysfunction, allergies/intolerances, sleep disturbances, and environmental exposures (e.g., EMFs). These biological markers significantly impact neurodevelopmental trajectories in children with ASD.

Psychological/Behavioral Factors

Socio-communicative difficulties, sensory processing disorders, repetitive behaviors/emotional regulation, expressive/receptive language alterations, and motor development challenges that define the core ASD phenotype.

Social Dimension

Parental stress, caregiver burden, educational barriers (lack of methodological adaptation and specialized support), family climate, and support networks that modulate symptom expression and intervention outcomes.

The integration of these comorbidities allows for the detection of functional patterns and guides referrals and early interventions through a comprehensive understanding of the child's multidimensional needs.

Theoretical Framework: Foundation of the Biopsychosocial Model

The understanding of Autism Spectrum Disorders (ASD) has undergone a profound transformation in recent decades, moving from reductionist models focused exclusively on behavioral or neuropsychological dimensions to an integrative approach that considers multiple determinants of health and development. The biopsychosocial (BPS) model, originally formulated by Engel in the 1970s and subsequently applied transversally in various fields of health, offers a particularly suitable interpretive framework for addressing the complexity of ASD.

This approach recognizes that the core symptoms of autism (socio-communicative alterations and repetitive behaviors) do not manifest in isolation but interact dynamically with medical conditions, psychological factors, and social contexts which, together, modulate clinical expression and functional prognosis. Traditional diagnostic models, based exclusively on behavioral criteria, while useful for nosological classification, are insufficient to explain the clinical heterogeneity and diverse developmental trajectories observed in children with ASD.

> Scientific literature increasingly supports the need for transversal frameworks that integrate biomedical, psychological, and social data to guide early, individualized, and evidence-based interventions.

The BPSConnect framework emerges from this need, proposing a systematic protocol that operationalizes the biopsychosocial approach into a clinically applicable tool for real-world settings, transforming theoretical understanding into a practical assessment methodology.

Biological Evidence and Comorbidities

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3-5x

Increased Risk

Children with ASD are three to five times more likely to experience micronutrient deficiencies compared to their typically developing peers.

80%

Food Selectivity

Prevalence of marked dietary restriction and food neophobia in children with ASD, contributing to nutritional vulnerabilities.

The biological dimension of ASD is characterized by a high frequency of medical comorbidities that significantly affect quality of life and functionality. Among these, nutritional deficiencies, metabolic alterations, and environmental epigenetic factors stand out. Numerous studies have documented vitamin D and iron deficiencies as recurrent findings in children with ASD, associating these parameters with greater severity of socio-communicative symptoms and an increased risk of cognitive and behavioral difficulties.

Food selectivity emerges as a particularly relevant phenomenon, characterized by marked dietary restriction, aversion to certain food textures, colors, or temperatures, and a preference for a limited range of foods. Recent studies demonstrate that food selectivity is not merely a behavioral trait but a direct risk factor for clinically relevant nutritional deficiencies. Sharp et al. (2013) reported significant correlations between food neophobia and reduced intake of fruits, vegetables, and proteins, thereby aggravating metabolic vulnerability.

The relationship between nutritional deficiencies and ASD symptoms has been widely documented. Low vitamin D levels have been associated with greater severity on standardized scales, indicating direct links between nutritional status and socio-communicative functioning. Similarly, iron and ferritin deficiencies correlate with sleep disorders, attention deficits, and executive dysfunction, representing a "second biological hit" that intensifies the core symptoms of autism.

Psychological and Behavioral Dimensions

Core Characteristics of ASD

ASD is primarily defined by alterations in social communication and restricted and repetitive behavior patterns. However, contemporary approaches emphasize the analysis of these characteristics in relation to other areas of psychological functioning, including sensory processing, emotional regulation, and language development.

Sensory processing has emerged as a critical area, with up to 80% of children with ASD exhibiting patterns of hyper or hyposensitivity that directly affect participation in school and family environments.

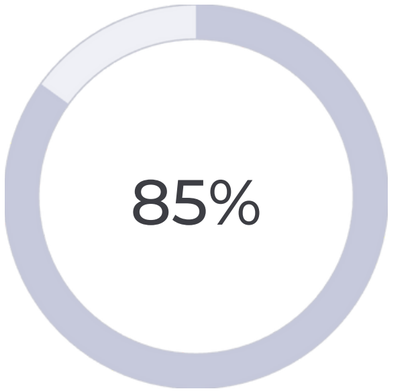
Language and Communication

Language constitutes a central axis where alterations in expressive and receptive skills predict the developmental trajectories of social and cognitive competencies. Recent research links the severity of language delays with nutritional deficiencies, particularly iron and vitamin D, reinforcing the biological-psychological interconnections.

Emotional and behavioral regulation, frequently compromised in ASD, is associated with both biological factors and social conditions, constituting key points for intervention.

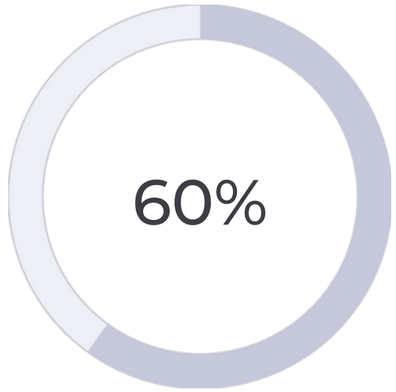
Longitudinal studies show that language alterations predict developmental trajectories, while sensory processing difficulties correlate with emotional regulation challenges and an increase in disruptive behaviors. The study by Mazefsky et al. (2013) shows that difficulties in emotional regulation not only intensify challenging behaviors but also mediate the relationships between sensory deficits and behavioral problems, thus constituting crucial points for interdisciplinary interventions.

Social and Family Dimension Impact



Parental Stress

Parents of children with ASD exhibit significantly higher stress levels than parents of typically developing children.



Educational Barriers

Lack of adequate school supports and methodological adaptations affecting child outcomes.

The social and family dimension is decisive in shaping the clinical presentation of ASD and determining intervention responses. Literature robustly documents that parents of children with ASD exhibit higher levels of stress, anxiety, and depression than parents of typically developing children or those with other neurodevelopmental conditions. Parental stress is not merely a consequence of diagnosis but is directly associated with symptom severity and the emergence of additional behavioral difficulties.

Several studies indicate that elevated parental stress correlates with a higher prevalence of emotional and behavioral regulation problems in children, generating negative feedback loops: higher caregiver stress reduces coping capacity, which exacerbates child symptoms. The absence of educational support—including a lack of curricular adaptations, insufficient specialized staff, or weak school-family coordination—amplifies parental burden and limits child learning opportunities.

> The bio-psycho-social framework cannot be fully understood without recognizing the relevance of family-school interaction, which constitutes a strategic axis for early intervention and an improved functional prognosis.

Inclusive education policies, when effectively applied, not only improve access to resources and school participation but also act as protective factors against chronic parental stress and secondary behavioral problems. This evidence underscores that the social dimension cannot be understood as secondary, but rather as an active modulator of the ASD clinical course, requiring systematic assessment in any diagnostic or intervention protocol.

BPSConnect Framework: Three-Dimensional Integration

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Biological Assessment

Systematic screening of nutritional deficiencies, metabolic alterations, and environmental epigenetic factors using innovative hair analysis technology.

Psychological Evaluation

Comprehensive assessment using validated scales (SRS-2, Vineland-3, SSP2/SP2) to capture socio-communication, adaptive behavior, and sensory processing.

Social Context Analysis

Evaluation of parental stress (PSI-SF), family climate (FES), and educational support systems to understand environmental modulators.

The BPSConnect model situates itself at the intersection of biological, psychological, and social interactions, proposing a systematic protocol that identifies correlations across dimensions and prioritizes intervention objectives based on functional patterns. The operational core is organized around dimension-specific checklists combined with internationally recognized scales, ensuring psychometric validity and cultural appropriateness.

The ultimate aim transcends data accumulation to generate functional correlations for intervention prioritization. Unlike traditional protocols providing isolated categorical diagnoses, BPSConnect establishes cross-dimensional relationships explaining why children manifest specific difficulties in given contexts and how these may be modified through comprehensive interventions targeting child, family, and school environments simultaneously.

Research Hypotheses and Endpoints

01

Biological-Psychological Correlation

Higher burden of biological signals, particularly nutritional deficiencies (vitamin D, iron), will associate with poorer socio-communicative, language, and executive function performance, and increased sensory alterations.

02

Social-Behavioral Association

Elevated parental stress levels will correlate with lower adaptive participation, increased behavioral difficulties, and poorer school performance requiring specialized support.

03

Educational Impact Relationship

Insufficient school support and inadequate methodological adaptations will relate to greater severity in socio-communicative and behavioral domains.

Primary and Secondary Endpoints

Primary Endpoint: Protocol feasibility, with success criteria including a >90% completion rate, an administration time of <60 minutes per dimension, and an absence of adverse events. These parameters demonstrate scientific soundness and operational sustainability.

Secondary Endpoints: Prevalence estimation of alarm signals by dimension, Spearman correlations between alarm indices and validated scales, and exploration of specific associations between nutritional deficiencies and key variables (communication, language, attention, executive functions, sensory processing). These endpoints enable model validation and the identification of relationships, justifying larger confirmatory studies.

Methodology: Cross-Sectional Observational Design

1 **Study Design**

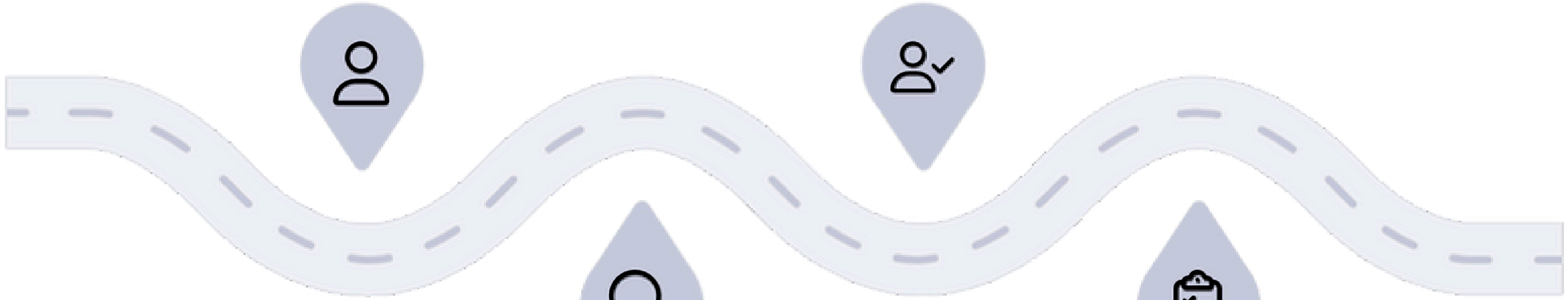
A cross-sectional observational pilot study conducted in a real-world clinical setting, designed to explore correlations without establishing causality, following STROBE methodological guidelines.

2 **Population & Recruitment**

Children aged 4-8 years with confirmed ASD diagnosis (DSM-5, ADOS-2 verification), recruited from the e-TherapyKids clinic in Barcelona (November 2024-June 2025).

3 **Sample Selection**

A convenience sample of 25 participants meeting inclusion criteria: age, diagnosis, and parental consent. Exclusion criteria included: severe neurometabolic disorders, refractory epilepsy, or consent refusal.



Assessment Tools and Validation Instruments

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1

Dimension-Specific Checklists

Percentage of alarm items computed in defined subdomains, with categorization thresholds: minimal (<25%), mild (≥25%), moderate (≥50%), severe (≥75%). Biological aspects included: gastrointestinal, neurological, ENT, ophthalmological, allergies, epigenetic biomarkers, and EMF exposure.

2

Validated Standardized Scales

ADOS-2 (for ASD diagnosis confirmation), SRS-2 (for socio-communicative impairment), Vineland-3 (for adaptive behavior), SSP2/SP2 (for sensory processing), PSI-SF (for parental stress), and FES (for family climate). All instruments were applied in their Spanish versions to ensure cultural validity.

3

Hair Epigenetic Biomarkers

Non-invasive Cell Wellbeing S-Drive analysis for the exploratory identification of nutritional deficiencies (vitamin D, iron) and environmental exposures (EMF, heavy metals). This is a non-diagnostic, preventive screening approach with high pediatric acceptability.

The psychological dimension encompassed language and communication, social skills, emotional-behavioral regulation, sensory processing, attention and executive functions, and motor development. The social dimension analyzed parental stress, family climate, support networks, adequacy of the school environment, curricular adaptation, and specialized support. This comprehensive framework captured functional complexity across multiple domains, generating differentiated risk profiles for individualized intervention planning.

The methodological decision to incorporate hair epigenetic analysis arose from an interest in exploring low-risk, low-cost, and highly acceptable tools in pediatric ASD populations, where invasive extractions are complex. Future validation phases will incorporate quantitative reference methodologies (ICP-MS, LC-MS/MS, dosimetry) for robust data triangulation.

Data Security and Statistical Analysis Plan

Data Management Protocol

Strict security and confidentiality protocols complying with the General Data Protection Regulation (GDPR) and the Spanish Organic Law on Personal Data Protection and guarantee of digital rights (LOPDGDD). Records are pseudonymized, stored on encrypted EU servers, and accessible only to authorized profiles. The retention period is five years, in accordance with observational study regulations.

Quality control measures included inter-evaluator review for professional consistency, double data entry to reduce transcription errors, and complete case analysis to avoid imputations that could introduce bias.

Statistical Approach

Phase 1 (Descriptive): Means ± standard deviation (SD) for normal distributions, medians/interquartile range (IQR) for non-parametric variables, and proportions with 95% confidence intervals (95% CI) using Wilson's method.

Phase 2 (Exploratory): Spearman correlations between alarm indices and validated scales, and simple linear models adjusted for age and sex describing trends without confirmatory inference.

The two-phase statistical structure balanced descriptive thoroughness with the generation of exploratory hypotheses. No missing data imputation was performed, maintaining analytical integrity through complete case analysis, consistent with the exploratory nature of the pilot study. This approach ensured solid preliminary findings while acknowledging the inherent limitations of exploratory research with small samples.

Ethical Framework and Participant Protection

Compliance with the Declaration of Helsinki

Adherence to international ethical principles, GDPR, and the Spanish LOPDGDD. Minimal risk assessment confirmed by the e-TherapyKids Research Ethics Committee (CEI BPS-TEA/2024-2025-11).

Informed Consent Process

Standardized process ensuring family understanding of the study's nature, objectives, voluntary participation, and right to withdrawal. Clear and accessible documentation (Annexes S-CI1, S-CI2) reviewed with legal parents/guardians.

Vulnerability Considerations

Special attention to the vulnerable condition of children with ASD and their families. Staff training in neurodiversity-adapted communication, emotional support mechanisms, and options for session interruption or rescheduling.

The study involved minimal risk through clinical/social evaluations via interviews, standardized scales, and non-invasive procedures. No drugs or harmful interventions were administered. Hair epigenetic analysis posed no medical risks and caused negligible discomfort to participants. Potential benefits included the integrated detection of alarm signals across various dimensions with early clinical/educational guidance for families.

Confidentiality and data security were priority ethical dimensions. Pseudonymization mechanisms were implemented from data collection, storage on encrypted EU servers with restricted access, compliance with a five-year retention period, and secure deletion protocols to prevent risks of undue disclosure.

Pilot Study Justification and Innovation

The implementation of this pilot study responds to highly relevant ethical, scientific, and methodological justifications. From an ethical perspective, the immediate large-scale implementation of BPSConnect without demonstrating its safety, applicability, and family acceptability would be unacceptable. The pilot design enables instrument refinement, the detection of difficulties, and procedure adjustments before exposing a larger number of participants, minimizing risks and ensuring safer, more efficient future trials.

European Pioneer

First European pilot to simultaneously integrate exploratory epigenetic biomarkers, standardized psychometric scales, and social factors in a single screening protocol.

Methodological Convergence

Broadens the clinical interpretation scope by enabling the integrated observation of biological, psychological, and social factor interactions in ASD symptom expression.

International Positioning

Establishes the foundation for future European and intercontinental multicenter studies, creating comparable evidence across cultural contexts.

Methodologically, the pilot is essential for estimating key outcome measure variance and calculating sample sizes for confirmatory studies with sufficient statistical power. The experience gathered provides crucial logistical resource anticipation for multicenter trials, establishing realistic parameters for administration times, family burden, and completion rates.

The innovative character emerges from methodological convergence, responding to the growing international demand for translational research models that combine biomedical precision with family and school context sensitivity. The consistency of preliminary findings with international literature supports the model's direction, suggesting that BPSConnect may become a useful tool for generating comparable evidence in future multicenter studies, positioning it within an international neurodevelopment research network.

Baseline Characteristics and Biological Findings

25

Total Participants

Complete sample with confirmed ADOS-2 diagnosis.

6.2

Mean Age (years)

±1.3 SD, an optimal developmental assessment window.

72%

Male Participants

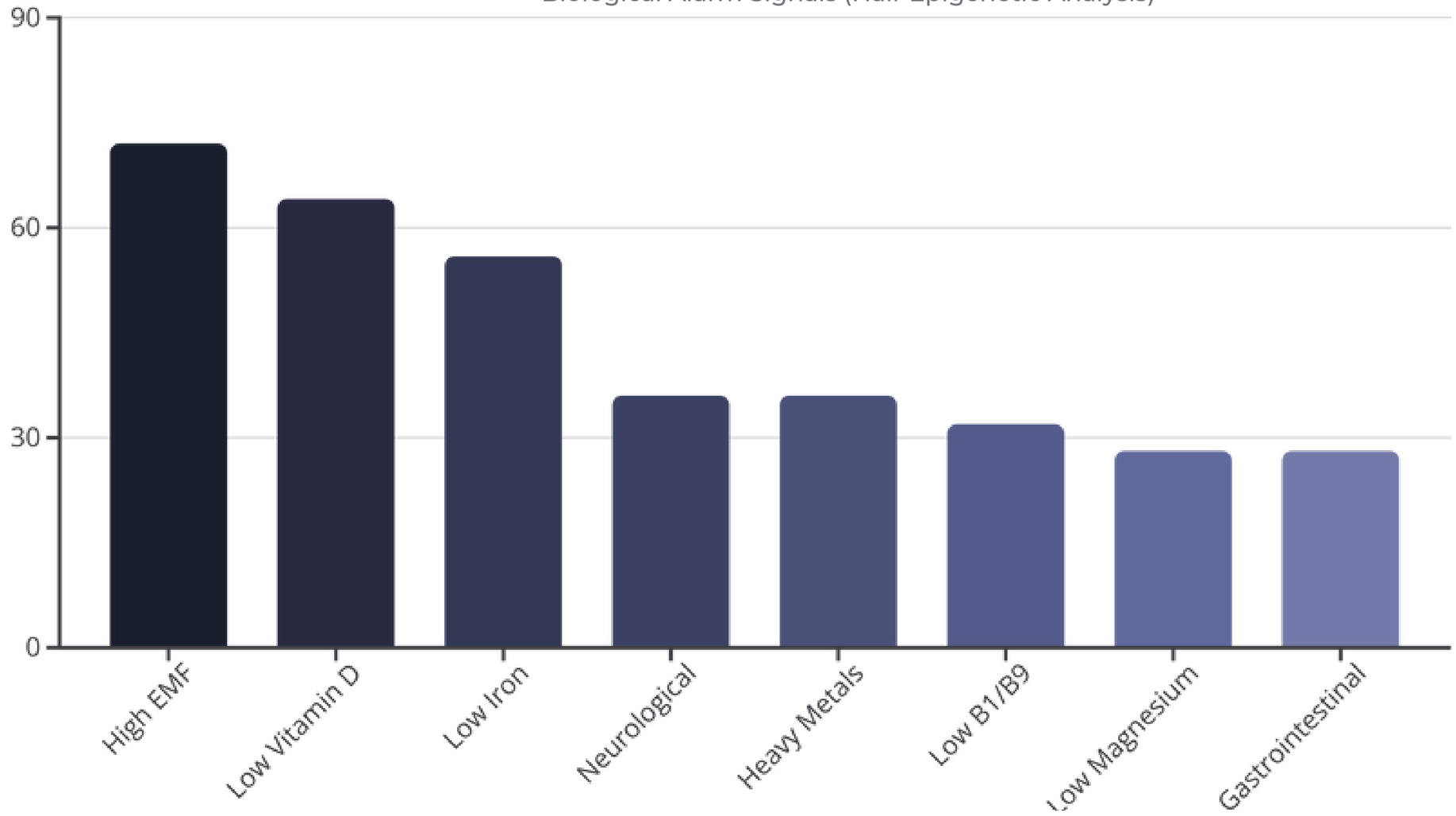
18 males, 7 females (28%), consistent with ASD prevalence patterns.

40%

Medical Comorbidity

10 participants with additional medical conditions.

Biological Alarm Signals (Hair Epigenetic Analysis)



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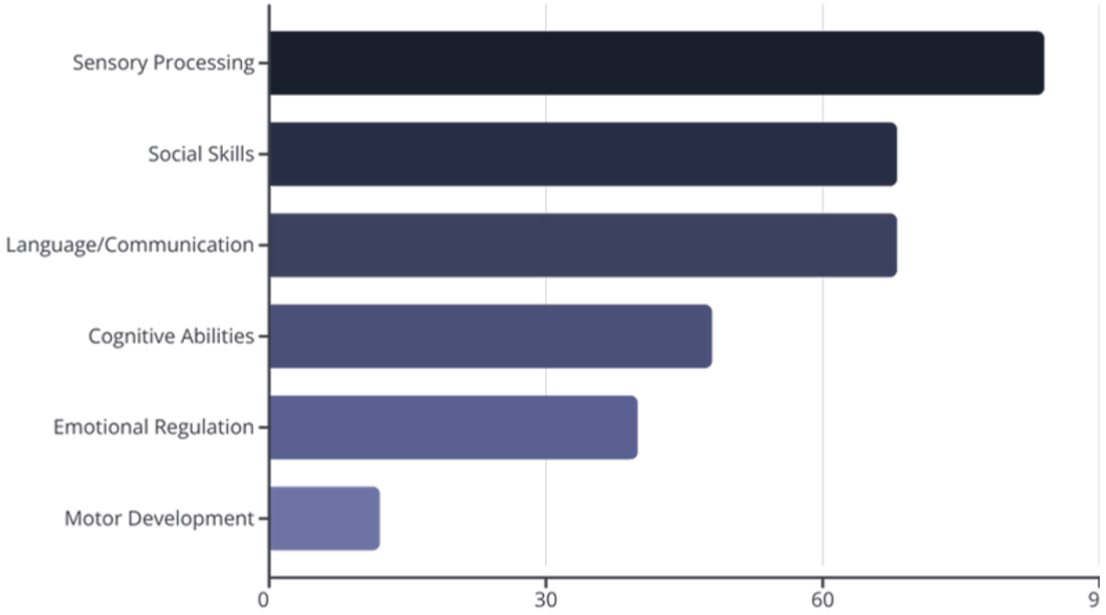
Psychological and Social Dimension Results

Psychological Alarm Signals (≥50% threshold)



Social Context Challenges

- **High parental stress:** 21/25 (84%)
- **Caregiver anxiety:** 20/25 (80%)
- **Poor family communication:** 15/25 (60%)
- **Insufficient classroom adaptation:** 11/25 (44%)
- **Insufficient specialized support:** 21/25 (84%)
- **Caregiver depression:** 6/25 (24%)

Psychological dimension results revealed the highest alarm prevalence in sensory processing (84%) and socio-communication domains (68%), consistent with core ASD characteristics. The substantial burden in these areas underscores the importance of comprehensive sensory and communication interventions. Social dimension findings highlighted critical family and educational support gaps, with 84% experiencing high parental stress and equivalent percentages lacking adequate specialized school support.

Exploratory Correlations: Cross-Dimensional Associations

VitD ↔ SRS-2

Low vitamin D correlated with socio-communicative impairment

Stress ↔ Adaptation

Parental stress negatively correlated with adaptive functioning

Stress ↔ Behavior

Higher parental stress linked to behavioral difficulties

Iron ↔ Language

Low iron associated with language/attention deficits

The exploratory correlation analysis identified clinically plausible associations, requiring cautious interpretation due to the small sample size. The most notable finding was the moderate positive correlation ($\rho \approx 0.41$) between vitamin D deficiency and socio-communicative dysfunction. This suggests that children with low vitamin D indicators manifested greater social interaction and communication difficulties, consistent with research linking vitamin D to neuronal plasticity and neurotransmitter synthesis.

Parental stress demonstrated a significant negative correlation with adaptive participation ($\rho \approx -0.38$) and positive correlations with behavioral regulation difficulties (in the 0.30-0.35 range). These findings underscore the influence of family context on adaptive skill expression and highlight caregiver well-being as a moderating variable in ASD developmental trajectories. Iron deficiency, present in >50% of participants, was positively associated with language/communication difficulties and attention/executive function challenges, consistent with iron's role in myelination and dopaminergic synthesis.

Environmental findings included a positive trend ($\rho \approx 0.28$) between electromagnetic field exposure and sensory processing alterations, warranting further exploration of environmental-sensory sensitivity interactions. These correlations, while exploratory, exhibit internal and external coherence, granting clinical plausibility as indicators guiding robust hypotheses for future multicenter validation.

Scientific Discussion: Cautious Interpretation and Innovation

The results of this pilot study support the feasibility and applicability of the BPSConnect protocol in real clinical contexts, demonstrating both family acceptability and its coherence with prior scientific literature. Integrating traditionally independent biological, psychological, and social dimensions enables the construction of more comprehensive explanatory frameworks for the experiences of children with ASD and the factors influencing their development.

Clinical Plausibility

Identification of plausible associations between nutritional deficiencies (vitamin D, iron) and socio-communicative/attentional difficulties, plus links between EMF exposure and sensory alterations, provides evidence suggesting that biological/environmental factors modulate ASD core symptom expression.

European Innovation

First European experience integrating exploratory epigenetic biomarkers, standardized psychometric scales, and social factors within a single screening protocol. This three-dimensional approach enhances ASD symptom interpretation from an integrative perspective, thus addressing research fragmentation.

International Consistency

The consistency of preliminary findings with published international multicenter studies demonstrating the influence of nutritional deficiencies, environmental factors, and parental burden on ASD developmental outcomes across cultural contexts lends methodological credibility.

The innovative character emerges from methodological convergence addressing the fragmentation typically observed when biological, psychological, and social domains are examined separately. By situating correlations within unified frameworks, BPSConnect offers the potential for generating holistic, clinically applicable evidence, providing professionals and families a clearer understanding of multifactorial symptom origins.

However, findings must be interpreted cautiously. The pilot nature implies observed associations should not be taken as conclusive evidence of causality but as preliminary signals guiding robust hypothesis formulation. The cross-sectional design limits the establishment of temporal relationships, and moderate correlation magnitudes require validation through larger samples and rigorous methodologies. The primary value lies in demonstrating the operationalization of a bio-psycho-social model within applicable clinical protocols.

Limitations and Future Research Directions

Sample Size Constraints

A small sample (n=25) restricts statistical power, prevents complex multivariate adjustments, and limits generalizability to broader, more diverse populations. Future studies require larger, multicenter recruitment for robust validation.

Biomarker Methodology

Cell Wellbeing capillary biomarkers are exploratory, non-quantitative, and non-validated for diagnostic purposes. Results require confirmation through gold-standard reference methods (LC-MS/MS, ICP-MS) for clinical validity.

Statistical Model Limitations

The sample size constrained sophisticated adjusted models controlling for age, sex, baseline ASD severity, or medical comorbidities. The absence of control groups prevented ASD-specific assessment, and the cross-sectional design limited longitudinal trajectory insights.

NeuroEpigenCare Project: Next Phase Requirements

Confirming preliminary findings requires larger-scale studies that overcome current limitations and move toward robust BPSConnect model validation. The NeuroEpigenCare project represents a necessary strategic next phase for comprehensive screening protocol consolidation with full clinical and scientific validity.

Critical requirements include: **multicenter validation**, ensuring result generalizability across clinical, geographic, and socio-educational contexts; **quantitative biomarkers** via standardized techniques (serum vitamin D, iron, trace elements through LC-MS/MS or ICP-MS); **psychometric validation** of BPSConnect checklists assessing internal consistency, temporal stability, and convergent/divergent validity; **adequate sample size calculation** for confirmatory hypothesis testing; and **longitudinal follow-up**, evaluating association stability and intervention sensitivity.

The transition toward multicenter studies with quantitative biomarkers, rigorous psychometric validation, adequate sample sizes, and longitudinal designs represents both a methodological requirement and an opportunity to position BPSConnect as an international reference in comprehensive ASD assessment, establishing reliable, scalable clinical instruments that guide personalized interventions integrating biological, psychological, and social neurodevelopmental dimensions.

Conclusions and Future Impact

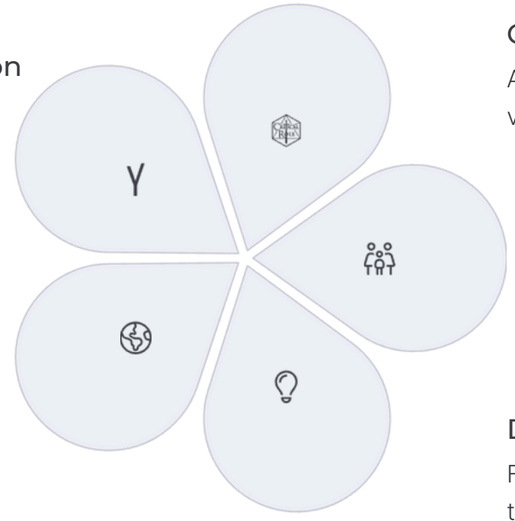
This pilot study successfully demonstrates the feasibility of the BPSConnect protocol in real clinical settings, confirming that its methodological structure adequately addresses professional and family needs. Feasibility was established through clinically reasonable completion times, the clinical team's capacity for application without process duplication, and positive acceptance from families and educational centers regarding structured, comprehensible procedures.

Dimensional Integration

Successfully integrates biological, psychological, and social dimensions within a single framework, breaking traditional compartmentalization.

International Positioning

Establishes groundwork for European and intercontinental multicenter studies.



Clinical Plausibility

Associations align with international literature, demonstrating convergent validity and robust potential.

Social Dimension Impact

Family well-being emerges as an active modulator, requiring systemic intervention approaches.

Digital Innovation

Foundation for a SaaS platform democratizing comprehensive diagnostic tools.

The preliminary clinical value lies in the protocol's integration of traditionally separate assessment dimensions, providing interaction patterns that guide decision-making with greater precision. Social dimension findings demonstrate that child well-being cannot be dissociated from family well-being, with educational support gaps compounding family burden and intensifying observable symptomatology.

The innovative character extends beyond simultaneous dimensional integration to its technological projection as a future digital SaaS platform. BPSConnect software development would enable automated data collection and analysis, generate clear reports, and provide integrated views of multifactorial symptom origins. Digitalization facilitates longitudinal comparisons, personalized follow-up, and the creation of population databases contributing to large-scale research and public policy formation.

Most significantly, this pilot establishes the foundation for the forthcoming NeuroEpigenCare project, providing indispensable operational parameters for confirmatory trial design, including administration time estimates, sensitive clinical domain identification, expected effect sizes, and endpoint definitions. The study should not be regarded as an endpoint but as a solid starting point providing preliminary evidence of the BPSConnect model's relevance and potential.

The BPSConnect model, validated in this pilot, emerges as a pioneering tool for future European and intercontinental multicenter neurodevelopment studies, representing a high-impact innovation potentially transforming autism understanding and management by providing unprecedented access to comprehensive assessments illuminating the complex interplay of biological, psychological, and social contexts in the lives of children with ASD.