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The main principles of automated detection of Neurodevelopmental Disorders: A Study of typically developing Greek children in a randomized controlled trial using face-to-face mobile technology

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The main principles of automated detection of Neurodevelopmental Disorders: A Study of typically developing Greek children in a randomized controlled trial using face-to-face mobile technology

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Abstract

Background: Neurodevelopmental disorders (NDs) are characterized by heterogeneity, complexity, and interactions among multiple domains with long-lasting effects in adulthood. Identifying and assessing children at risk for NDs is crucial. However, many children remain misdiagnosed, missing out on opportunities for effective interventions. Digital tools can help clinicians assist and identify NDs. The concept of using serious games to enhance healthcare has gained attention among a growing group of scientists, entrepreneurs, and clinicians.

Objective: This study aims to define the main principles of automated mobile NDs detection.

Methods: In this study, 229 children aged 4 to 12 participated after responding to an open call. Children with neurodevelopmental disorders, other conditions, or those taking medication were not included in the study. Parents provided consent for their children to participate. Children interacted face-to-face with a mobile serious game called 'Apsou'. The game was designed to measure 18 primary domains including speech, language, psychomotor, cognitive, psychoemotional, and hearing abilities. The measurements were based on the children's performance in specific tasks such as gameplay and verbal responses. The data collected was analyzed using descriptive statistics and Principal Component Analysis (PCA).

Results: A sample of 229 typically developing preschoolers and early school-aged children played the Apsou mobile serious game for automated detection of NDs. Performing a PCA, the findings identified five main components accounting for about 80% of the data variability that potentially have significant prognostic implications for a safe diagnosis of neurodevelopmental disorders. Varimax rotation explained 61.44% of the total variance. The results underscore key theoretical principles crucial for the automated detection of Neurodevelopmental Disorders. These principles encompass communication skills, speech and language development, vocal processing, cognitive and sensory functions, and visual-spatial skills. The components identified in this study align with the theoretical principles of typically developmental domains described in other studies, further validating the robustness of our findings.

Conclusions: The findings of this study underscore the core developmental domains, crucial for a comprehensive model leading to highly accurate predictions and classifications for automated screening, diagnosis, prognosis, or intervention planning in NDs. Importantly, these findings offer valuable insights for creating machine learning applications to support clinical decision-making. Clinical Trial: 18435-15.05.2020 approved by the Research Ethics Committee of the University of Ioannina, Greece, https://ethics.ac.uoi.gr/

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Abstract

Background: Neurodevelopmental Disorders (NDs) are characterized by heterogeneity, complexity, and interactions among multiple domains with long-lasting effects in adulthood. Early and accurate identification of children at risk for NDs is crucial for timely intervention, yet many cases remain undiagnosed, leading to missed opportunities for effective interventions. Digital tools can help clinicians assist and identify NDs. The concept of using serious games to enhance healthcare has gained attention among a growing group of scientists, entrepreneurs, and clinicians.
Objective: This study aims to explore the core principles of automated mobile detection of NDs in typically developing Greek children, using a serious game ('Apsou') designed to evaluate multiple developmental domains through Principal Component Analysis (PCA).
Methods: A total of 229 typically developing children aged 4 to 12 years participated in the study. The recruitment process involved open calls through public and private health and educational institutions across Greece. Parents were thoroughly informed about the study's objectives and procedures, and written consent was obtained. Children engaged under clinician's face-to-face supervision with the 'Apsou' serious game, which assesses 18 developmental domains, including speech, language, psychomotor, cognitive, psychoemotional, and hearing abilities. Data from the children's interactions were analyzed using PCA to identify key components and underlying principles of NDs detection. **Results:** A sample of 229 typically developing preschoolers and early school-aged children played the Apsou mobile serious game for automated detection of NDs. Performing a PCA, the findings identified five main components accounting for about 80% of the data variability that potentially have significant prognostic implications for a safe diagnosis of neurodevelopmental disorders. Varimax rotation explained 61.44% of the total variance. The results underscore key theoretical principles crucial for the automated detection of Neurodevelopmental Disorders. These principles encompass communication skills, speech and language development, vocal processing, cognitive skills and sensory functions, and visual-spatial skills. These components align with the theoretical principles of child development and provide a robust framework for automated NDs detection.
Conclusions:
The study highlights the feasibility and effectiveness of using serious games for early NDs detection in children. The identified principal components offer valuable insights into critical developmental domains, paving the way for the development of advanced machine-learning applications to support highly accurate predictions and classifications for automated screening, diagnosis, prognosis, or intervention planning in NDs clinical decision-making. Future research should focus on validating these findings across diverse populations integrating additional features such as biometric data and longitudinal tracking to enhance the accuracy and reliability of automated detection systems.

Keywords: main principles; automated detection; Neurodevelopmental Disorders; PCA; Principal Component Analysis; early screening; early intervention

Introduction

Child development refers to a child's growth, in speech, language, hearing, psychomotor, cognitive, and psychoemotional domains [1].

Speech and language development involves verbal and nonverbal communication skills [1]. Speech development refers to a child's capacity to speak and communicate, starting from infancy with cooing and babbling and leading to single words, phrases, and sentences as the infant matures. It includes voice, articulation, and fluency [1,2]. Language development involves receptive and expressive language processes and includes vocabulary, grammar, syntax, interpreting complicated sentences, and social language use for communication [3,4].

Infancy begins with primary gestures and sounds and progresses to complicated language skills. Hearing underpins speech and language. Early hearing detection with regular hearing screenings [5] contributes towards the early identification and treatment of hearing abnormalities supporting children to communicate with others [6,7].

Psychomotor development refers to gross motor skills, fine motor skills, and visual-motor integration [1]. Thoroughly, gross motor skills involve using and coordinating vast muscle groups to crawl, walk, jump, run, and climb stairs and help children move and play [8]. Fine motor skills involve the coordination of small muscle groups, particularly those in the hands and fingers. Tasks such as picking up small objects, holding a pencil, cutting with scissors, and tying shoelaces require fine motor abilities. Visual-motor integration refers to vision and movement coordination, enabling children to replicate shapes, write, and accomplish various hand-eye coordination activities [1].

Cognitive development is a child's capacity to problem-solve, think, reason, and understand the environment [9,10]. Genetics, environment, education, and explorative experiences impact cognitive development. Critical thinking includes memory (recalling information), attention (focusing and ignoring distractions), problem-solving, and abstract thinking (the ability to think beyond tangible experiences and grasp abstract notions).

Social-emotional development involves Emotional Development, Social Development, Self-Concept, Self-Esteem, and Emotional Intelligence [11]. Emotional development entails not only the awareness and expression of one's feelings but also the ability to regulate those feelings in an appropriate manner. Emotional development is an important factor affecting children's well-being and interpersonal relationships [12]. Social Development is an aspect of a child's development focusing on the ability to interact with other people and the capacity to create and sustain connections. Empathy, sharing, taking turns, and a grasp of social standards are all important components of a social life [13]. Self-Concept and Self-Esteem refer to how children think about themselves, their capabilities, and their overall value [11].

Overall, the many aspects of a child's development are intertwined, and advancement in one area often facilitates development in others. Both the importance of developing gross motor skills as well as cognitive development for school readiness and long-term academic success has been recognized [14], and motor and cognitive development, along with social and emotional development, form the three main, interrelated developmental areas in the early years of learning and development [8]. In an Australian toddler' sample, levels of gross motor skills are positively associated with cognitive development [8]. Additional evidence of a close relationship between fine motor abilities and intelligence in children, both with and without a diagnosis of Attention Deficit Hyperactivity Disorder (ADHD), has been reported. Nevertheless, children diagnosed with ADHD exhibit stronger relationships [15]. Essentially, it is crucial to a child's healthy growth, learning, and overall well-being to have a comprehensive understanding of their development and to provide help in these areas. Genetics, environment, and individual strengths and obstacles also impact a child's domain advancement. Tracking and encouraging development in all domains promotes holistic growth and success in school, relationships, and well-being.

The clinical manifestation of abnormal development exhibits notable variations among newborns, toddlers, and teenagers and the impact on young children can be significant, leading to a range of health conditions with detrimental effects on their personal, academic, social, and occupational functioning [16].

Children and adolescents exhibiting deficits in the developmental domains and significantly impacting their quality of life commonly face a disorder [17]. Indeed, Neurodevelopmental disorders (NDs) are a set of conditions, often manifest in childhood, characterized by deficits in brain development that impact numerous facets of an individual's capacity to function, including communication, learning, social interaction, behavior, cognitive processes, and emotional well-being [18–20]. The clinical features of various NDs are used to describe the disorders presented in the Diagnostic and Statistical Manual of Mental Disorders DSM-5). DSM-5 defines NDs including Intellectual Disability (ID), Autism Spectrum Disorders (ASD), ADHD, Specific Learning Disorder (SLD), and Communication Disorders (CD) [21]. The DSM-5 assigns certain features to the profiles of these disorders, including exaggerations, weaknesses, and delays in reaching developmental milestones [21,22]. A summary of the profile features of included NDs in DSM-5 is shown in Figure 1, which visualizes their patterns.

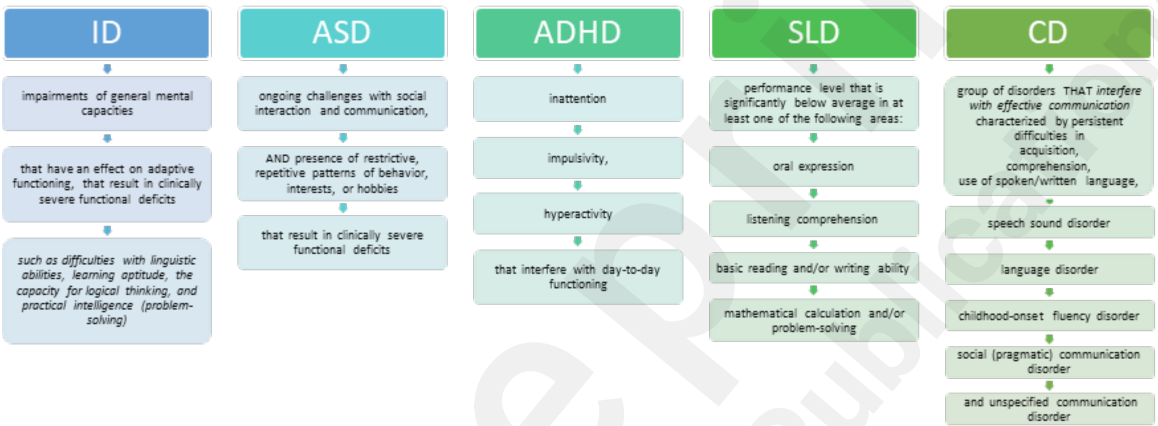

Figure 1. *DSM-5 Visualization of included NDs Profile Patterns*

It is essential to distinguish between normal development and disorders that emerge in the early stages of development to understand neurodevelopmental disorders (NDs). This statement refers to the different aspects of human development, including genetic, neural, cognitive, and socio-emotional domains [23]. As NDs form a considerable heterogeneous group with a broad spectrum of clinical features characterized by convergent boundaries and common co-occurrence [24], differentiation among NDS is also required. In addition, the early emerging and continuing course of NDs emphasizes the need for early diagnosis and intervention [25].

Developmental tests are required to predict the phenotype of children's delays in achieving developmental milestones, as well as to monitor their later progress [26]. They obtain information from observation in multiple domains [20], clinical history, and standardized assessments [27–30].

Moreover, assessment processing can be advantageous in distinguishing between these disorders due to their high prevalence and significant inter-individual variability [31]. It is crucial to thoroughly test chosen measures for their construct reliability and validity [32]. Besides, new and flexible diagnostic procedures would lead the clinician to consider the type of neurodevelopmental disorder to design proper policies and educational practices, thus facilitating the implementation of well-specialized and individualized comprehensive interventions [23,33].

It is well-documented that games play an important role in child development [34–37]. Serious Games (SG) are games created with a primary goal other than pure entertainment [38]. SG are utilized in many sectors such as education, training, healthcare, sustainability projects, marketing purposes, scientific investigation, crisis management, environmental planning, engineering, politics,

art, and more.
SG have been utilized in various health issues, encompassing chronic diseases, mental health disorders, rehabilitation with physical activity, substance abuse/management, obesity and eating disorders, geriatric care and cognitive impairment, chronic pain management, and asthma management [39]. In the present era, there has been a notable increase in the utilization of Artificial Intelligence (AI) [40–42]. Consequently, integrating AI with SG aims to provide a personalized and engaging healthcare experience. Diverse AI algorithms have been employed to address a range of health concerns through the utilization of SG, with motor impairment as the most targeted one [43]. Furthermore, SG commonly employ artificial intelligence (AI) for various purposes including rehabilitation, diagnosis, personalized screening, performance assessment, monitoring, risk modeling, drug discovery, and therapy response prediction. The main purposes of AI in a SG have been noted to be (i) disease/disorder detection and (ii) user-performance evaluation [43].
Neurodevelopmental difficulties can be monitored through serious games, which can be used for screening, early detection, diagnostic assessment, objective measurements, engagement, motivation, and personalized therapy [22,43–45]. Empowered Brain, a wearable technology combining smart glasses with AI-powered software and an augmented reality game, was found to improve social communication and attention in teenagers with ASD and ADHD [46]. A new iPad tool utilizing the TrueDepth camera tracks emotions and attention to diagnose ASD and ADHD, showing 78% and 45% accuracy in tests on adults and children. However, additional research is needed to enhance accuracy [47]. The ADHD360 project aims to create a platform for the early detection and management of ADHD in children interacting with a serious game, "Pizza on Time" using advanced machine learning algorithms. Preliminary results indicate that the system can predict ADHD in participants aged 7-16 with up to 85% accuracy [48]. Galexia is a game-based tool designed to diagnose dyslexia in children aged 6-12. It is a cost-effective and non-intrusive alternative for large-scale screening, with future work aiming to develop a comprehensive tool for specific learning difficulties [49]. Kim et al. utilized convolutional neural network analysis to explore the correlation between developmental disabilities and motor skills in DoBrain mobile games, revealing significant differences [50].
Diagnostic tests and objective measurements are standardized and repeatable [51] and digital health tools can improve diagnosis time [52]. Additionally, SG can motivate children with neurodevelopmental problems to engage in pleasant upgraded and anxiety free procedures. These studies collectively highlight the significant advancements and the growing potential of SG and digital diagnostics in ND detection. They underscore the need for continued research to improve accuracy, expand diagnostic capabilities, and ensure these tools are accessible and effective across diverse populations and settings towards individualized, efficient, and effective clinical experiences in communication, cognition, emotion, and behavior.
In this study, we are exploring the key elements of automated detection based on the aforementioned theoretical developmental domains, using a new SG. We conducted a PCA analysis on typically developed Greek children as part of this process.

Methods

This section describes the study's ethical considerations, the study design, the study sample, the SG and activities, data collection sources and formulation, and the analytical procedure.
This study is part of an ongoing research project titled “Smart Computing Models, Sensors, and Early diagnostic speech and language deficiencies indicators in Child Communication”, with the acronym “SmartSpeech” funded by the Region of Epirus and supported from European Regional Development Fund (ERDF).

Next follows a detailed presentation of the study's ethical considerations.

- Ethics Review and Approvals: The study was conducted in accordance with the Declaration of Helsinki and approved by the Research Ethics Committee of the University of Ioannina, Greece (protocol code 18435, approved on 15 May 2020). The project's nature, purpose, and procedures were thoroughly explained to parents during an informative meeting, ensuring compliance with the General Data Protection Regulation (GDPR).
- Informed Consent: All participating parents gave informed written consent after being provided with detailed information regarding the study's objectives, procedures, and ethical guidelines. The informed consent process ensured that parents understood the study's compliance with GDPR regulations (see Suppl. File *Consent Form*).
- Privacy and Confidentiality: To protect participant privacy, the data collected in this study were de-identified. All necessary measures were taken to ensure the confidentiality of participant information throughout the study.
- Compensation: No compensation was provided to participants.
- Participant Identification: Care was taken to ensure that no individual participants or users could be identified in any images included in the manuscript or supplementary materials.

The research was conducted in educational and healthcare settings across Greece. As this is a randomized trial The CONSORT 2010 checklist was utilized to report information included in this study (Included in Suppl. File *CONSORT 2010 checklist for SG APSOU)*. Participants were recruited through an open call distributed via private and public health and educational establishments across the country. The recruitment focused on parents of typically developing children aged 4 to 12 years. Parents were invited to informational meetings where the study's objectives, procedures, and ethical guidelines were explained. This session covered the study's purpose, the nature of the SG 'Apsou,' and the expected involvement of their children. Parents received comprehensive information about the study during these sessions and were asked to provide informed written consent for their children's participation to ensure compliance with GDPR and ethical considerations. The study included typically developing preschool and school-aged children without neurodevelopmental disorders, other medical conditions, or medications that could affect the results. Under clinicians' face-to-face supervision, during the period of 2021-2022, children played the serious game 'Apsou,' designed to measure various developmental domains, including speech, language, psychomotor, cognitive, psychoemotional, and hearing abilities [44]. This structured approach ensured comprehensive and ethical recruitment, engaging parents and children while adhering to ethical guidelines and data protection standards.

The study included 229 preschool and school-age children, 118 of whom were boys and 111 of whom were girls. The mean age of the children was 6.88±1.94 years old. All the children in the sample were attending typical educational settings. We notify that all participants included in the sample completed the whole SG.

The SG APSOU, version 1.0.1, developed within the SmartSpeech project, is designed to detect children at risk of NDs. It offers an interactive platform with various activities targeting different developmental skills, making the assessment process engaging and effective. The game is designed around a narrative plot, allowing players to use existing skills or acquire new ones in a scenario focusing on motivation, narrative, and fun [53]. The digital gamified environment utilizes video game mechanics to turn evaluation into a game, leveraging Unity's capabilities for smooth gameplay with high-quality graphics and animations. [54,55]. The game is designed for mobile devices (Android, iOS, Windows) and collects data from parents, clinicians, and the child's gameplay, providing a comprehensive dataset for analysis [54,55]. The validation process for the APSOU game involves several steps to ensure its effectiveness in assessing NDs, including data analysis using various AI algorithms. The game's effectiveness is evaluated by comparing the performance of typically developing children and children diagnosed with NDs. The Integer-bounded Neural Network outperforms other methods, paving the way for future research to improve the game's

detection effectiveness [22,44].
To assess neurodevelopmental skills, an interdisciplinary team designed this SG based on theories that measure speech and language, psychomotor, cognitive, psychoemotional, and hearing skills. There are 18 main variables in total, and each domain is measured by the child's performance on specific tasks within the SG activities. The SG software assesses NDs in various domains, and Table 1. ('Apsou' SG variables used to assess NDs Domains) describes the variables used to assess NDs domains.

Table 1. 'Apsou' SG variables used to assess NDs Domains

Domains of Assessment	SG NDs Variables of Assessment
Speech & language development	Verbal And Intellectual Ability
	Verbalization after Instruction
	Targeted Voicing Activities
	Articulation
	Phonology
	Syntax
	Pragmatic Perception
Psychomotor Development	Fine Motor Skills
	Pre-writing Skills
	Spatial Orientation
	Sequencing
Cognitive Development	Memory
	Recognition
	Perception/Discrimination
	Sustained Attention
	Cognitive Flexibility
Psychoemotional Development	Empathy
Hearing	Conditioned Play Audiometry

Upon completion, the child's responses are processed and evaluated using a scoring system [44]. The system collects and examines the scores in the 18 variables of the game assessment to create a developmental individualized profile for the child. All variable scores are computed on a scale of 0 to 100.

The SG was developed to collect children's responses during play time [54,56], represented as variables that fall into one of these input sources categories:

(i) hand moving on the touch screen (i.e., forming sequencing procedures, sentence formation/reordering objects),
(ii) verbal responding to questions or executing instructions (i.e., verbalization after initiation, word recognition (speech to text), used in articulation, pragmatics perception),
(iii) clicking buttons and objects or drag & dropping on screen (i.e. pictures with animals, shapes etc.)

The SG automatically generated scoring performance for touch screen hand movement responses according to accuracy. The rest of the variables were analyzed as follows.
SmartSpeech uses speech-to-text (STT) to recognize child's verbal responses during the SG. Participants were asked to pronounce characters' names and objects, with predetermined correct answers. CMUSphinx, a free, fast, and offline speech-to-text program, was used [57]. A Greek recognition model was constructed and trained in the software [58], detecting the best word to match

the child's input, to determine a correct answer. The software detected the word best matches what the child had said and, consequently, whether the child gave a correct answer or not. The recognized speech responses by the STT software are evaluated to the predetermined set of words that constitute a correct answer and thus turning into scores by assigning 0 to falses and 1 to trues.
The system is also designed to connect and collect biometric data from the child, such as heart rate and eye-tracking metrics, but these are outside the scope of this study [22,44].
Descriptive statistics were used to analyze TD children's gaming performance. Z-scores as standardized scores were calculated to provide information about the distance and direction of each observation from the mean value for that specific variable. We examine our variables with a reliability test analysis via Cronbach's alpha coefficient, which is used to evaluate the internal consistency of our measurements. To reduce the number of original features present in the dataset while retaining crucial information, the widely recognized PCA method for dimensionality reduction was used [59]. PCA analysis was used to examine the data structure and determine the main principles for automated detecting NDs. For the analysis following, we used the IBM SPSS Statistics v28.

Results

In this study, 229 children (M: 118, F: 111), mean age 6.88±1.94 years old, during 2021-2022, completed the SG different activities and tasks that are meant to assess specific neurodevelopmental issues. These tasks are grouped into 18 variables, each related to a different skill. The mean scores and standard deviations (SD) of the children's performance in the 18 variables are listed in Table 2.

Table 2. Mean scores and SD of the 229 TD Greek children's performance in the 18 variables of 'Apsou' Game

Variable	**Mean**	**Standard Deviation**
Verbal And Intellectual Ability	31.00	10.46
Verbalization after Instruction	15.28	36.06 ***
Targeted Voicing Activities	35.07	25.19
Articulation	14.57	16.08 ***
Phonology	81.12	24.17
Syntax	37.69	37.16
Pragmatic Perception	83.29	18.26
Fine Motor Skills	70.74	28.54
Pre-writing Skills	31.27	18.51
Spatial Orientation	36.62	11.38
Sequencing	60.61	15.77
Memory	23.29	21.28
Recognition	26.64	9.21
Perception/Discrimination	38.43	14.10
Sustained Attention	28.40	8.83
Cognitive Flexibility	63.39	18.74
Empathy	38.25	13.13
Conditioned Play Audiometry	26.64	26.05

The dataset was standardized, and z-scores of all the above variables were computed to take values with a mean of 0, and a standard deviation of 1. This coefficient takes values between 0-1, with the higher value resulting in a higher degree of reliability.
For our dataset, Cronbach's alpha coefficient was 0.805, a relatively high value according to the literature [60]. The internal consistency of the data, calculated using the SPSS, was found to be

satisfactory. As part of the procedure, the alpha coefficient was calculated iteratively by removing a variable from the set each time. The coefficients showed slight deviations, but the variable "Pre-writing Skills" had the greatest impact. If this variable is removed from the dataset, the alpha coefficient for the remaining 17 variables is calculated as 0.810.

- In order to identify the key components in our data, we utilized PCA analysis to retain as much of the original information as possible. To ensure that PCA was suitable for analyzing the study's data, we made the following assumptions: The Kaiser-Meyer-Olkin measure of sampling adequacy was calculated at 0.738, greater than 0.70, signifying that the current data was appropriate for applying PCA.
- Furthermore, Bartlett's Test of Sphericity (p<0.001) was presented in Table 3., rejecting the null hypothesis that the correlations between the variables were all 0.
- Both tests indicated that this study's data was suitable for applying PCA.

Table 3. KMO and Bartlett's Test for dataset’s suitability for PCA on 18 variables measured in the SG 'Apsou' among 229 TD Greek children

Kaiser-Meyer-Olkin Measure of Sampling Adequacy.		.738
Bartlett's Test of Sphericity	Approx. Chi-Square	1637.912
	df	153
	Sig.	<.001

We first examined the extraction process of the initial components and focused on the Initial Eigenvalues to understand the significant components. Table 4 shows the communalities of the variables in our analysis and explains the proportion of each variable's variance. The values closer to 1 are considered better. Fine ‘Motor Skills’ (0.863) was the most crucial variable in our observation, while ‘Verbalization after Instruction’ (0.235) was the least important one.

Table 4. Communalities of the variables in the PCA

Variable	**Initial**	**Extraction**
Verbal And Intellectual Ability	1.000	0.853
Verbalization after Instruction	1.000	0.235
Targeted Voicing Activities	1.000	0.857
Articulation	1.000	0.786
Phonology	1.000	0.523
Syntax	1.000	0.618
Pragmatic Perception	1.000	0.517
Fine Motor Skills	1.000	0.863
Pre-writing Skills	1.000	0.637
Spatial Orientation	1.000	0.798
Sequencing	1.000	0.499
Memory	1.000	0.472
Recognition	1.000	0.340
Perception/Discrimination	1.000	0.481
Sustained Attention	1.000	0.850
Cognitive Flexibility	1.000	0.731
Empathy	1.000	0.639
Conditioned Play Audiometry	1.000	0.361

Extraction Method: Principal Component Analysis.

We used the eigenvalue-one criterion to determine the number of 'meaningful' components for this

PCA. According to Table 5 (Total Variance Explained), the five (5) principal components (PCs) the total cumulative variance explained 61.44% of the initial variance. We confirmed the selection of these five PCs with eigenvalues greater than 1 using the scree plot (Figure 2). Precisely, the PCA revealed new features, the Principal Components 1 - 5 (PC1 – PC5). PC1 explained the most variance (24.914%), PC2 explained the second most variance (12.513%), PC3 explained the third most variance (11.713%), PC4 explained the fourth most variance (6.657%), and PC5 explained the fifth most variance (5.643%). The first three principal components, PC1, PC2, and PC3, explain a total cumulative variance of 49.139% of the initial variance, where the other two (PC4 and PC5) with eigenvalue greater than one explained a total cumulative variance 12.301% of the initial variance. In other words, the components explained a total cumulative variance 61.440% of the initial variance and as Figure 2 shows, components PC1-PC5 cannot explain all the variability. Thus, we applied a varimax rotation.

Table 5. Total Variance Explained by Principal Components

Component	**Initial Eigenvalues**			**Rotation Sums of Squared Loadings**		
	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %
1	4.484	24.914	24.914	4.484	24.914	24.914
2	2.252	12.513	37.427	2.252	12.513	37.427
3	2.108	11.713	49.139	2.108	11.713	49.139
4	1.198	6.657	55.797	1.198	6.657	55.797
5	1.016	5.643	61.440	1.016	5.643	61.440
6	.975	5.416	66.857			
7	.831	4.616	71.473			
8	.811	4.504	75.977			
9	.736	4.086	80.064			
10	.692	3.842	83.906			
11	.620	3.442	87.348			
12	.544	3.020	90.368			
13	.485	2.695	93.063			
14	.440	2.447	95.510			
15	.362	2.011	97.521			
16	.190	1.054	98.575			
17	.176	.977	99.551			
18	.081	.449	100.000			

Extraction Method: Principal Component Analysis.

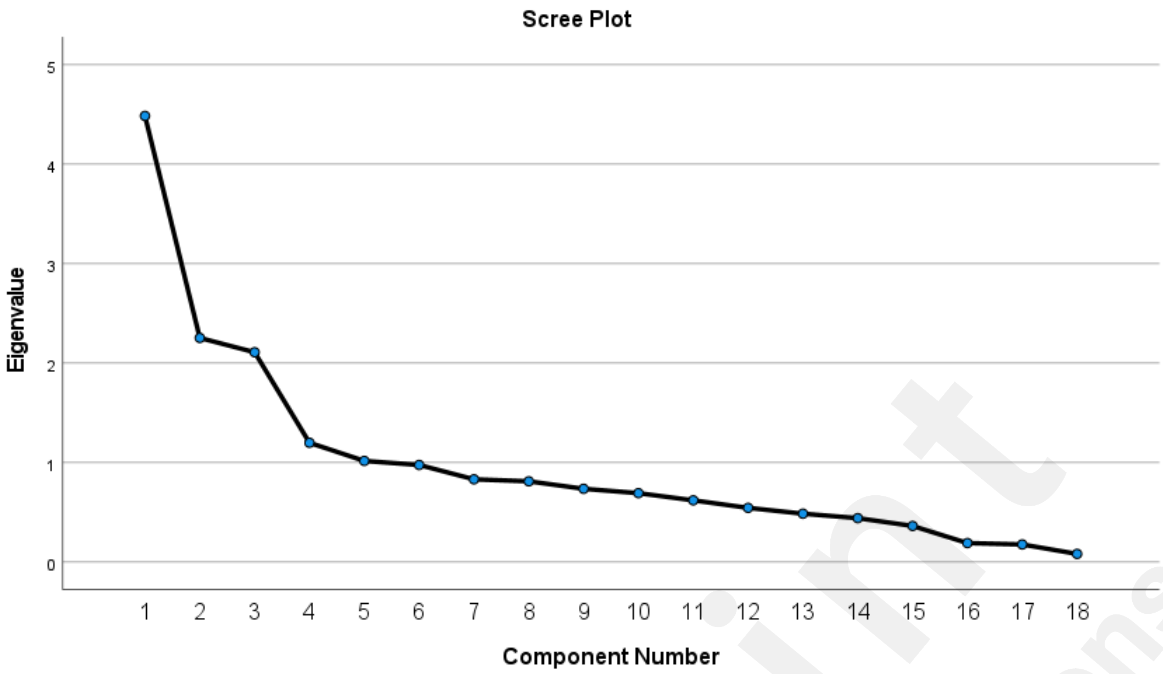

Figure 2. Eigenvalues of Five Main Principal Components in PCA Scree Plot of NDs measured by the SG 'Apsou'

As such, we employed a rotated component matrix using Varimax with Kaiser Normalization. By doing this, we determined the 'loads' placed on the various original features for each of the five principal components. Table 6 illustrates the rotated component matrix that reports the stronger correlations between the principal components and the initial variables. The correlation coefficients with absolute values lower than 0.4 are hidden for better readability.

Table 6. Rotated Component Matrix Using Varimax Rotation

Variable	**Component**				
	1	2	3	4	5
Pragmatic Perception	0.704				
Syntax	0.669				
Sequencing	0.665				
Phonology	0.615				
Memory	0.609				
Perception/Discrimination	0.518				0.458
Recognition	0.494				
Verbal And Intellectual Ability		0.899			
Articulation		0.877			
Empathy		0.746			
Targeted Voicing Activities			0.925		
Spatial Orientation			0.882		
Cognitive Flexibility			0.806		
Sustained Attention				0.893	
Fine Motor Skills				0.820	
Conditioned Play Audiometry				0.586	
Pre-writing Skills					0.784

Extraction Method: Principal Component Analysis.
Rotation Method: Varimax with Kaiser Normalization.

For each PC, the most critical original features are:

- PC1 → Pragmatic Perception, Syntax, Sequencing, Phonology, Memory, Perception/Discrimination and Recognition.
- PC2 → Verbal and Intellectual Ability, Articulation, and Empathy
- PC3 → Targeted Voicing Activities, Spatial Orientation, Cognitive Flexibility
- PC4 → Sustained Attention, Fine Motor Skills, Conditioned Play Audiometry
- PC5 → Pre-writing Skills, Perception/Discrimination

All original variables exhibit correlations with their respective principal components, indicating a strong association among them.

The current PCA analysis indicates the main Principal Components, PC1-PC5, suggesting accordingly Communication skills, Speech and Language Development, Vocal processing, Cognitive Skills & Sensory Functions, and Visual Spatial Skills.

Discussion

This study conducted data analysis on typically developed preschoolers and first school-aged children, exploring the main principles towards automated detection of neurodevelopmental disorders (NDs) and the underlying theoretical principles. The age range of 4-12 years was selected for this study because NDs often become apparent during the early school years and persist into adulthood. It is important to identify these disorders early for timely intervention. During this age range, children reach important developmental milestones in speech, language, cognition, and motor skills. By examining this age group, we can gain insight into standard developmental paths and the natural variations within them, and we can carry out a thorough assessment during a crucial stage of growth. This ensures that the 'Apsou' serious game can efficiently recognize and assist children at a pivotal moment. This strengthens the significance and influence of the study on early childhood and primary education.

The PCA analysis resulted in five principal components, as per the Kaiser rule. Only the PCs having eigenvalues greater than 1 were retained. These components describe a cumulative variance of 61.44%, which is due to the intra-individual differences in children's performance across some domains [61].

As noted by Van Geert & Van Dijk “Intra-individual variability can be defined as differences in the level of a developmental variable within individuals and between repeated measurements” [62]. Developmental change is often preceded by variability, which plays a crucial role in exploration and selection processes.

It has been observed that individuals exhibit a wide range of performances in different tasks, such as verbalization after instruction as shown in Table 2. These variations in performance can be attributed to individual skillfulness, level of readiness, and the acquisition of different skills and milestones. These findings emphasize the complexity of typical development, which is characterized by variations in child developmental rhythm, abilities, and performances at each stage. These results are consistent with other research findings [1,63,64].

It is widely acknowledged that the distinctions observed in child development indicate various developmental phases. Although children may attain developmental milestones at varying ages, the sequence in which they achieve these milestones can differ among children [61,65].

Besides, these results pinpoint findings on preschoolers and first school-aged children as the current study establishes the fundamental developmental skills that support the automated digital system's ability to classify the child's performance per developmental stage. Relevant findings regarding developmental age have been reported [55]. Further, children may temporarily sample advanced milestones but may not fully master them until later and can jump between stages [61,65]. Thus, individuals' actions are inherently unique, contributing to the observed variability in human behavior. Diversity is crucial for children's development as it manifests unique problem-solving approaches, highlighting inter-individual diversity. The recorded total variation is expected to underline typical multifaceted heterogeneous profiles of children with NDs.

Furthermore, researchers from various scientific fields have shown a growing interest in early human development [66]. This growth in interest can be attributed to the recognition of the wide range of NDs, which are characterized by significant genetic and phenotypic differences. Also, there is a critical need to enhance our understanding of the similarities and differences among various syndromes, disorders, and disease processes. The primary focus of studying early human development and predicting neurodevelopmental outcomes is to examine critical aspects such as the presence and progression of distinct physical and neurological characteristics, as well as potential abnormalities in neurobehavioral and psychopathological patterns.

The results of the current study revealed five main new features (PC1-PC5). These PCs are logically aligned with the original features to establish their compatibility with the domains examined in the traditional manner of assessing NDs. According to the results of the PCA, the first three principal components explain about 50% of the total cumulative variance. Further, this study's findings agree with the globally accepted theoretical principles [26] and are also in line with other research work as follows.

The first new feature (PC1) explaining the most variance in the PCA, includes original features (i) Pragmatic Perception, (ii) Syntax, (iii) Sequencing, (iv) Phonology, (v) Memory, (vi) Perception/Discrimination, and (vii) Recognition with the most important loads. These skills are pointing towards Communication Skills, and are in line with the theoretical principles of NDs (Intellectual Disability, Global Developmental Delay, Communication Disorders, Autism Spectrum Disorder, Attention-Deficit/Hyperactivity Disorder, Specific Learning Disorder, Motor Disorders, Other Neurodevelopmental Disorders) [1,3,26] that demonstrate deficiencies in "… *mental functions in conceptual (language, reading, writing, mathematics, memory, insight, knowledge, interpretation), social (empathy, compassion, social judgment, communication and interaction skills, amicability, harmony) and practical (personal care, school and/or occupational responsibilities and organization, financial management, entertainment, hobby) aspects* …" [67].

It has been found that the second new feature (PC2), is responsible for explaining the second highest variance in the PCA, which includes the original features of Verbal and Intellectual Ability, Articulation, and Empathy, with the second most significant loads. PC2 indicates Speech and Language Development and is in accordance with recent research underlying that observing a child's speech and language development is crucial for their emotional well-being, especially in the early years [1,67]. Additionally, as children grow, their speech intelligibility improves over time. Typically, it starts at around 25% by the age of two and gradually gets better until they reach complete intelligibility by the age of four. However, if a child is constantly struggling with their speech and language, such as using infantile language, mispronouncing words, or lacking spontaneous speech, it may indicate a delay in their speech and language development [68,69].

The third new feature (PC3), explains the third most variance in the PCA, including original features (i) Targeted Voicing Activities, (ii) Spatial Orientation, and (iii) Cognitive Flexibility, with the subsequent most necessary loads. The interaction of these three original features indicates vocal processing, which is also described in accordance with another research. It is also considered a fundamental predictor of cognitive development along with language development [70]. For example, the observed modulation in pleasure vocalizations underscores an increasing association between the act of looking towards the caregiver (spatial orientated emotional communication), while a gradual evolution undergoes because of the simultaneous presence of early spontaneous behaviors (vocal activities) and intentionally driven behaviors (cognitive flexibility) [71].

The fourth new feature (PC4), points to Cognitive Skills & Sensory Functions, and explains the following most variance in the PCA, including original features: (i) Sustained Attention, (ii) Fine

Motor Skills, and (iii) Conditioned Play Audiometry, with subsequent most important loads. In the same direction, current NDs commonly result in cognitive deficits such as attention and executive function problems [72]. For instance, measurements of visual/auditory sustained attention, vigilance, and impulsivity in children with ADHD often exhibit executive dysfunction-like behavior, which impairs their development. ADHD children have long-term neuropsychological deficits, including poor performance on visual/auditory vigilance tasks, response inhibition, attention, and goal-directed behavior [73]. Also, children with developmental language impairments often display minor motor impairments [74] and reduced coding of spoken syllables and phonemes [75], which are frequently overlooked. However, identifying and treating non-language impairments is advantageous to aid the children's language development (i.e. phonological processing) [76] preventing in the long run the development of cognitive deficits [77].

Lastly, the fifth new feature (PC5) suggesting Visual-Spatial Skills, explains the next most variance in the PCA, including original features (i) Pre-writing Skills, (ii) Perception/Discrimination with the later most important loads. In the same direction, it is well established that deficiencies in visual-spatial and visual-perceptual abilities, and difficulties solving problems early, associated with reading and attention problems, while language-based skills and IQ remain normal, are the hallmarks of nonverbal SLD [1]. Further, consistent with previous research, weaknesses in visual-spatial abilities, including pre-writing skills, are reported in children at risk of SLD [78]. Moreover, consistent with other studies, a spectrum of visuospatial abilities (or visuospatial dimension), ranging from gifted to impaired abilities, exhibit early impairments in various areas, including visual-spatial attention [79], visual-constructive, spatial working memory and fine-motor skills, and poor performances in educational subjects such as mathematics, as well as emotional and social problems [80].

Utilizing a sample of typically developing children is fundamental to establish a robust normative baseline against which deviations can be measured. By understanding the typical developmental trajectories and their inherent variability, atypical patterns that signify NDs can be more accurately pinpointed. This differentiation between normal developmental variations and clinically significant deviations ensures that automated detection methods are both sensitive and specific. It's interesting to note that the five principal component analysis (PCA) factors identified in this study were also found in a parallel relevant study [81] involving TD and ND children. Apsou SG, factor analysis, and machine learning with logistic regression were used to create a strong predictive model. The model achieved an AUC of 0.730, accuracy of 0.815, F1 score of 0.776, precision of 0.823, and recall of 0.815, clearly indicating the predictive potential of these factors.

A shortcoming of this study is the absence of implementation of a diagnostic test of intelligence. To complement this limitation though, we took into consideration that (i) all the participants were attending the typical educational settings and (ii) the Apsou clinical administrators confirmed the nonexistence of NDs in participants using the child's developmental and communicative background provided by the parent, and the observation approach applied during their interaction with the child during the game.

The accuracy of the transcription provided by Speech-to-Text (STT) software is a limiting factor in this research. We used the highly accurate CMUSphinx STT program [58], trained to convert adult verbal responses to text, but as the software improves over time, also the accuracy of models relying on these transcripts will improve as well. Further research may also employ innovative other open sources for this purpose.

Although PCA is a justified method to reveal the most important features of NDs representing 61.44% of the variance, additional methods can be used to explore features validity like Deep Learning Approaches, Genetic and Molecular Data Analysis, Machine Learning and Statistical Analysis, Biological Markers, Neurophysiological and Electrophysiological Measures, Nonlinear Dimensionality Reduction Techniques, Manifold Learning, and more.

The current findings have the potential to guide future research toward improving automated classification and prediction. This progress can play a crucial role in the timely and precise identification and treatment of neurodevelopmental disorders in clinical and educational settings. Understanding typical and atypical developmental patterns, including neurodevelopmental disorders (NDs), can significantly enhance clinical practice with advanced AI tools. Future research should combine these findings with cutting-edge AI and machine learning techniques to explore additional features such as biometric data and longitudinal tracking. This combined effort will not only enhance the accuracy and reliability of automated detection systems but also lead to more effective and personalized interventions. These developments will enable more tailored and holistic approaches to supporting individuals with NDs, ultimately improving their long-term outcomes and quality of life. Furthermore, future studies may strive to validate these findings across diverse populations, ensuring broader applicability and generalizability.

Conclusions

In this study, the main principles for automated detection of Neurodevelopmental Disorders were explored. A sample of 229 typical developed preschoolers and early school aged children played a unique serious game, 'Apsou', developed to measure developmental domains.
Using principal components analysis, we unveiled five core principles, signifying (i) communication skills, (ii) speech and language development, (iii) vocal processing, (iv) cognitive skills & sensory functions, and (v) visual spatial skills, thus corroborating the theoretical principles regarding typically developmental domains. These findings open the door for future research to harness them for further analysis in refining automated screening, diagnosis, prognosis, and treatment planning to support clinical decision-making on NDs.

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Data Availability Statement

The data sets generated and analyzed during this study are not publicly available, as participants did not give written consent for their data to be shared publicly, but they are available from the corresponding author upon reasonable request.

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Multimedia Appendix 1: Apsou v1.0.1 Screenshots

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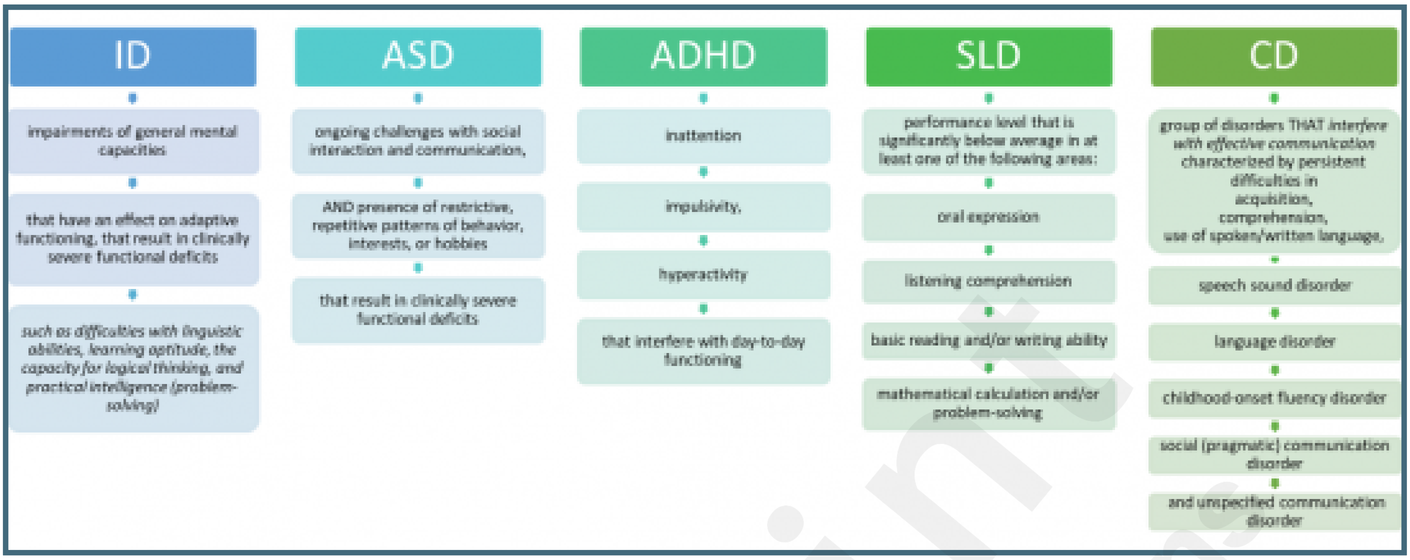
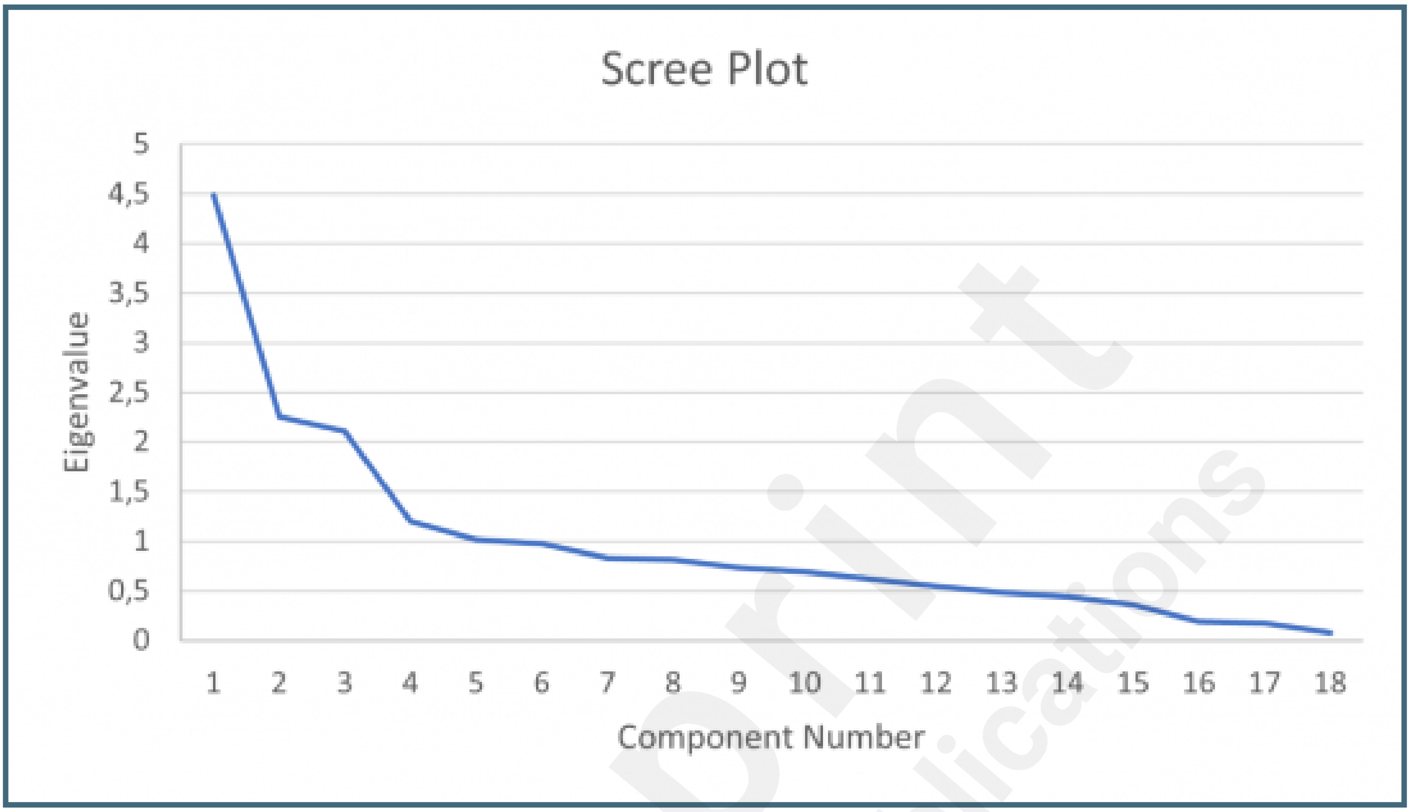
Supplementary Files

Figures

DSM-5 Visualization of included NDs Profile Patterns.



Eigenvalues of Five Main Principal Components in PCA Scree Plot of NDs measured by the SG 'Apsou'.



Multimedia Appendixes

Apsou v1.0.1 Screenshots.
URL: http://asset.jmir.pub/assets/b25c0592e65df05ffb19a5ca25a2276f.pdf

CONSORT (or other) checklists

CONSORT 2010 checklist for SG APSOU.
URL: http://asset.jmir.pub/assets/80d0067adce488fcc3981b2f05dea7f8.pdf

Related publication(s) - for reviewers eyes onlies

This is a related publication (cited in the manuscript) currently in print. Toki, E. I.; Zakopoulou, V.; Tatsis, G.; Plachouras, K.; Pange, J. (2023). Markers for the support of clinical Tele-assessment: The case of autism spectrum disorders. [in print] In: Open Science in Engineering, Proceedings of the 20th International Conference on Remote Engineering and Virtual Instrumentation, ISBN 978-3-031-42466-3,Springer, Cham, https://doi.org/10.1007/978-3-031-42467-0_72.
URL: http://asset.jmir.pub/assets/4f16c2ffbb6d55c96634dbe1e47c835a.pdf