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Review article

Serious Games in the new era of digital-health interventions: A narrative review of their therapeutic applications to manage neurobehavior in neurodevelopmental disorders

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ABSTRACT

Children and adolescents with neurodevelopmental disorders generally show adaptive, cognitive and motor skills impairments associated with behavioral problems, i.e., alterations in attention, anxiety and stress regulation, emotional and social relationships, which strongly limit their quality of life. This narrative review aims at providing a critical overview of the current knowledge in the field of serious games (SGs), known as digital instructional interactive videogames, applied to neurodevelopmental disorders. Indeed, a growing number of studies is drawing attention to SGs as innovative and promising interventions in managing neurobehavioral and cognitive disturbs in children with neurodevelopmental disorders. Accordingly, we provide a literature overview of the current evidence regarding the actions and the effects of SGs. In addition, we describe neurobehavioral alterations occurring in some specific neurodevelopmental disorders for which a possible therapeutic use of SGs has been suggested. Finally, we discuss findings obtained in clinical trials using SGs as digital therapeutics in neurodevelopment disorders and suggest new directions and hypotheses for future studies to bridge the gaps between clinical research and clinical practice.

1. Introduction

Neurodevelopmental disorders (NDDs) are disabling conditions induced by an impairment of brain development and functioning occurring during the foetal/neonatal developmental window due to known but often unknown etiologies linked to genetic or environmental factors (Morris-Rosendahl, 2020). According to the International Classification of Diseases 11th Revision (ICD-11, https://icd.who.int/en) and the Diagnostic and Statistical Manual of Mental Disorders *DSM5* (American Psychiatric Association, 2013), neurodevelopmental disorders can be categorized in communication, attention deficit, hyperactivity, learning and visual-motor disorders. In this context, diseases with well-defined genetic alterations associated with multi-system and developmental abnormalities, such as Fragile X (FXS), RETT (RTT), cyclin-dependent kinase-like 5 (CDKL5) and Down (DS) syndromes, are considered neurodevelopmental disorders (Vacca et al., 2019;

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Salcedo-Arellano et al., 2020; Bach et al., 2021; Van Bergen et al., 2022). Other related conditions include Autism Spectrum Disorders (ASD) and Attention-Deficit Hyperactivity Disorder (ADHD), where a more complex etiological profile seems to be associated with nonlinear genetic, epigenetics and environment alterations (Panisi et al., 2021; Balogh et al., 2022). Intellectual disability (ID), ranking from mild to severe, is often related to these diseases (Dubovický, 2010; Li et al., 2019) as it is associated with limitations of cognitive functions and adaptive skills, such as interpretation, conceptualization and executive functions, that negatively impact on autonomous living and social interactions (Schalock et al., 2021; Müller-Oehring and Schulte, 2014).

A broad spectrum of concurrent emotional and behavioral problems in children and adolescents with NDDs typically emerges during the early preschool period and beyond (Ogundele and Morton, 2022). Anxiety, stress and depression are typical emotional problems occurring in NDDs as well as behavioral abnormalities characterized by attention, oppositional, irritability and hyperactive disturbs (May et al., 2021). These might need neurophysiological and neuropsychiatric evaluation and often treatment with psychiatric drugs (Halvorsen et al., 2019; Hodgins et al., 2022). Moreover, it is worthy to mention that such problems related to NDDs have a serious negative impact on quality of life of family members, particularly on caregivers (Gardiner et al., 2018; Vernhet et al., 2022).

Great efforts have been made to design novel therapeutic interventions able to correct cognitive and behavioral symptoms or to support standard pharmacological therapies. Besides medical/pharmacological options, technological development has offered a more accessible and holistic perspective in the field of non-pharmacological interventions (Balzotti et al., 2019; Palomaa et al., 2021), proposing digital-therapeutic as training tools to improve learning, general skills and behavior in children and adolescents with intellectual disabilities and behavioral problems. Indeed, recently, a growing number of studies have been focused on designing and demonstrating the efficacy of instructional videogames, or Serious Games (SGs), to help people with mental illness and behavioral problems, with particular attention to people with ASD and ADHD (Kokol et al., 2020; Silva et al., 2021; Dewhirst et al., 2022; Vallefuoco et al., 2022). SGs, usually provided as video platform, are mainly designed to train and educate players towards specific skills, and to improve the skills learned. At the same time, they can entertain and motivate the player by applying gaming technologies with objectives and rules, through an interactive and predictable environment with virtual rewards (Caserman et al., 2020; Whyte et al., 2015; Alvarez and Djaouti, 2011; Brown et al., 2013).

For these peculiar features, SGs have been used in numerous health settings showing promising results in emotion recognition (Serret et al., 2014; Grossard et al., 2017; Tang et al., 2019a) and in improving cognitive (Grossard et al., 2017; Macoun et al., 2021) and social (Xavier et al., 2022) skills.

Many systematic reviews, meta-analysis studies and clinical trials have described the effectiveness of SGs on general population with ID (Tsikinas and Xinogalos, 2019; Sochocka et al., 2020; Derks et al., 2022), or, particularly, on people with ASD (Kokol et al., 2020; Silva et al., 2021) with high affinity for technology and interest in videogames (Lofland, 2016). Regarding the other NDDs, interactive-technologies have aroused wide attention (Oliveira Ribas et al., 2023), although to date there is no objective clinical demonstration of SGs therapeutic efficacy where many clarifications are still to be made before they can be applied to clinical practice.

This narrative review aims at critically analyze published scientific data about the effectiveness and suitability of SGs as digital therapeutics (DTs) in assisting neuropsychologists, neuropsychiatrists and therapists to manage behavioral disturbs and ID in children and adolescent patients with NDDs. We examine and discuss, with a multi-disciplinary approach, the clinical research activities undertaken to date, with the intent to consider the suitability of SGs application in clinical practices and disseminate research findings. Therefore, we first provide insights concerning the SGs implementation approaches for DTs purpose and the human-machine interaction in SGs development. Then, we describe neurobehavioral alterations occurring in some specific neurodevelopmental ID-related diseases, orphans of cure, where a potential therapeutic use of SGs has been suggested. Finally, we discuss the results of clinical studies obtained from the use of SGs in neurobehavioral disorders to foster information, effectiveness and practices.

2. Methods for literature search and study identification

The scientific literature search was conducted using PubMed, Web of Science, Scopus, Google scholar and clinical-trials.gov online databases with the following keywords, either singularly or in combination: “Serious games”, “Serious game health”, “digital therapeutics”, “Human-Machine Communication”, “neurodevelopmental disorders (or diseases, or neurodevelopment)”, “development” “neurobehavior”, “technologies”, “Autism spectrum disorder”, “Attention-Deficit Hyperactivity Disorder” (or ADHD, “Down syndrome” (or trisomy 21), “Fragile X syndrome”, “FMR1-related disorders”, cognitive skills”, “adaptive skills”, “motor skills”, “social skills” and emotional skills”.

The search was restricted to the time interval between 2010 up-to date (January 2023) as it is related to the release of 3D depth sensors and the advancements in the technology of the SGs softwares and devices. The search was refined using the following inclusion criteria: (1) articles introducing and/or testing SGs in subjects with NDDs up to 18 years old; (2) reviews (narrative and systematic), protocols, trials, observational studies and feasibility studies, preprints; (3) English language. On the other hand, the exclusion criteria were: (1) out of topic; (2) editorials, abstracts, letters, and case reports. The ‘review’ article types were also used to identify other potentially eligible articles based on their titles and abstracts. The reference lists of the selected articles were further inspected for potentially relevant papers. The study diagram summarizing the literature selection process used for this study is showed in Fig. 1. The search criteria with the keywords “Serious games”, or “neurodevelopment disorders and neurobehavior” generated a total of 1860 and 2250 papers respectively, after duplicated articles excluded. The other keywords mentioned above, used in combination or separately with “Serious games”, yielded 190 articles identified as potentially eligible based on the evaluation of titles and abstracts, and the inclusion and exclusion criteria. Following a full-text evaluation, 36 articles were excluded (out of topic) and the remaining 158 were retained to prepare the present manuscript.

It is worthy to mention that the literature searching combining “Serious games” with “Autism” or “Attention-Deficit Hyperactivity Disorder” or “Down syndrome” or “Fragile X syndrome” keywords, produced less than 50 total eligible articles, where only six focuses on DS and FXS (see Fig. 1). This indicates that SGs as digital therapeutics in NDDs is yet a research field that need to be deeply explored.

3. Serious games as digital therapies: how they can work

SGs, games designed not for pure entertainment but as educational tools, are well known for their effectiveness in practicing skills and achieving learning outcomes in an engaging way (Charsky, 2010). SGs offer an amusing, immersive and safe environment where to foster competencies and learn by doing (Vaz De Carvalho et al., 2021). Apart from their main application in education, cultural heritage and marketing, SGs are increasingly exploited in health-related purposes (Sardi et al., 2017) both by physicians and patients. For instance, they have been proposed as educational tools for medical trainees to simulate patient flow management, improve surgical skills and foster social and communication strategies (Chon et al., 2019; Augello et al., 2015).

For patients, SGs can be classified as: (i) *preventative* games promoting physical or mental activity to mitigate risks of undesired events, (ii) *assessment* games used for symptoms detection or impairments, and (iii) *therapeutic* games aiming at patient care and rehabilitation (Muñoz

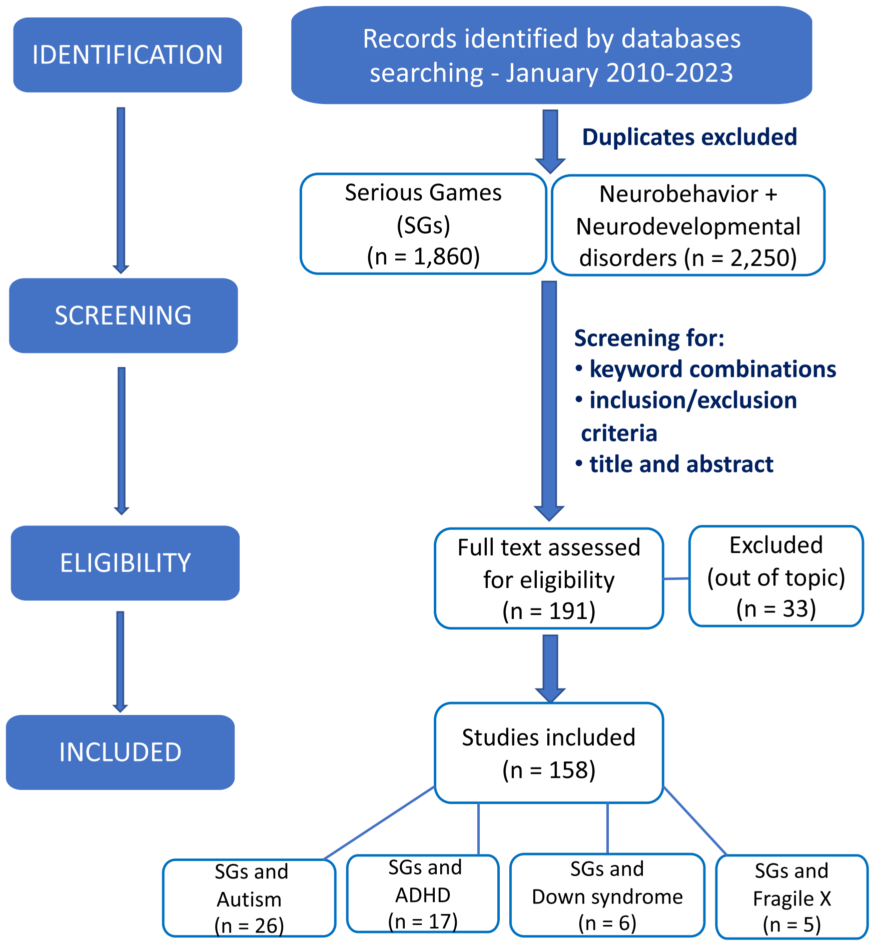

Fig. 1. Flow chart and study design of the literature selection process.

et al., 2022). The last category includes games used for DTs, software-driven therapeutic interventions, substituting or complementing other therapies in order to enhance patient care and optimize health outcomes (Dang et al., 2020). In fact, patients can learn the correct execution of an exercise or a therapy through customized and remotely monitored solutions (Caggianese et al., 2018), where their motivation to embrace the treatment can be increased. In addition, SGs can also be a mean of distracting patients from painful symptoms and treatments (Chirico et al., 2020).

Many factors may contribute to patients' engagement and consequently to the proper effectiveness of a SG as DTs. These depend on the elements that characterize the game, the technology used (in particular its robustness and usability), and the presence of narrative and aesthetic aspects (see Fig. 2).

In the following, SGs for DTs are discussed focusing on implementation approaches, technological aspects and human-computer issues, and providing an overview of SGs-based therapeutic interventions for children with neurodevelopmental diseases.

3.1. Implementation approaches and technologies

Currently, many approaches are adopted in the implementation of a Serious Game as DTs. These can vary according to the patient category, the intended purpose and the possible requirements, such as the need for data acquisition to monitor the patient's progress and/or to provide feedback regarding the adaptation on the game. In addition, the underlying technologies used in SGs as DTs play a key role in achieving the intended outcomes by enabling the patients to interact with the elements of the game mechanics (see Fig. 3).

In this context, the low-cost availability of smartphones and tablets offer an important asset to their extensive use in a SGs implementation framework. (Verschueren et al., 2019; Kollins et al., 2020; Martins et al., 2020). Nonetheless, with the advent of immersive augmented or virtual reality (AR/VR) systems, it became possible to create more attractive and immersive environments. At the same time, the introduction of acquisition devices, such as electroencephalogram (EEG) helmets, wristbands, and motion sensors to track users' movements and their vital parameters have found rapid applications to monitor game activities and acquire physiological information to use as biofeedback (Adinolfi et al., 2016; Barba et al., 2019; Iliadou et al., 2021). The age of users significantly influences the preference type of gaming platforms being technological platforms favored by younger people (González-González et al., 2022). Smart wearable devices allow a direct interaction with the AR/VR: velocity, angles of movements, and applied forces can be detected and evaluated by therapists to optimize training plans (Martins et al., 2020). For instance, Liu et al. (2017) created a Brain Power System (BPS) based on computerized smartglasses designed to be a wearable socio-affective aid. The smartglasses sensors are used in real-time to capture users' behaviors and give visual and auditory feedback in a gamified AR application providing coaching for emotion recognition, eye contact, and behavioral self-regulation. Another proposed approach is a SG communicating with a balance board with inertial sensors (Noveletto et al., 2018). Relying on the flow theory, the patient attention is kept high by the game dynamics in order to have a level of difficulty neither too easy, to avoid the patient's boredom, nor too hard, to avoid frustration. Regarding the quality of digital health software, González-González et al. (2019) suggested the use of a "recommender system" that analyzes user interaction and provide the

Fig. 2. Main factors contributing to achieving the objectives of using Serious Games for digital therapy. The scheme is inspired by the Elemental Tetrad (Schell, 2008).

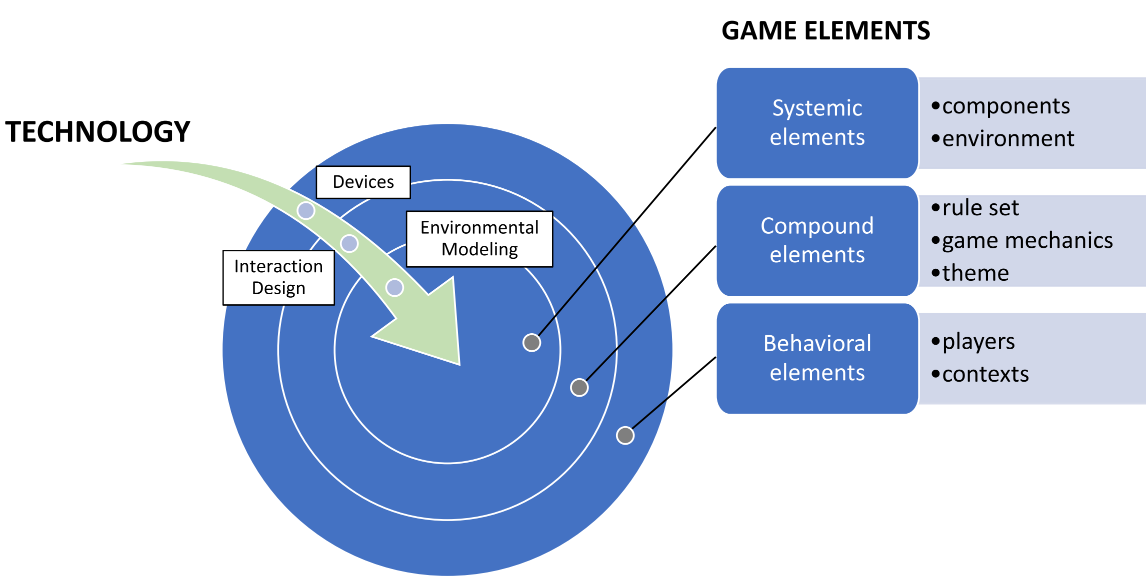

Fig. 3. Technology-Game elements relationship. The arrow pinpoints the technology used by the player to interact with the game elements. The game elements are classified according to the taxonomy discussed in (Järvinen, 2008).

user with a personalized game mode based on his own history and preferences. However, Kokol et al. (2022) emphasizes the need to cover significant gaps in this research field to enhance its quality and to achieve more satisfactory results.

3.2. The Human-Machine Communication research

The complex nature of human-machine interaction in SG and virtual learning environments for health education has been explored since the early internet and web diffusion. Billions of people, including children, are increasingly relating to highly communicative machines throughout their daily lives. This modification from communicating with humans to communicating with intelligent machines and interdigital actors may challenge emotional and social responses to machine interaction (Murero, 2020). Social practices and subjectivities are more and more negotiated through technological architecture (Chia et al., 2022). Emerging technologies no longer fit into a medium-only role but they acquired the function of the main communicator.

The evaluation and treatment of health states through innovative technology based on human-machine communication (HMC) is a key aspect of contemporary communication research. HMC focuses on the meaning-making that unfolds when people engage directly with technology as a communicative subject (Guzman, 2018), such as virtual and augmented realities, digital assistants, artificial intelligence (AI), smart and Internet of Things (IoT) devices, social robots, and cyborgs (Human-Machine Communication ICA Interest Group, https://humanmachinecommunication.com/).

The interaction of young adults with contemporary information and communication technologies is of fundamental importance since it can generate multi-disciplinary in-game and off-game metrics that help define a user's state of health and wellbeing (WHO, 2022) in innovative ways (Ricciardi and De Paolis, 2014). However, digital systems are rarely designed to regulate technical interoperability and its implications for creative practice and cultural production (Chia, 2019). As a result, many SG software platforms rarely consider crucial elements that assess the young patient improvement process through HMC, personal commitment, or digital literacy. This issue will be a challenge for the SG design and development in the future.

3.3. Serious game-based therapeutic interventions for children with NDDs

As discussed in the paragraph 3.1, in recent years, technological advances have improved the development of video game-based assessment and therapeutic tools to complement traditional approaches (Peñuelas-Calvo et al., 2022). SG-based therapeutic interventions have been well accepted by children with cognitive disabilities such as ASD, ADHD, DS and FXS. In general, they showed to be effective in improving cognitive areas, social interaction, and motor skill function (see Chapters 4 and 5 for additional insights).

SGs designed for cognitive training as theoretical framework, generally transfer cognitive skills to the real world with the aim to train memory and improve concentration, inhibitory control, facial expression and emotion recognition. The games applications are available through PC platforms, mobile devices apps, software and video game consoles (Davis et al., 2018; Dovis et al., 2015; Serret et al., 2017; Jouen et al., 2017; García-Redondo et al., 2019; Macoun et al., 2021). The names of SGs, the characteristics, the procedure as DTs and their patients target used for cognitive training are summarized in Table 1.

SGs with physical exercise functions, are also called exergames, offer physical training programs to promote physical activity with the final aim of improving also cognitive functioning (Alba-Rueda et al., 2022). These programs provide a combination of visual and graphical virtual support of video games and actual physical exercises. The whole body becomes the tool imparting the commands of the game, which potentially improve the balance, the perceived abilities, and cognitive performance. The challenge level increases gradually, motivating the player to reach upper levels of playing based on his capability. Another important principle of these platforms is that they offer pleasant and not repetitive activities, creating in children the will to move forward with their gaming experience. According to psychotherapists some exergame platforms provide positive reinforcements to encourage an active participation of the children through visual and auditory message like "excellent", "very good", "you can do it", and by offering an awards ceremony at the end of the game (Torres-Carrión et al., 2019).

The SGs developed in this framework are reported in the Table 2 (Anderson-Hanley et al., 2011; Brandão et al., 2014; Travers et al., 2017; Edwards et al., 2017; Benzing and Schmidt, 2019). The games included Nintendo Wii-based applications and video game consoles. New types of

Table 1

SGs designed for cognitive training in neurodevelopmental diseases. The name of Serious Game with the run platform, characteristics, procedure, outcomes and effectiveness for cognitive training in children and adolescents with neurodevelopmental diseases (NDDs) are listed. Studies and NDDs are selected as reported in the Method section. Studies are in alphabetical order for diseases and in chronological order within the diseases.

NDDs	Age (years)	SG/ platform	Characteristics	Outcomes	Procedure	Effectiveness	Study Reference
ADHD	6–16	Boogies academy and cuibrain/ Tablet	10 Serious games based on Gardner's Theory of Multiple Intelligences	Attention	10 min session, 2 days a week, 14 weeks	Yes	García-Redondo et al. (2019)
ADHD	8–12	Project EVO/Ipad	Action video game-like interface, employment of a perceptual discrimination Attention/Memory task and a continuous visuo-motor driving task	Attention	30–45 min session, 5 days per week, 4 weeks	Yes	Davis et al. (2018)
ADHD	8–12	Braingame brian/ PC	Adventure/craft video game with 25 sessions aimed at improving working memory, inhibition or cognitive flexibility	Executive functions	35–50 min session, 25 sessions	Yes	Dovis et al. (2015)
ASD	6–12	Caribbean Quest/ PC	Single player aimed to improve EF and attention	Attention	30 min session, 3 times a week, 8 weeks.	Yes	Macoun et al. (2021)
ASD	5–8	GOLIAH/PC	Multi-player gaming platform with 11 serious games aimed to stimulate and improve imitation and join attention	Executive function	30 min session, 4 sessions per week at home + 1 h session per week at the hospital	Limited	Jouen et al. (2017)
ASD	6–11	SEMA-TC/PC	Single player puzzle game aimed to improve literacy skills. Learning to read	Attention	4 h session per week untill game completion; comparison with a control group receiving no intervention	Yes	Serret et al. (2017)
Different NDDs: DS, ADHD, Developmental delay	3–6	"Kids Free"/App	This game is specifically designed for children to train their memory while having fun.	Attention	Children had 5 min to carry out the activity on a tablet.	Yes	Durango et al. (2015)
FXS	10–17	Computerized cognitive training/ PC and App	A distance-delivered parent-implemented narrative language intervention	Attention	Weekly homework sessions recorded by the parent	Yes	Nelson et al. (2018)

Table 2

SGs designed for physical training in neurodevelopmental diseases. The name of Serious Game with the run platform, characteristics,procedure outcomes and effectiveness for physical training in children and adolescents with neurodevelopmental diseases (NDDs) are listed. Studies and NDDs are selected as reported the Method section. Studies are in alphabetical order for diseases and in chronological order within the diseases.

NDDs	Age (years)	SG/ platform	Characteristics	Outcomes	Procedure	Effectivenes	Study Reference
ADHD	8–12	Shape Up/Xbox Kinect	Exergame aimed to improve attention, impulsivity, hperactivity, motor ability and reaction time	Motor abilities; Executive function	At least 30 min session, 3 times per week, 8 weeks	Yes	Benzing and Schmidt (2019)
ASD	7–17	Ninja Training Game/Kinect + Nintendo Wii	Single player exergame aimed to improve body balance. Biofeedback-based balance training	Visual-based Biofeedback training; Balance function	60 min session, 3 times a week, 6 weeks (18 sessions)	Yes	Travers et al. (2018)
ASD	6–10	Kinect Sports Seasons 1 and 2/Xbox Kinect; Kinect Sports Seasons 1 and 2; Sports Rivals and Kinect Adventures/ Xbox Kinect	Single player in-home to improve OC skills and feasibility with play-based active video games	Motor abilities	ADS group 45–60 min session, 3 days a week, 2 weeks (6 sessions). Control group: 50 min once a week, 6 weeks (6 sessions)	Limited	Edwards et al. (2017)
ASD	10–18	DDR/PC	Single player exergame aimed to improve repetitive behavior and cognition physical training	Motor abilities; Executive function	20 min once participants and their own control	Yes	Anderson-Hanley et al. (2011)
DS	3–7	Game JECRIPE/PC	Promote cognitive development of disabled children in the context of inclusive education	Executive function	Not reported	Not evaluable	Brandão et al. (2014)
DS	7–12	Wii bowling, baseball, rhythm boxing; snowboarding/Nintendo Wii	Wii game may elicit improvements in highly practiced motor skills and postural control	Motor abilities	20 min session, 4 sessions per week, 8 weeks	Yes	Berg et al. (2012)

therapeutic interventions are based on the use of multiplayer gaming, providing a combination of avatar and 3D technology (Berg et al., 2012; Wang et al., 2018). These games create a collaborative virtual learning environment widely used more to develop correct social interaction often compromised in children with NDDs. SGs through gamification mechanics and cognitive training, promote behavioral changes and increase user participation and engagement. In particular, SGs-based cognitive training can help in the formation and restructuring of neurobiological pathways especially in children characterized by greater neuroplasticity than adults.

Social robots have been also exploited with success in therapies aimed at improving the quality of life of children with physical/intellectual disabilities by stimulating social, cognitive and physical skills. For example, the socially assistive robot MARIA T-21 is provided with an embedded mini-video projector to display SGs on the floor or walls (Panceri et al., 2022). It is used in therapies for DS children meant to improve their proprioception, postural balance and gait as well as in psychosocial therapies for children with ASD.

4. Emotional, social and behavioral disorders in NDDs: a focus on mild/moderate intellectual disability conditions

SGs are increasingly used in rehabilitation for improving cognitive, emotional and behavioral problems. In this Section we describe neurobehavioral disturbs, focusing on the two pathological conditions for which the use of SGs is prevalently reported, ASD and ADHD. In addition, as also mentioned in Section 3 (Tables 1 and 2), we describe two genetic neurodevelopmental syndromes associated with intellectual disability, DS and FXS, where the possibility to use SGs as digital therapy has been suggested in the scientific literature.

4.1. Autism spectrum disorders

ASD is a neurodevelopmental disorder characterized by persistent deficits in social communication and interaction across multiple contexts, associated with restricted, repetitive patterns of behavior, interest, or activities (American Psychiatric Association, 2013). The etiopathogenesis of ASD, still unknown to date, is oriented towards a multifactorial causality, with a genetic, bioenergetic and environmental substrate, where a great relevance given to gene-environment interactions highlighting the possible role of epigenetics in the onset of these disorders (Panisi et al., 2021). The main characteristics of ASD are impaired social communicative profile, unusual interests and restrictive behavior, difficulties in understanding other people's emotions and intentions, strongly compromising social interaction (Lehnhardt et al., 2013). The clinical pictures of ASD can be widely variable and can be defined based on severity levels, depending on the extent of the functional impairment found in each area.

Individuals with a lower cognitive function and a more severe autistic phenotype often require lifelong extensive support (Cohen et al., 2014). They exhibit a much more complex diagnostic picture with associated comorbidities and can present "serious behavioral disturbances such as tantrums, aggression, environmental destruction, socially inappropriate behavior and self-injurious behavior" (Cohen et al., 2014).

Mild phenotypes of ASD are characterized by deficit in complex problem solving, language, and memory and concept formation tasks. These difficulties lead to problems in building relationships as individuals are not able to respond correctly to social cues especially those related to emotional context and to common social expressions (Kumar, 2013). In these mild phenotypic forms of ASD, due to the better introspective capabilities of these patients, it is common to develop secondary pathologies such as social anxiety, psychosis, tic and depression. (Tebartz van Elst et al., 2013).

4.2. Attention-Deficit Hyperactivity Disorder

ADHD is a persistent neurobiological disorder and is one of the most common neuropsychiatric condition in childhood. According to the manual DSM-5 (American Psychiatric Association, 2013), ADHD is considered a neurodevelopmental disorder rather than a disruptive behavioral disorder.

The diagnosis of ADHD is based on age-inappropriate symptoms of inattention and/or hyperactivity-impulsivity, that impair psychosocial functioning in a range of contexts (including social, academic and occupational settings), affecting perceptions of well-being that can change over time. (Nigg et al., 2010). The onset occurs before 12 years of age, with symptoms present in multiple settings sometimes combined with comorbidities of other NDDs and psychiatric conditions (including communication disorders, intellectual disabilities, sleep disorders, specific learning disabilities, mood disorders, disruptive behavior, anxiety disorders, tic disorders, ASD and substance abuse disorders), that contribute to ADHD heterogeneity aspect and influence treatment planning (Reale et al., 2017).

The results of a complex interaction and involvement of brain structures, neurotransmitters and functions characterize ADHD phenotype. The neurocognitive domains more frequently reported as impaired in individuals with ADHD include, sustained attention, intelligence/achievement, vigilance, working memory, response inhibition, visuospatial and verbal working memory, planning, temporal information processing and timing, speech and language, memory span, processing speed and response time variability, arousal and activation and motor control (Faraone et al., 2015; Pievsky and McGrath, 2018; Luo et al., 2019). No single factor is responsible to cause ADHD, as it is the result of a complex interplay between genetic and environmental risk factors affecting the structural and functional capacity of brain networks (Faraone et al., 2015).

4.3. Down syndrome

DS, or chromosome 21 trisomy, is a genetic disorder caused by the presence of all or part of a third copy of chromosome 21. It is a common chromosomal aneuploidy and a major genetic cause of developmental delay and intellectual disability. Recent studies have shown that emotional, social and behavioral disorders co-occur over the entire lifespan are common in DS (van Gameren-Oosterom et al., 2011; Startin et al., 2020; Rivelli et al., 2022; Esbensen et al., 2022). These problems are related to the age, the gender and the degree of intellectual disability (Naerland et al., 2017; Startin et al., 2020). Behavioral problems are more frequent in males compared to females. Females with DS have better cognitive abilities, speech production and receptive language abilities compared with males (van Gameren-Oosterom et al., 2011; Startin et al., 2020). In children, peer problems are very frequent and are more prevalent in adolescents than in junior school period (Naerland et al., 2017), probably due to a limited repertoire of strategies to cope with frustration, and to a deficit affecting the emotional lexicon and a lack of understanding of emotional verbal labels (Pochon and Declercq, 2014; Pochon et al., 2022). Children with DS have more emotional/behavioral problems and significantly lower gross motor skills, autonomy and social functioning compared with the general population (van Gameren-Oosterom et al., 2011). ASD prevalence rates in DS range from 5% to 42% (Moss et al., 2013; Oxelgren et al., 2017). Autistic behavior is related to cognitive impairment and is most common in individuals with profound intellectual disability (Startin et al., 2020). The prevalence of ADHD among DS children is also very high, ranging from 34% to 43.9% (Naerland et al., 2017; Oxelgren et al., 2017). The premature birth is related to inattentive and hyperactive/impulsive symptoms in children and adolescents with DS (del Hoyo Soriano et al., 2020). ADHD in DS children can be more frequently associated to medical problems such as sleep disorders, disruptive behavior disorder, allergies and seizures, where more attention should be given to plan early interventions.

4.4. Fragile X syndrome

FXS is a neurodevelopmental disorder caused by the full mutation (> 200 CGG repeats) and the consequent aberrant hypermethylation and silencing of the Fragile X messenger ribonucleoprotein 1 (*FMR1)* gene promoter (Santoro et al., 2012). In affected males, FXS is characterized by developmental delay and intellectual disability (mean IQ 40–45) (Sansone et al., 2014) along with a variety of behavioral problems. Among these, ASD is a common comorbidity, present in 50%– 70% of individuals (Kidd et al., 2020). Females heterozygous for the *FMR1* full mutation may be paucisymptomatic or may manifest neurobehavioral problems in milder forms, depending on X-chromosome lyonization (Bartholomay et al., 2019). Behavior is a major issue in all ages. Behavioral problems beyond ASD-associated symptoms include anxiety, hyperactivity, impulse control deficit, distractibility, perseverative speech, irritability, aggression, and self-injurious. Anxiety and irritable/aggressive behavior may increase during or after puberty. Anxiety is very disabling in FXS; the symptom may be generalized or related to performance or separation stress. Social phobia or other specific phobias are common as well (Weber et al., 2019). No specific treatment is available for FXS. Depending on the severity of the behavioral phenotype, patients are so far treated with supportive approaches associated sometime with pharmacological treatments. Current therapies include behavioral intervention, speech therapy, occupational therapy, and individualized educational support. Augmentative and alternative communication may aid if speech is severely impaired (Schladant and Dowling, 2020). Technological devices in this field take advantage of both low-tech or high-tech categories, including voice-generating tools. The stimulation of sensorimotor abilities and of social interplay, the achievement of independence in daily life skills, computer skills, money management are among treatment goals (Jalnapurkar et al., 2019). Language is also affected in FXS. To improve this area, shared storytelling (Nelson et al., 2018) and music therapy have been shown to be beneficial to enhance communication skills and reduce anxiety (Haessler et al., 2016). Finally, physical activity has been greatly recommended to improve attention and cognitive control (Gitimoghaddam et al., 2021).

5. Serious games targeting some NDDs symptoms: clinical trials and meta-data analysis

As discussed above, SGs could be potentially effective as DTs for neurodevelopmental disorders where some of them have prompted clinical trials in particular among ASD population. However, a very recent meta-data analysis reported that general technology is promising for NDD population but with high risk of bias (Oliveira Ribas et al., 2023). In addition, some other meta-data analyzes of studies dealing with SGs have reached discordant conclusion about their translational impact or clinical efficacy. Herein, we will present and critically discuss the effects of particular SGs on cognitive, adaptive behavior, motor-visual and social-emotional skills as reported in clinical trials and meta-data analysis studies in children and adolescent with NDDs-linked disturbs. Notably, the evaluation of SGs therapeutic potential through randomized clinical trials occurred almost exclusively in children with ADHD and ASD (Table 3). This presumes that SGs as digital therapy for neurobehavioral disturbs in NDDs is yet a research field mostly unexplored.

5.1. Effects on cognitive and adaptive behavior skills

As described in the Chapter 4, children with NDDs often experience serious limitations of their adaptive skills often associated with impaired cognitive capabilities (Schalock et al., 2021). Adaptive behavior skills can be separated into three domains: conceptual adaptive skills (e.g., functional skills, such as reading and writing), social adaptive skills (e.g., social problem-solving skills), and practical adaptive skills (e.g., personal health care and self-safety, home and school living) (Oakland and Harrison, 2008). In this context, effective intervention programs are needed to support children with ID in improving their adaptive and cognitive skills and in strengthening their daily functioning and social participation (Delavarian et al., 2015). Certainly, the role of professional educators is fundamental in defining personalized goals and applying the appropriate teaching methods, where SGs could be useful tools in the rehabilitation programs. Viewed this way, an important aspect is the demonstration of their real effectiveness.

Table 3
Randomized controlled trials using Serious Games as Digital Therapeutics for children and adolescents with neurodevelopmental diseases. The randomized controlled trials using SGs involving children and adolescents with NDDs are listed. Studies are selected as reported the Method section. In bracket the trial identification number, where present. NR, not reported.

NDDs	Age (years)	Participants number	Name of SG	Procedure	Outcomes	Type of measurement	Results	Study Reference
ADHD	8–12	180 patients 168 controls	AKL-T01 STARS-ADHD software ClinicalTrials.gov, NCT02674633	25 min session per day; 5 days per week; length: 4 weeks	Attention	Test of Variables of Attention; Attention Performance Index	Improve objectively measured inattention in ADHD; mild adverse events (frustration and headache in 2–3% of children).	Kollins et al. (2020)
ADHD	8–15	28 patients	RECOGNeyes	3 times per week session; time per session NR; length: 3 weeks	Cognitive; Visual attention	ADHD, severity, impulsivity index, dyslexia, index, performance, enjoyability	Improvement in impulsivity, reaction time and visual attention system	García-Baos et al. (2019)
ADHD	8–12	170 patients	Plan-it Commander (International Standard Randomized Controlled Trial Number: 62056259)	19 guided sessions, 11 days in the closed social community; 10-weeks post-treatment follow-up	Cognitive; Adaptive	Parent, teacher and self-reports, management behavior questionnaire	Positive effect on time management and social skills	Bul et al. (2016)
ADHD	7–11	104 patients	Neurofeedback	6-months post-treatment follow-up after 40 sessions	Emotional; Attention; Cognitive	Conners 3-Parent Assessment Report, the Behavior Rating Inventory of Executive Function Parent Form	Improvements in ADHD symptoms, which were sustained at the 6-month follow-up	Steiner et al. (2014)
ASD	6–12	25 patients	Comprehensive Attention Training System, CATS	50 min per session; length: 8 sessions	Executive functions (cognitive)	Wisconsin Card Sorting Task; Trial-Making Test	Improvement of executive functions and contribute to long-term communication skills	Chen et al. (2020)
ASD	10–12	19 patients 28 control	It's Me	10–15 min session at school; behaviour scored at different times; different phases organization	Social functions	Ad hoc created questionnaire	easy to use; potential in stimulate personal conversations among children.	Terlouw et al. (2020)
ASD	8–12	42 patients	BRAVE, NET	60 min per session; 10 sessions; length: 10 weeks	Emotion; Anxiety	Spence Children's Anxiety Scale (SCAS; PROM)	Reduction in number of self and parent reported anxiety symptoms, increase in overall functioning	Conaughton et al. (2017)
ASD	6–9	36 Sweden patients 38 Israel patients	Emotiplay	Minutes per session: NR; Number of sessions: NR; Length: 8 weeks	Emotion; Cognition; Understanding	Emotion recognition task; Adaptive Behavior Scales (VABS-II)	Improvement recognition of emotion in all modalities	Fridenson-Hayo et al. (2017)
ASD	8–12	121 patients	Braingame Brian	40 min per session; 25 sessions; length: 6 weeks	Executive functions; Adaptive; Cognitive	The Behavior Rating Inventory of Executive Function	Improvement in cognitive flexibility, attention, but not in inhibition	De Vries et al. (2015)

(continued on next page)

Table 3 (*continued*)

ASD	6–15	49 patients	FaceSay	10–25 min per session; 12 sessions; length: 6 weeks	Emotion; Facial recognition	Photographs and schematic drawings Benton Facial Recognition Test	Improvements in facial recognition, emotion recognition, and social interactions.	Hopkins et al. (2011)
ASD	7–15	42 patients 37 controls	Let's Face It!, LFI!	Minutes per session NR; number of sessions NR; length: 20 h	Facial identity; Social emotion	The Let's Face It! (LFI!) SkillsBattery	Improvement of recognition of mouth features and face recognition skills	Tanaka et al. (2010)
DS	18–29 *Cognitive age 6–8*	6 patients	TANGO:H	20 min per session; 1 session per week; length: 4 weeks	Cognitive; Visual-motor	"Illinois Test of Psycholinguistic Abilities (ITPA)	Results from observation: improvement in visual-motor cognitive skills; statistical analysis: not significant differences	Torres-Carrión et al. (2019)
DS and other ID	4–11	76 patients	Training Attention and Learning Initiative, TALI (Australian New Zealand Clinical TrialsRegistry ACTRN12613001180707)	20 min per session; 5 sessions per week; length: 5 weeks	Cognitive; Attention	Wilding Attention battery (WATT); Normal behaviour scale (SWAN)	Improvement in selective attention, not effective in attentional control	Kirk et al. (2016)

Many meta-analyzes studies have examined the efficacy of SGs in broader contexts, such as their effect on symptoms related to mental health (Lau et al., 2017; David et al., 2020; Dewhirst et al., 2022) and on the knowledge improvement and self-management of young people with chronic diseases (Charlier et al., 2016) highlighting their usefulness in term of feasibility and acceptability in specific chronic conditions (Malizia et al., 2021; Ferrante et al., 2021). These analyzes showed modest effects of SGs on the enhancement of various skills in users of different ages and target groups. A meta-analysis study analyzing virtual reality, augmented reality and mixed reality studies, showed promising results of SGs compared to traditional interventions for improving cognitive abilities (Rosa et al., 2016), indicating the potentiality of these games to train and transfer such complex skills into daily life in various contexts.

Tsikinas and Xinogalos (2019) reviewed the literature focusing on the effects of SGs on young and adults with cognitive disability or ASD, reaching a conclusion of a possible efficacy in improving adaptive skills. Although this review reported many knowledges about SGs for adaptive skills, not all the evaluated studies follow a randomized controlled trials schema or report efficacy data. For these reasons, the effectiveness of the games still represents a knowledge gap that needs to be filled due to the lack of a solid assessment based on clinical trials data.

In a recent observational study, the efficacy of Intelligent Serious Games (ISGs) for children with learning difficulties was evaluated (Flogie et al., 2020). The aim of the study was to produce and assess a series of ISGs based on accessible learning objectives to improve key cognitive skills, such as personal development and work sustainability. The survey confirmed a substantial improvement in all observed aspects.

Specifically for individuals with DS, Brandão and colleagues developed a game called JECRIPE for children in pre-scholar age (Brandão et al., 2014) and Kirk et al. (2016), in a double blind randomized controlled trial including children with DS, showed an enhancement of selective attention after a computerized specific attention training program delivered on a touch screen tablet.

In their recent study, Derks and colleagues provided a meta-analysis on data from several trials evaluating the effectiveness of SGs in improving adaptive and cognitive abilities in the pediatric population with NDDs (Derks et al., 2022). Their results, supplemented by an updated data of literature reviews and meta-analyzes, clearly emphasize the efficacy of SGs for this specific target group of children and the importance of early interventions for children with intellectual disabilities and ASD (Fuller and Kaiser, 2020) highlighting a new developmental psychology perspective.

There is evidence that children with ADHD may also benefit from SGs, in particular to improve working memory (Bul et al., 2015; Dovis et al., 2015; Bul et al., 2016), attention span (Avila-Pesantez et al., 2018), visuospatial short-term-memory along with inhibitory performance and interference control (Dovis et al., 2015). Interestingly, girls are more likely to improve hyperactivity symptoms than boys (Bul et al., 2018). A recent randomized, double-blind, parallel-group, controlled trial of pediatric ADHD patients showed a global attentive improvement (Kollins at al, 2020)).

5.2. *Effects on motor and visual-motor skills*

In children with NDDs, the deficit in visual-motor coordination (i.e., coordinating limb movements with visual stimuli) can compromise the ability to perform daily activities (e.g., getting dressed, playing sports), the independence and the overall life satisfaction (Kim et al., 2016). In these circumstances, practicing physical exercises can help to improve limb movements, although they can be boring in the long run.

Recently, several studies have shown that the use of virtual and computational technologies as playful tools, can be successfully employed to stimulate, through the visual field, global motor skills, body scheme and spatial organization, making therapeutic exercises more fun and enjoyable (Boato et al., 2022). In this context the SGs are also called exergames, which are based on a technology that also requires the movement of the body or in any case a physical reaction (Alba-Rueda et al., 2022) (see chapter 3.3 for insight).

Due to the great variability of NDDs, the range of motor skills can extremely vary from one individual to another. For this reason, exergames include mechanisms of adaptability in order to tailor the game according to each individual need (Raygoza-Romero et al., 2021). Some platforms provide the user with a personalized learning experience based on the historical data of the user's interaction, recommending exercise levels (games), types of resources, and activities (Torres-Carrión et al., 2019).

The contribution of technology through exergames and SGs in general in improving the visual-motor skills of children with developmental disabilities, is widely reviewed (Kokol et al., 2020; Raygoza-Romero et al., 2021). Two studies on DS individuals are particularly interesting as they tried to validate the level of improvement in visual-motor abilities and consequently cognitive skills following the use of virtual games. In the first pilot study involving 6 adolescents with DS, a gestural interaction platform, called TANGO:H has been developed. It has been used to design both teaching and physical exercises as well as cognitive training activities using a kinetic sensor (Torres-Carrión et al., 2019). In the other exploratory study, by means of a DS children's evaluation survey of some SGs, clear correlation was confirmed between the "players′performance" and the "demonstration of interest" variables suggesting that SGs should be fun and easy to play in order to reach child's expected performance (Pelosi et al., 2019).

These studies have incentivized the use of SGs for young people with developmental disabilities, however, our opinion is that the importance of these tools for improving some NDDs symptoms are still underestimated and need further and deeper investigations.

5.3. Effects on social-emotional skills

Social and emotional skills are a broad range of flexible abilities that enable individuals in regulating their own thoughts and perception, managing emotions, interpersonal emotion regulation and intrapersonal social interactions, thus influencing a number of personal and social outcomes (Schleicher, 2022). Therefore, building emotional regulation/recognition abilities has been the goal of several types of SGs, first developed for healthy children and adolescents, with the effort to set protocols able to evaluate their effectiveness in targeting interpersonal emotions (Mittmann et al., 2021). A good example of SG targeting emotional skills is REThink, a therapeutic game aimed to increase resilience in a Rational Emotive Behavioral Therapy framework for healthy young population (David et al., 2019a). A randomized pilot clinical trial study involving REThink in children and adolescents of the general population has demonstrated how scores of different game levels (focusing on different skills) are differently associated with improvements in mental health, emotion regulation abilities and psychological functioning (David et al., 2019b; David et al., 2022).

On these bases, in recent years it has been developed a series of social-emotional computer games for individuals with developmental disabilities including ASD, DS, Cerebral palsy or Fetal alcohol spectrum with the aim to assess the benefit of SGs application in managing emotional-social skills (Fridenson-Hayo et al., 2017; Grossard et al., 2017; Kokol et al., 2020; Terlouw et al., 2020; Terlouw et al., 2021). Accordingly, Terlouw et al. (2021) developed an escape room, as activity-based experience, to initiate social interaction and communication between children with ASD and their normal peers. The same authors have previously designed a digital comic creator serious game, named "It's Me", to facilitate social skills training for ASD children reporting its potential to stimulate the starting of personal conversations among children (Terlouw et al., 2020). Additional meta-data analyzes reveal that most of the studies were conducted on ASD patients, who presented alterations in emotion recognition and regulation as hallmarks (Bal et al., 2010; Mazefsky et al., 2013); the analyses however conclude that, although there are promising results regarding the potential reduction of anxiety, stress regulation, and emotion recognition, the clinical evidence of SG specific treatment for these children appears to be unclear and requires additional investigations (Kokol et al., 2020).

Grossard et al. (2017) performed a literature screening on a total of 626 data sets collecting SGs data coming from teaching social interactions and focusing on individuals with ASD. This analysis employs a variety of design approaches to target emotion recognition skills, ranging from those very simplistic using photographs and videos of emotions (Russo-Ponsaran et al., 2016) to others with more sophisticated gamification techniques including the elaboration of virtual environments or narratives (Serret et al., 2014). In this study, the authors also conclude that SGs seem promising in training social skills, despite the limitations in terms of the methodology used to demonstrate their clinical benefits such as the absence of large samples, control groups, randomized trials, longer treatment periods, and follow-up assessment of changes stability (Grossard et al., 2017).

Deeper aspects have been examined very recently in a multicenter randomized controlled trial designed to investigate emotional skill maintenance and their transfer to functional behavior in children with ASD by using a parent-assisted SG named Zirkus Empathico (ZE) (Kirst et al., 2022). This study finally demonstrated with a rigorous scientific methodology, the clinical efficacy of a non-pharmacological training therapy in improving emotional awareness and emotion regulation with a consequent mitigation of the general autism symptomatology. Given the generally high acceptance, feasibility, treatment satisfaction of serious game effects, this clinical study gave the cue to the real application of Zirkus Empathico-like SG technology for a possible autism therapeutic intervention. In this line and given the obtained results by another randomized controlled trial for ADHD (Kollins et al., 2020), Nature Biotechnology launched the news of a SG developed by Akili Interactive Labs, as the first digital game-based therapeutic for ADHD approved by the Food and Drug Administration (FDA) (Waltz, 2020).

Interesting Tang et al. (2019b) reported the perspective of the SGs utilization from two different point of view, i.e. from the users (young adolescents with ASD) and professionists (experts on pedagogical concepts). While for users it is very important to have a "motivating storyline", for professionists the emphasis should be focused on "goal directed learning" and on "generalization of skills to everyday contexts" (Tang et al., 2019b). These differences underline the importance of a coordinated work among clinicians, technology engineers, pedagogics, parents as well as key stakeholders in designing the SG in order to obtain major clinical efficacy on social emotional difficulties.

6. Concluding remarks

This review aims to critically report, with a narrative style, the current trends regarding SGs as new digital-health therapeutic options for neurodevelopmental disabilities. The review can help clinicians, therapists and caregivers as well as researchers to plan their strategies in the care and the study on children with NDDs. In what follows, our remarks and indications are summarized (Fig. 4).

Despite the promising data, the clinical research in the field of digital therapeutic interventions is actually at an early stage. For instance, in NDDs, randomized clinical trials have been addressed only to selected neurodevelopmental disorder populations such as ASD and ADHD (Table 3). Likewise, clinical research trials should also be expanded to various NDDs in particular to those diseases for which the use of SGs is recommended, such as DS and FXS where very few clinical studies have been published.

Further, the effectiveness of SGs is actually underestimated for NDDs and could be potentiated, for instance, by integrating typical characteristic therapeutic elements of cognitive-behavioral therapies. On the other hand, SGs development is still encountering many obstacles due to the high demanding cost, low commercial interests and the lack of important elements such as the fun and motivation (Wang et al., 2022). For that, the SGs design process requires multidisciplinary teamwork including not only game developers, but also researchers, patients and their families, policy makers and publishers (Baranowski et al., 2016).

A crucial point to be considered in the international debate around the raising field of SGs and HMC is the complexity of the phenomenon, its opportunities, and its multi-disciplinary implications. Actually, the limitation of regulation, still failing to protect fragile children's sensitive in-game and off-game data thoroughly, is a rising concern and a challenge in contemporary HMC debate.

In addition, as suggested by recent studies, SGs can be used not only for treatment purpose, but also as a potential screening tool for

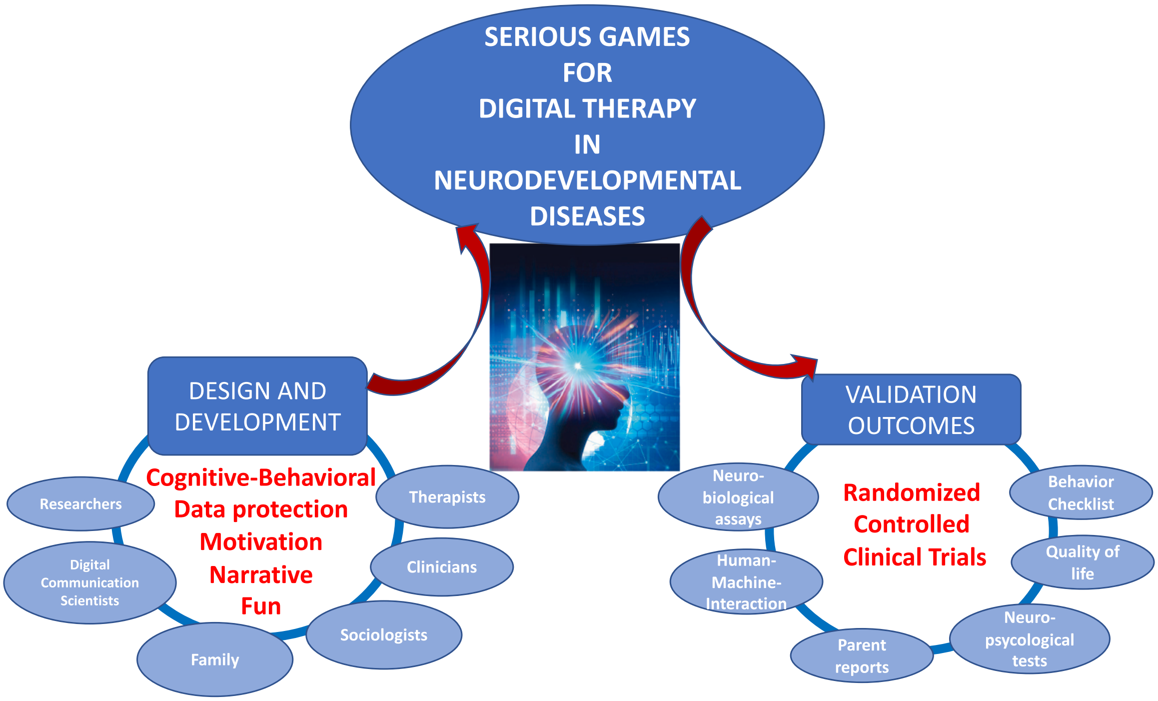

Fig. 4. Elements for designing and validation of a Serious Game in a Digital Therapeutics perspective.

developmental disabilities. For instance, they can be used in detecting and differentiating children with heterogeneous developmental disabilities through different scores in the game-derived index or in applying specific machine learning algorithms (Bang et al., 2019; Oliveira Ribas et al., 2023).

Finally, the progressively increase of SGs use in mental health care makes it necessary to investigate the neurobiological mode of action on the brain. The impact of SG-derived psychosocial and well-being experiences on specific neurobiological pathways or on gene expression regulating neurobiological pathways are aspects that should be assessed as specific outcomes in clinical trials in order to give unbiased and correct biological validation of SGs for therapeutic purposes.

Paradigms regarding people with behavioral problems and intellectual disability have fortunately been gradually changed during the last decades. According with the WHO guidelines (WHO, 2021), the social approach has been moved from the only consideration of these persons' limitations with the consequent social segregation, toward a social citizenship that overcomes social barriers and hindrance aimed to help boost and promote their capabilities. This occurs through long and challenging social inclusion and integration paths involving families, institutions, trainers and clinicians. In this context, the development of digital therapeutic strategies, including SGs, for the management of some NDDs symptoms, is an opportunity to empower cognitive, emotional and relational skills of these young patients and their consequent social inclusion.

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Declaration of interests

The authors declare that they have no conflict of interest.

Data Availability

No data was used for the research described in the article.

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