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Technologies to support the diagnosis and/or treatment of neurodevelopmental disorders: A systematic review☆

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ABSTRACT

In recent years, there has been a great interest in utilizing technology in mental health research. The rapid technological development has encouraged researchers to apply technology as a part of a diagnostic process or treatment of Neurodevelopmental Disorders (NDDs). With the large number of studies being published comes an urgent need to inform clinicians and researchers about the latest advances in this field. Here, we methodically explore and summarize findings from studies published between August 2019 and February 2022. A search strategy led to the identification of 4108 records from PubMed and APA PsycInfo databases. 221 quantitative studies were included, covering a wide range of technologies used for diagnosis and/or treatment of NDDs, with the biggest focus on Autism Spectrum Disorder (ASD). The most popular technologies included machine learning, functional magnetic resonance imaging, electroencephalogram, magnetic resonance imaging, and neurofeedback. The results of the review indicate that technology-based diagnosis and intervention for NDD population is promising. However, given a high risk of bias of many studies, more high-quality research is needed.

1. Introduction

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association, 2013), Neurodevelopmental Disorders (NDDs) are a group of conditions with an early onset, characterized by various deficits that impair one's functioning in the personal, academic, social, or occupational area. Within recent years, NDDs became one of the most common diagnoses in the pediatric population (Trauner, 2019), among which, the most frequently diagnosed are learning disabilities, with a prevalence of approximately 8 % (Boat and Wu, 2015), developmental language disorders (7 %) (Laasonen, 2018), Autism Spectrum Disorder (ASD, 2 %) (Baio, 2018; Xu, 2018; Schendel and Thorsteinsson, 2018), and Attention-Deficit Hyperactivity Disorder (ADHD, 2 %) (Boat and Wu, 2015; Willcutt, 2012). The diagnosis itself can be challenging, as various co-morbidities are less of an exception and more of a rule within the NDD population (Yeargin-Allsopp, 2008; Uddin et al., 2019). Another challenge is a certain degree of phenotypic overlap between different disorders, as well as a great variability of symptoms and functioning levels across individuals with the same diagnosis (Wall, 2012; Coe et al). Early detection of NDDs is of great importance as it allows fast intervention that improves children's prognosis and maximizes treatment outcomes (Wu, 2019) due to high neuroplasticity in the first years of human life (Ismail et al., 2017). However, patients referred for an NDD assessment often experience major delays in receiving a diagnosis. According to a recently published study (Hollis, 2018), 40 % of families referred for an ADHD assessment were still awaiting a diagnosis six-months after the initial visit. Also, research conducted in Canada (Penner et al., 2018) indicated that the median total waiting time from referral to receipt of ASD diagnosis is 7 months. Moreover, once diagnosed, the families often deal with substantial delays in treatment initiation and a lack of satisfactory treatment monitoring (Hall, 2016). For instance, only 20 % of young people with Tourette Syndrome have access to behavioral tic therapy and those who do receive it, typically get to attend less than half of the recommended number of sessions (Cuenca, 2015; Verdellen, 2004). One of the reasons for this situation is a lack of trained therapists, especially in

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geographically remote regions (Hollis, 2017), as well as insufficient clinical time that would allow delivering best care practices (Hall, 2016). Therefore, the importance of identifying time-effective and easy-to-access strategies for both diagnosis and treatment of NDDs is clear.

Technology has the potential to improve the availability of early screening, as well as later treatment. The number of technological interventions targeting NDDs has been growing exponentially (Valentine, 2020). For instance, there has been a lot of interest in supporting ASD diagnosis using machine learning technology (Baygin, 2021; Bajestani, 2019; Caly, 2021; Cavallo, 2021). Across the literature, it is applied to different types of data such as neuroimaging data, eye movement data, kinematic data, audio samples, or standardized assessments (e.g., Autism Diagnostic Interview, Revised (Rutter et al., 2003) or the Social Responsiveness Scale (Constantino and Gruber, 2012) (Hyde, 2019). In the last case, the researchers often seek to improve the accuracy of standard tests, given that they sometimes fail to distinguish one condition from another (Hyde, 2019). Growth in volume and variety of available data can be observed largely due to the affordability of instruments and infrastructure used to collect it but also thanks to the trend of sharing it between scientists and clinicians all over the world. One example of such an initiative is the widely used Autism Brain Imaging Data Exchange (ABIDE) dataset (http://fcon_1000.projects.nitrc.org/indi/abide/) (Di Martino, 2014) that includes resting-state functional magnetic resonance imaging (rs-fMRI) data along with corresponding structural MRI and phenotypic information of ASD and neurotypical participants. Another example is the ADHD-200 repository (Bellec, 2017) which contains the same type of neuroimaging data but acquired from ADHD and typically developing (TD) subjects. On top of that, the availability of many open-source machine learning toolkits in combination with rise in computational power and processing technologies create opportunities for researchers to utilize machine learning in diagnostic processes (Hyde, 2019).

The term 'technology' encompasses a broad range of devices, modalities, and techniques: virtual reality, eye-tracking, wearable technology, mobile apps/tablets, different forms of medical imaging, neurofeedback, biofeedback, robots, transcranial magnetic stimulation, electroencephalogram (EEG), mixed reality, serious games, and others. Recently published systematic review conducted by Valentine and colleagues (Valentine, 2020) explored clinical efficacy, service efficiencies, economic and user impact, as well as readiness for clinic adoption of technologies used to assess, monitor, and treat NDDs. The authors explored studies published until August 2019 and excluded technologies related to neuroimaging, neuro-stimulation/modulation/feedback/training, or biomarker tests/devices. In our work we did not exclude these technologies in order to have a full picture of the current trends. Moreover, in order to not overlap with the mentioned review, and to give an overview of the most updated technologies, we decided to start our search period from August 2019. Although it might seem like a short time to be covered in a systematic review, given the recent rapid growth of technology-related publications and technological development per se, covering nearly 3 years of research can be arguably more meaningful than synthesizing evidence from a very long period of time. There is an urgent need to update clinicians, therapists, and professionals in general, on the latest advances regarding the use of technology in NDD diagnosis/treatment and summarizing the recent findings can provide them with a clearer view of what has been achieved so far. Additionally, it will support researchers in making decisions regarding their future study directions. Recent systematic reviews focused mostly on the use of specific technologies applied to a specific disorder only, e.g., serious games for people with intellectual disability (Terras, 2018), social robots in ASD therapy (Pennisi, 2016), or the use of neurofeedback in ADHD (Van Doren, 2019). Given the great interest in utilizing technology in mental health research that has been observed within recent years, the aim of this review is to analyze and organize the newest trends in technology application for diagnosis and treatment of NDDs. The present work synthesizes existing quantitative research and methodically explores the current state of evidence in this area.

2. Methods

2.1. Search strategy and inclusion/exclusion criteria

The review has been elaborated following The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (Page, 2021). The review protocol was registered and can be accessed through PROSPERO (CRD42020160939). The search was carried out in PubMed and APA PsycInfo databases. The structure of our search strategy was based on Population, Intervention, Comparison, and Outcomes (PICO) domains (Table 1). It was then developed using Medical

Table 1
Search strategy based on Population, Intervention, Comparison, and Outcomes (PICO) for PubMed.

Domain	Search strategy
Population	„Neurodevelopmental Disorders"[Mesh] OR „Neurodevelopmental disorder" OR „Developmental disorder" OR "developmental delay" OR "developmental delays" OR "developmental difficulty" OR "developmental difficulties" OR "Pervasive development" OR „pervasive developmental disorder" OR "Pervasive disorders" OR "Child Development Disorders, Pervasive"[Mesh] OR „PDD" OR "Global Developmental Delay" OR "Attention Deficit and Disruptive Behavior Disorders"[Mesh] OR "Attention Deficit Disorder with Hyperactivity"[Mesh] OR „ADHD" OR „Hyperkinesis" [Mesh] OR "Autism Spectrum Disorder"[Mesh] OR "Asperger Syndrome"[Mesh] OR "Autistic Disorder"[Mesh] OR „Autis* " OR „ASD" OR „Asperger" OR "Communication Disorders"[Mesh] OR "Childhood-Onset Fluency Disorder"[Mesh] OR "Social Communication Disorder"[Mesh] OR "Speech Sound Disorder"[Mesh] OR "language disorders"[Mesh] OR "Developmental Disabilities"[Mesh] OR "Intellectual Disability"[Mesh] OR „Mentally Disabled Persons" [Mesh] OR "Specific Learning Disorder"[Mesh] OR "Learning Disabilities"[Mesh] OR "learning disorders" OR "Dyscalculia"[Mesh] OR "Dyslexia"[Mesh] OR "Dyslexia, Acquired"[Mesh] OR „Specific reading disorder" OR „Disorder of written expression" OR „Mathematics disorder" OR "Motor Skills Disorders"[Mesh] OR "Stereotypic Movement Disorder"[Mesh] OR "Tic Disorders"[Mesh] OR "Tourette Syndrome"[Mesh] OR "Neurodevelopmental motor disorder" OR "Developmental Coordination Disorder" OR „Rett Syndrome" [Mesh] OR „Speech articulation disorder" OR „phonological disorder" OR "language development disorders" [Mesh] OR "Receptive language disorders" OR "Receptive language disorder" OR "stuttering"[Mesh] OR „stammering" OR „cluttering" OR "speech disorders"[Mesh]
Intervention	"technology" [Mesh] OR "evoked potentials" [Mesh] OR "magnetoencephalography" [Mesh] OR "diffusion tensor imaging" [Mesh] OR "positron-emission tomography"[Mesh] OR "tomography, emission-computed, single-photon" [Mesh] OR "spectroscopy, near-infrared" [Mesh] OR "transcranial magnetic stimulation" [Mesh] OR "robotics"[Mesh] OR "Electroencephalography" [Mesh] OR "eye movements" [Mesh] OR "eye movement measurements"[Mesh] OR "eye tracker" OR "eye tracking" OR "eye-tracker" OR "eye-tracking" OR "wearable electronic devices"[Mesh] OR "galvanic skin response" [Mesh] OR „sensor" OR "magnetic resonance imaging" [Mesh] OR "Neurofeedback" [Mesh] OR "Artificial Intelligence"[Mesh] OR "Diffusion Magnetic Resonance Imaging" [Mesh] OR "wireless technology" [Mesh] OR "remote sensing technology" [Mesh] OR "biomedical technology" [Mesh] OR "Technology Assessment, Biomedical" [Mesh] OR „Machine Learning" [Mesh] OR „Deep Learning" [Mesh] OR „Neural Networks, Computer" [Mesh] OR „Computational Intelligence" OR „Inventions" [Mesh] OR „Telemedicine" [Mesh] OR „eHealth" OR „mHealth" OR „telehealth" OR „mobile applications" [Mesh] OR „Video Games" [Mesh] OR „Videoconferencing" [Mesh] OR „fitness trackers" [Mesh] OR „real-time monitoring device" OR „Virtual Reality" [Mesh] OR „augmented reality" [Mesh] OR „interactive multimedia" OR „interactive software" OR „digital media" OR „software" [Mesh] OR „interactive technolog* " OR „wearable technolog* " OR „mHealth technolog* " OR "mobile technolog* " or "sensor technolog* "
Comparison	Not applicable
Outcome	Not applicable

Subject Headings (MeSH) terms to properly detect the available literature on the topic. We decided to not focus only on devices per se but on any technological support for diagnosis/treatment that could potentially improve the current methods, therefore the Intervention section also includes terms related to machine learning and artificial intelligence. The PubMed search was limited to humans. In APA PsycInfo, we also chose to search for correlated and equivalent terms. There was no language restriction. We performed a systematic search strategy of articles indexed from August 2019 to February 2022. We chose to start our search in August 2019 because the latest systematic review on the field ended its search strategy in that period (Valentine, 2020).

Inclusion criteria: 1) studies involving human subjects, 2) using at least one of the technologies reported under Intervention in Table 1 (in addition to technologies considered by Valentine and colleagues (Valentine, 2020), the Intervention domain in Table 1 includes other most commonly used types of technologies identified through a preliminary search in PubMed), 3) including participants with at least one of the NDDs described in Table 1, and 4) focusing on treatment and/or diagnosis (in order to identify technologies potentially applicable in clinical practice). Moreover, to test the direct use of technology within the population of interest, technology had to be used directly on the individuals with NDDs and not e.g., on subjects' parents, practitioners etc.

Exclusion criteria: editorials, comments, surveys, theses dissertations, case studies, case series, animal studies, studies including participants without NDDs and analyzing them together with those with an NDD diagnosis (in order to avoid confounders), or focusing on genetic data, or biological samples such as fecal or blood samples (to avoid excessive heterogeneity of the included studies).

2.2. Study selection process

The works retrieved using the search strategy were imported into Rayyan (Ouzzani, 2016), which is a web and mobile application that supports conducting systematic reviews and collaborating with other authors. The process of identification, screening, and inclusion of studies is presented in the PRISMA Flow Diagram (Fig. 1; (Page, 2021). One author (MOR) removed the duplicates, and two independent authors (MOR and MM, or AC) checked the records for eligibility, first by screening the abstracts and then making their final decisions by reading the full articles. In case of any conflicts between the two authors regarding the inclusion/exclusion of a certain study, a third author was consulted.

2.3. Risk of bias/quality assessment

For the risk of bias/quality assessment evaluation, various tools, depending on the study design, were used. For the case-control and cohort studies the appropriate tools from Newcastle – Ottawa Quality Assessment Scale (NOS) were chosen (Wells, 2017). The maximum number of points for both types of studies is 9, and higher scores indicate higher quality. The included randomized controlled trials (RCTs) were evaluated with the revised Cochrane risk of bias tools for parallel-group trials (Yang et al., 2017) or crossover trials, accordingly (Wu et al., 2017). The tool is divided into 5 or 6 domains, depending on the study design, such as, for instance, *Bias arising from the randomisation process*, *Risk of bias arising from period and carryover effects in a crossover trial*, or *Bias due to deviations from intended intervention.* Each domain includes a few questions that can be answered with Yes, Probably Yes, No, Probably no, No information, or Not applicable. The quality of the before-after (pre-post) studies with no control group was assessed using The National Institutes of Health (NIH) quality assessment tool (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools). As suggested in (Ma, 2020) for controlled before-and-after study, The Effective Practice and Organisation of Care (EPOC) Risk of Bias Tool for randomized trials (https://epoc.cochrane.org/resources/epoc-resources-review-authors) was used, scoring the first two items: "random sequence generation" and "allocation concealment" as "higher risk".

2.4. Data extraction

The extracted information for each study included: title, author, year of publication, country, funding source, conflicts of interest, type of the study design, description of the target population (number of

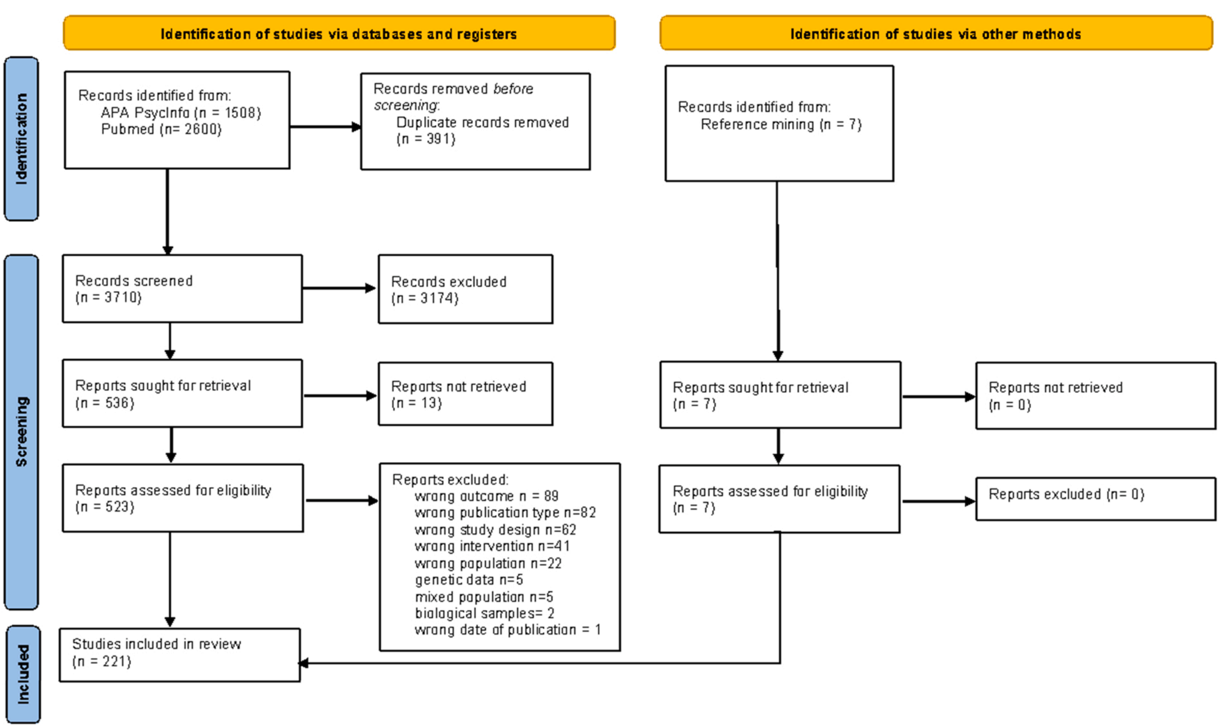

Fig. 1. PRISMA 2020 Flow Diagram (Page, 2021) presenting study screening and selection process.

participants, gender, age, and type of NDD diagnosis), tool(s) for the NDD assessment, inclusion/exclusion criteria of the target population, technology used for diagnosis and/or intervention, its operator, and where it was applied (e.g., home, laboratory), targeted (bio)marker/ symptoms, and outcomes. Full information can be seen in the Supplementary material I. Due to the large heterogeneity of the included studies, not only in terms of wide range of NDDs and used technologies but also study design, age and gender of the population, outcome measures, and follow-up periods, it was not possible to conduct a meta-analysis. Therefore, we chose to synthesize the studies narratively.

3. Results

Between August 2019 and February 2022, 4108 studies were identified through the database search. Additional 7 records were selected for screening by reference mining. After removing the duplicates, 3717 remaining records were checked for eligibility by two independent authors (first through abstract screening, and then by reading 543 full articles). Finally, 221 studies were included.

The included research was conducted in 42 different countries. The biggest number of articles come from the USA (22.6 %), followed by China (19.5 %), Italy (5.9 %), Spain (4.5 %), Iran, and India (both 4.1 %). The number of publications per country is presented in Fig. S1, in the Supplementary material II.

In 23.1 % of publications (n = 51) the number of female/male participants was not specified. Only 10.4 % of the studies (n = 23) enrolled at least 50 % of female subjects. Moreover, 6.3 % of studies (n = 14) were conducted on entirely male sample.

In 66.1 % of studies (n = 146), the authors declared no known competing interests, 18.6 % (n = 41) of publications did not include any information in this regard, and 15.4 % (n = 34) disclosed certain conflicts of interest.

More studies (68.8 %) used technology for diagnosis rather than treatment of NDDs. The vast majority of articles (61.1 %) focused on ASD (Baygin, 2021; Bajestani, 2019; Caly, 2021; Cavallo, 2021; Abdulhay et al., 2022; Alcañiz, 2022; Al-Hiyali, 2021; Alvarez-Jimenez, 2020; Amat, 2021; Ameis, 2020; An, 2021; Antão, 2020; Ardulov, 2021; Asgari et al., 2021; Bakheet and Maharatna, 2021; Beaumont, 2021; Brittenham, 2022; Carpenter, 2021; Casanova, 2021; Chen, 2021; Chen, 2021; Cibrian, 2020; Crimi, 2021; Crowell, 2020; De Luca, 2021; de Moraes and A.P, 2020; Direito, 2021; Eill, 2019; ElNakieb, 2021; Emanuele, 2021; Frasch, 2021; Fu, 2021; Fujino, 2021; Gabard-Durnam, 2019; Ganesh et al., 2021; Gao, 2021; Gepner, 2022; Germann, 2021; Ghosh and Guha, 2021; Górriz, 2019; Graa and Rekik, 2019; Grossi, 2019; Grossi et al., 2021; Gui, 2021; Gürbüz and Rekik, 2021; Haweel, 2021; Haweel, 2021; He, 2021; Hu, 2021; Huang, 2020; Huberty, 2021; Ingalhalikar, 2021; Jensen, 2021; Jiang, 2020; Jiang, 2020; Kang, 2019; Kang, 2021; Kashef, 2022; Khozaei, 2020; Khullar et al., 2021; Kim, 2022; Kojovic, 2021; Konicar, 2021; Kou, 2019; Kumar, 2020; Kumar and Das, 2021; Lanka, 2020; Leblanc, 2020; Li, 2021; Li et al., 2020; Li, 2019; Li, 2019; Liang et al., 2021; Long, 2021; Ma et al., 2021; Manic, 2021; Marino, 2020; Meera, 2021; Mujeeb Rahman and Monica Subashini, 2022; Nabil et al., 2021; Nag, 2020; Ni, 2021; Oliveira, 2021; Peck, 2021; Penev, 2021; Peng, 2021; Pereira, 2019; Perochon, 2021; Pham, 2020; Putra, 2021; Rafiei Milajerdi, 2021; Rinaldi, 2021; Romero-García, 2021; Ruan, 2021; Salem, 2021; Sarovic, 2020; Shao, 2021; So, 2019; So, 2020; Sosnowski, 2022; Spiegel, 2019; Spronk, 2021; Squarcina, 2021; Sun, 2021; Sun, 2021; Tawhid, 2021; Tummala, 2021; van den Berk-Smeekens, 2020; Van der Donck, 2019; Vukićević, 2019; Wang et al., 2019; Wang, 2019; Wang, 2020; Wang, 2021; Wang, 2022; Wang, 2022; Wang, 2022; Washington, 2021; Wieckowski and White, 2020; Xipolitopoulos et al., 2021; Xu, 2021; Yalçin and Rekik, 2021; Yang, 2021; Yang, 2021; Yin et al., 2021; Zhang, 2021; Zhang, 2021; Zhang and Wang, 2022; Zhao, 2020; Zhao, 2021; Zhao, 2021; Zhao, 2021; Zheng, 2020; Zorcec, 2021; Zu, 2019) followed by ADHD (24.9 %), (Ardulov, 2021; Jiang, 2020; Lanka, 2020; Spronk, 2021; Zu, 2019; Abbas, 2021; Aggensteiner, 2019; Aggensteiner, 2021; Aradhya et al., 2020; Arnold, 2021; Barth, 2021; Benzing and Schmidt, 2019; Bleich-Cohen, 2021; Boroujeni et al., 2019; Cai, 2021; Cai, 2021; Chang, 2019; Chen et al., 2019; Dallmer-Zerbe, 2020; Damiani, 2021; Das and Khanna, 2021; Deiber, 2021; Dobrakowski and Łebecka, 2020; Gallen, 2021; Gao et al., 2020; Griffiths, 2021; Groeneveld, 2019; Gu, 2021; Ha, 2022; Hadas, 2021; Häger, 2021; Hasslinger et al., 2022; Johnstone, 2021; Kaur, 2019; Khan, 2021; Kiiski, 2020; Kim, 2021; Laniel, 2020; Liu, 2021; Medina, 2021; Moghaddari et al., 2020; O'Neill, 2022; Owens, 2021; Öztekin, 2021; Purper-Ouakil, 2022; Qi, 2021; Shema-Shiratzky, 2019; Shi, 2021; Skalski, 2021; Tang, 2022; Tor, 2021; Tosun, 2021; Wang, 2021; Zhang-James, 2021; Zhao, 2022), and learning disabilities (8.1 %) (Appadurai and Bhargavi, 2021; Devillaine, 2021; Drotár and Dobeš, 2020; Ebrahimi, 2022; Eroğlu, 2021; Formoso, 2021; Maggio, 2021; Marchesotti, 2020; Pecini, 2019; Pérez-Elvira et al., 2021; Peters, 2021; Ramezani, 2021; Rello, 2020; Rodríguez, 2021; Svensson, 2021; Usman, 2021; Zahia, 2020; Zhang, 2021). Fewer scientists focused on DCD (2.7 %) (EbrahimiSani, 2020; Grohs, 2020; Kuijpers, 2019; Neto, 2020; Neto, 2021; Smits-Engelsman et al., 2020), language disorder/language delay/specific language impairment/developmental speech-language disorders (1.8 %) (Borovsky et al., 2021; Justice et al., 2019; Sharma and Singh, 2022; Zhao, 2021), Tourette syndrome (1.4 %) (Duan, 2021; Dyke, 2019; Kahl, 2021), intellectual disability (1.4 %) (Ha, 2022; Ahn, 2021; Smith, 2021), developmental delay (0.9 %) (Lloyd, 2021; Ouyang, 2020), and Rett syndrome (0.5 %) (Fabio, 2022). Numbers of studies investigating specific conditions are reported in Table 2.

The most common technologies used for support of diagnosis of NDDs were: machine learning (n = 135, 61.8 %), functional magnetic resonance imaging (fMRI, n = 45, 20.4 %), EEG (n = 37, 16.7 %), magnetic resonance imaging (MRI, n = 26, 11.8 %), and eye-tracking (n = 11, 5.0 %), followed by mobile apps/tablets (n = 5, 2.3 %), computer vision (n = 3, 1.4 %), motion capture systems (n = 3, 1.4 %), virtual reality (n = 2, 0.9 %), and magnetoencephalography (MEG, n = 2, 0.9 %). Furthermore, single studies used: Raspberry Pi with Touch Screen, transcranial magnetic stimulation, functional near-infrared spectroscopy (fNIRS), magnetic resonance spectroscopy (MRS), ultrasonography (USG), electrocardiography (ECG), thermal imaging, smart glasses, smartphone, digitizer that allowed kinematic analysis of handwriting movements, force plate, robot, and a computer

Table 2
Number of studies and their type (investigating diagnosis/treatment) for each condition.

Condition	No. of studies	No. of studies covering treatment	No. of studies covering diagnosis
ASD	130	31	99
ADHD	49	17	32
Learning disabilities	18	9	9
DCD	6	6	0
Both ASD and ADHD covered in one article	5	0	5
Tourette syndrome	3	2	1
Developmental Delay	2	0	2
Intellectual Disability	2	2	0
Intellectual Disability and ADHD covered in one article	1	1	0
Rett syndrome	1	1	0
Language disorder	1	0	1
Language delay	1	0	1
Specific language impairment	1	0	1
Developmental Speech-Language Disorders	1	0	1
Total	**221**	**69 (31.22 %)**	**152 (68.78 %)**

ASD: Autism Spectrum Disorder, ADHD: Attention-Deficit/Hyperactivity Disorder, DCD: Developmental Coordination Disorder application with a dry-sensor single-channel portable EEG headset.

Regarding the treatment studies the most frequently used technologies included: neurofeedback (n = 17, 7.7 %; based on EEG, n = 15, fNIRS, n = 1, or fMRI, n = 2), mobile apps/tablets (n = 10, 4.5 %), virtual reality (n = 8, 3.6 %), robots (n = 7, 3.2 %), transcranial magnetic stimulation (n = 6, 2.7 %), eye-tracking (n = 5, 2.3 %), transcranial current stimulation (n = 4, 1.8 %), and Xbox Kinect (n = 4, 1.8 %). Less popular technologies included: biofeedback (n = 3, 1.4 %, hemoencephalographic, or based on electromyogram, or heart rate variability), computer game-based intervention (n = 3, 1.4 %), telehealth (n = 3, 1.4 %), Nintendo Wii Console (n = 2, 0.9 %), and mixed reality (n = 2, 0.9 %). Moreover, single studies utilized: elastic touch-display "BendableSound", online software package that simultaneously slows down visual and auditory signals for slowness therapy, augmented reality, motion capture system, smart speakers, computerized magnocellular-based visual-motion training, and radio electric asymmetric conveyer (REAC). It should be noted that some of the studies included more than one type of technology, therefore the given numbers do not add up to 221.

3.1. Risk of bias results

Out of 33 randomized parallel-group trials included, only 1 was scored as having a low risk of bias, 21 had a high risk of bias, and 11 raised some concerns (Supplementary material II, Fig. S2). The lowest scores were observed in the following domains: *Bias due to missing outcome data* and *Bias in measurement of the outcome*. In each of these domains 11 studies were scored as having a high risk of bias (Supplementary material II, Fig. S3). Also, since most of the researchers did not pre-register their data analysis intentions, the majority of studies (n = 26) were scored as raising some concerns in the *Bias in selection of the reported result* domain. All 5 randomized cross-over trials had a high risk of bias (Supplementary material II, Fig. S4). None of them had a low risk of bias in the following domains: *Bias arising from the randomisation process*, *Bias due to deviations from intended interventions in a crossover trial (effect of assignment to intervention)*, and *Risk of bias in selection of the reported result in a crossover trial* (Supplementary material II, Fig. S5). NOS assessment scale results are reported in Supplementary material II, Figs. S6, and S7. Regarding the results of the EPOC tool, only 1 out of 10 studies was scored as having "lower risk" (Supplementary material II, Fig. S8). None of the 21 included pre-post studies was rated as having a good quality (Supplementary material II, Fig. S9). The detailed assessment of each included study is available in Supplementary material II (Tables S1-S8).

3.2. Investigated (bio)markers and targeted symptoms

In this section we summarize the investigated (bio)markers and symptoms covered in the included studies. We organized them into three relatively wide categories and presented a summary of findings from each of them. Taking into consideration the large number of studies, as well as their variety, results of each of them can be accessed in the Supplementary material I.

3.2.1. Brain structure and activity

56.6 % (n = 125) of included studies investigated brain structure and/or activity. 85.6 % (n = 107) of them were focused on diagnosis. Specifically, there was a big interest in detection of ASD (n = 69) and ADHD (n = 33), followed by dyslexia (n = 4), developmental delay (n = 2), learning disability (n = 1), Tourette Syndrome (n = 1), and developmental speech-language disorders (n = 1). The treatment studies covered the following conditions: ADHD (n = 9), ASD (n = 5), Tourette Syndrome (n = 2), learning disability (n = 1), and dyslexia (n = 1). Half of them applied neurofeedback training, and others utilized either transcranial magnetic stimulation (n = 4), transcranial current stimulation (n = 3), virtual reality therapy (n = 1), or game-based intervention on an iPad (n = 1).

The brain activity and structure were investigated using various tools. 47 studies analyzed data from EEG, out of which 35 covered diagnoses. For instance, Bakheet and Maharatna (Bakheet and Maharatna, 2021) acquired EEG signals from autistic and TD children while presenting to them three types of face expression. The algorithm trained on the happy stimulus dataset reached 100 % accuracy in differentiating between ASD and TD participants. Also, Peng and associates (Peng, 2021) screened autism by acquiring and analyzing EEG data of subjects under positive and negative emotional stimulation. In another study, Zhao and colleagues (Zhao, 2021) conducted a recurrence quantitative analysis (RQA) that allowed derivation of features such as: determinism (DET), recurrence rate (RR), and length of average diagonal line (LADL) of EEG signals from different brain regions of autistic and neurotypical participants. Using data from the whole brain area and a support vector machine the authors achieved a maximum classification accuracy of 84 %. Other researchers examined EEG signals of the brain's C3 channel and presented differences among the topological features of complex networks as a method of ASD detection (Baygin, 2021). Furthermore, Gabard-Durnam and co-writers (Gabard-Durnam, 2019) found that EEG power trajectory during the first postnatal year differentiates ASD outcomes at the age of 3. The study by Kang and colleagues (Kang, 2021) revealed differences in EEG entropy, power, coherence, and bicoherence between low-functioning autistic subjects and TD controls.

EEG was also used to support ADHD diagnosis. For instance, Boroujeni and associates (Boroujeni et al., 2019) analyzed the chaotic behavior of the EEG signals that allowed them to distinguish ADHD subjects from controls with an accuracy of 96.05 %. Chang and colleagues (Chang, 2019) studied multiple EEG features to detect ADHD of combined type in males. Examples of those features included: power ratio of the alpha/gamma bands, the average of the EEG signal, or power of the beta band in all spectral bands of the signal in male ADHD participants. Other ideas for utilizing EEG in ADHD detection were: reconstructing the phase space of EEG signals (Kaur, 2019) or extracting features from RGB images that were formed from the theta, alpha, beta, and gamma frequency bands from continuous mental task EEG samples (Moghaddari et al., 2020).

Only three studies included in this review utilized EEG for conditions other than ASD and ADHD. One of them was conducted by P é rez-Elvira and associates (Pérez-Elvira et al., 2021) who applied live z-score NF training for quantitative EEG normalization in school children with learning disabilities. Another one is a study by Lloyd and co-writers (Lloyd, 2021) who found that multichannel EEG recorded in preterm infants is a strong predictor of developmental delay at the age of 2 years. The last one successfully discriminated between participants with and without Tourette Syndrome by analyzing spatial patterns of the resting-state EEG network (Duan, 2021).

Nearly 20 % of studies included in this systematic review presented analysis of either structural, functional, or effective brain connectivity. Most of them used public datasets such as ABIDE (Di Martino, 2014) and ADHD-200 (Bellec, 2017). In fact, among the 221 included studies, 35 conducted an analysis of data from ABIDE dataset and 12 analysed data from ADHD-200. For example, Shao and colleagues (Shao, 2021) attempted to identify abnormal functional connections that could be a biological ground for diagnosis of ASD. They proposed a combined method of deep feature selection process and graph convolutional network. In the first step, each functional connectivity feature is weighted and a subset of them is chosen accordingly, (which is possible thanks to adding a sparse one-to-one layer between the input and the first hidden layer of a multilayer perceptron), and then, based on the chosen features and additional phenotypic information, the subjects are classified as ASD or TD. The authors verified this approach using the pre-processed ABIDE dataset and achieved an accuracy of 79.5 %. Very promising results were obtained by ElNakieb and associates (ElNakieb, 2021) whose method reached the highest classification accuracy on ABIDE dataset among the included studies. The authors analysed white matter connectivity, using diffusion tensor imaging (DTI) data of 125 ASD and 120 TD subjects from ABIDE-II initiative. The high global balanced accuracy over the 5 imaging sites was up to 99 % with 5-fold cross-validation. Importantly, they were also able to identify the brain-area pairs that mostly contributed to reaching the final decision (e.g., retrolenticular part of the internal capsule in the left hemisphere & fornix cres/stria terminalis). Furthermore, those areas aligned with the findings from other studies investigating autism impairments (ElNakieb, 2021). For instance, the internal capsule microstructure was previously shown to have an increased connectivity in subjects with ASD from childhood to adulthood (McLaughlin, 2018).

20 studies investigated the brain anatomy (e.g., cortical surface area, cortical thickness, white matter volume) in order to distinguish between cases and controls. For instance, Sarovic and colleagues (Sarovic, 2020) analysed structural MRI data of individuals with and without ASD and found significant differences between the two groups within subcortical gray matter structures and limbic areas. The authors also estimated each subject's individual summed total index that indicates whether their gross morphological brain pattern is in the direction of cases or controls and achieved a maximal 78.9 % cross-validation classification accuracy. Furthermore, Gürbüz and Rekik (Gürbüz and Rekik, 2021) investigated cortical surface area and minimum principle area in individuals with ASD, and Squarcina and associates (Squarcina, 2021) found increased cortical thickness in various brain regions of ASD children. On the other hand, a study by Öztekin and co-writers (Öztekin, 2021) showed that measures of cortical anatomy have little incremental value in distinguishing between children with and without ADHD.

A few studies (n = 6) investigated brain activation in response to certain tasks or stimuli using an fMRI. 4 of them focused on diagnosis (ASD, n = 2; dyslexia, n = 1; ADHD, n = 1). Zahia and colleagues (Zahia, 2020) attempted to detect dyslexia based on volumes containing brain activation areas during three different reading tasks. The participants were divided into dyslexia, typical development, and monocular vision groups. The model was trained using a 3D Convolutional Neural Network and reached an overall average classification accuracy of 72.73 %. Haweel and co-writers (Haweel, 2021) used task-based fMRI to create a brain map (indicating ASD severity level for each brain area), that can contribute to personalized diagnosis and treatment plans. The brain activation data was recorded during participants' natural sleep, while an audio record of a narrator telling a story was played. Another study focused on ADHD detection by analyzing activation during tasks of working memory, inhibitory control, and reward processing (Owens, 2021). Regarding the treatment studies, one of them utilized real-time fMRI-NF in order to achieve up-regulation of fusiform face area in individuals with ASD (Pereira, 2019), whereas another, targeted neural activity in the attention network of ADHD participants with deep transcranial magnetic stimulation (Bleich-Cohen, 2021).

Brain activity was also assessed using fNIRS technology (n = 2). For instance, Xu and associates (Xu, 2021) analysed short-term spontaneous hemodynamic fluctuations and abnormalities of inferior frontal gyrus and temporal lobe, and successfully classified ASD and TD children with 90.6 % sensitivity and 97.5 % specificity. Another study utilized fNIRS-NF training in order to reduce ADHD global scores (Barth, 2021). The authors showed that 61.9 % of the participants learned how to regulate the NF target parameters where the task was either to decrease ("deactivate") or increase ("activate") prefrontal O_2Hb concentration. Also, magnetoencephalography (MEG) was used in two studies. Results of one of them (Zhao, 2021) showed, that infants' neural non-native speech discrimination can significantly predict both individual differences in spoken grammar skills at 6 years of age and a presence or absence of a potential speech-language disorder. Specifically, the predictor was the prefrontal but not temporal mismatch response from the MEG experiment at 11 months. The other study (An, 2021) found alterations in oscillations and oscillatory coupling, reflecting the dysregulation of motor gating mechanisms in autism and used these findings to classify ASD vs. control subjects, obtaining an AUC equal to 0.971.

3.2.2. Core symptoms and other NDD related difficulties

This category contains studies (n = 104) that targeted not only core symptoms of specific NDDs but also difficulties related to them that are common, yet not crucial for obtaining a diagnosis. 62.5 % (n = 65) of them utilized technology for treatment rather than diagnosis. Most of the studies focused on ASD (n = 53), ADHD (n = 26), and learning disabilities [n = 13; dyslexia (n = 8), unspecified learning disability (n = 2), dysgraphia (n = 2), and mathematical learning disability (n = 1)], followed by developmental coordination disorder (DCD, n = 6), intellectual disability (n = 3), specific language impairment/ language disorder/delay (n = 3), Tourette Syndrome (n = 2), and Rett syndrome (n = 1).

41.3 % of studies (n = 43) targeted various cognitive processes such as attention (n = 11), executive functions (n = 10), reading (n = 6), language (n = 4), and others (e.g., perception, information processing speed). For instance, in a study by Gallen and co-writers (Gallen, 2021) neural, behavioral, and clinical metrics of attention were assessed in ADHD children before and after a 4-week at-home intervention on an iPad that targeted midline frontal theta circuitry. The results indicated improvements on both neural and behavioral measures of attention after the intervention. Furthermore, Peters and associates (Peters, 2021) conducted a study on population with dyslexia, which demonstrated that visual attention plays an important role in reading and might be trained using Action Video Games. The authors suggest it can be a motivational, fun, and engaging intervention for dyslexia. Ameis and colleagues (Ameis, 2020) conducted an RCT in which they compared repetitive transcranial magnetic stimulation (rTMS) targeting dorsolateral prefrontal cortex vs. sham stimulation impact on executive functions performance in ASD participants. The outcomes were measured using The Cambridge Neuropsychological Test Automated Battery SWM total errors and BRIEF Metacognition Index scores (Gioia, 2002). Even though the efficacy of a 4-week 20 Hz rTMS was not proved, an improvement in executive functions was observed in participants with lower baseline functioning in the active vs. sham group. Reading abilities were often targeted in intervention studies on population with dyslexia. In a controlled before-and-after study, Eroğlu and associates (Eroğlu, 2021) investigated impact of a mobile app (Auto Train Brain) with EEG neurofeedback and multi-sensory learning methods on reading comprehension, reading speed and other reading abilities. The results indicated a significantly higher improvement in reading comprehension in the experimental compared to treatment-as-usual group and improved phonemic awareness and nonword spelling in both groups. Another study, conducted by Zorcec and colleagues (Zorcec, 2021), found an improvement in several developmental domains, including language skills, in autistic children, after interacting with a child-sized humanoid robot Kaspar and using a complementary app at home. The robot used facial and bodily expressions, gestures, as well as pre-recorded speech for interaction. A common measure of cognitive functioning was a reaction time, as well as omission, and commission errors (n = 6). In a study from Brazil (Antão, 2020), children with autism who played an augmented reality game, in which they had to identify correct numbers and alphabet letters, improved their reaction time after the intervention.

Moreover, the ASD related symptoms covered in this review included social deficits (n = 14), motor skills (n = 8), emotion recognition and comprehension (n = 7), communication problems (n = 6), social attention (n = 5), or anxiety (n = 3). 25 studies focused on diagnosis and 28 covered various treatment approaches. One of the intervention ideas was to introduce a robot in a therapy program. For instance, in a study by Marino and associates (Marino, 2020) a plastic-bodied humanoid robot acted as a co-therapist and provided emotional and communication prompts, as well as reinforcements. The social robot successfully boosted learning of socio-emotional understanding skills. Other researchers utilized an interactive virtual reality system with eye-tracking that allowed them to successfully enhance gaze sharing and gaze following in individuals with ASD (Amat, 2021). Furthermore, Nag and colleagues (Nag, 2020) used smart glasses in order to analyze gaze patterns of children with ASD and neurotypical controls during an emotion recognition task. They trained a classifier that distinguished between the two groups but was unable to significantly outperform other models that used only age and gender features. Crowell and colleagues (Crowell, 2020) used mixed reality experiences with full-body interaction to check whether it could help reduce anxiety and encourage social initiation in children with ASD during play with a TD child. The mixed reality system, called The Lands of Fog (Mora-Guiard), consisted of a virtual environment projected onto a floor, physical objects, such as a butterfly net with LED lights tracked by the system, as well as visual and sound effects. The authors compared this approach with a standard LEGO social intervention strategy that uses toys, and construction tools as an aid to a caregiver, psychologist, or a therapist. The results showed that children in the experimental and control setting generated the same number of social initiations, and no significant differences in the reported anxiety were found. Furthermore, in three studies (Leblanc, 2020; Nabil et al., 2021; Washington, 2021) researchers aimed to detect autism by analyzing behavioral features from home videos. The evaluated features included expressive language, echolalia, eye contact, spontaneous gestures, emotion expression, communicative engagement, responsiveness, comforting others, aggression, sharing of excitement etc. They were rated by people with no previous experience in ASD detection. The best classification accuracy of 91.79 % was obtained by Nabil and colleagues (Nabil et al., 2021) using backwards feature selection and support vector machine. They also worked with the biggest dataset, out of the three included studies, consisting of 116 subjects with autism, and 46 TD participants. An example of study investigating motor skills is a randomized crossover controlled trial conducted by de Moraes and associates (de Moraes and A.P, 2020). The authors investigated motor learning and transfer between real and virtual environments in young people with ASD and found that virtual methods may enhance learning of motor skills. Also, Li and colleagues (Li et al., 2020) used machine learning to automatically identify postural control patterns of subjects with ASD. A force plate was used to collect a centre of pressure data during two conditions: eyes open and eyes closed. Using the naïve Bayes classifier, they managed to discriminate between children with and without autism with the highest accuracy of 0.90, specificity of 1.00, and sensitivity equal to 0.83. It is also worth mentioning, that 8 studies applied machine learning to already known standard tools, often along with some additional questions about the characteristics of an individual such as age, gender, ethnicity, whether the child was born with jaundice etc. In this case, rather than looking for new markers of NDDs, researchers attempted to optimize already existing screening processes. More specifically the used tools included: Quantitative Checklist for Autism in Toddlers (QCHAT) (Mujeeb Rahman and Monica Subashini, 2022; Romero-García, 2021), Autism Spectrum Quotient Adult (AQ-10 Adult) (Kumar and Das, 2021), AQ-10 Child (Xipolitopoulos et al., 2021), First Year Inventory 2.0 (Meera, 2021), Autism Diagnostic Interview-Revised (ADI-R) (Ardulov, 2021), and DSM-5 Diagnostic criteria for ASD-299.00 (Khullar et al., 2021). Also, one study utilized non-verbal aspects of social interaction from filmed Autism Diagnostic Observation Schedule (ADOS) assessment (Kojovic, 2021). Some of these studies produced promising results. For instance, Mujeeb Rahman and colleagues (Mujeeb Rahman and Monica Subashini, 2022) used deep neural networks for ASD detection, and the AUC on QCHAT and QCHAT-10 datasets with Polish toddlers were 97.18 % and 100 % respectively.

Regarding the ADHD related symptoms and difficulties, the studies included in this review covered: inattention, hyperactivity, and/or impulsivity (n = 15), working memory (n = 5), motor skills (n = 3), as well as associated conduct problems, general psychopathology, emotional problems, and peer problems (n = 2). The majority of studies focused on treatment (69.2 %, n = 18) and most of them utilized neurofeedback (55.6 %, n = 10) and virtual reality (16.7 %, n = 3). For instance, Purper-Ouakil and associates (Purper-Ouakil, 2022) attempted to demonstrate noninferiority of personalized at-home EEG neurofeedback training versus methylphenidate treatment. Even though they failed to do so, the results in both treatment groups showed significant pre–post improvements in core ADHD symptoms, as well as in a broader range of problems. Dobrakowski & Łebecka (Dobrakowski and Łebecka, 2020) found a significant and long-term improvement of working memory in ADHD children who did 10–12 sessions of neurofeedback training with theta and beta frequency ranges individually adjusted to the child's peak alpha frequency. Furthermore, Wang and colleagues (Wang, 2021) found that after theta/beta neurofeedback training, parents reported fewer ADHD symptoms in their children on the Inattention and Hyperactivity/Impulsivity of the Strengths and Weaknesses of ADHD and Normal Behavior (SWAN) rating scale (Swanson, 2012). On the other hand, the RCT by Barth and colleagues (Barth, 2021) on an adult sample, showed equally significant core ADHD symptom improvements in semi-active electromyography biofeedback, fNIRS neurofeedback, and EEG neurofeedback group, suggesting placebo- or non-specific effects. Other examples of research targeting ADHD symptoms include a study from 2019 (Benzing and Schmidt, 2019), where Benzing and Schmidt found positive effects of exergaming (in which users were projected directly into virtual reality on the screen and controlled the console through their body movements) on executive functions, general psychopathology, and motor abilities. Also, Shema-Shiratzky and co-writers (Shema-Shiratzky, 2019) investigated the impact of virtual reality on behavior and cognitive functions in children with ADHD. The participants of the study walked on a treadmill with a safety harness, while negotiating virtual obstacles. The post-training parental reports indicated a significant improvement in children's psychosomatic behavior and social problems. Moreover, memory and executive functions were improved, and the effects were maintained at 6-weeks follow-up.

Furthermore, 8 studies focused on diagnosis. In one of them, researchers conducted a kinematic analysis of fast pen strokes in children with ADHD and controls (Laniel, 2020). They found that those with the diagnosis demonstrated poorer motor planning and execution, as well as greater variability in motor control. These differences allowed them to successfully distinguish between the two groups with the highest Area Under the Curve (AUC) score equal to 0.91. Also, Ardulov and colleagues (Ardulov, 2021) applied machine learning to ADI-R items to distinguish ASD from ADHD. Other researchers used pupillometric variation during a visuospatial working memory task as a marker of ADHD (Nag, 2020). The support vector machine classifier, trained on the obtained data, achieved 77.3 % sensitivity, and 75.3 % specificity in discriminating between cases and controls. The rest of the studies applied machine learning to either ADHD symptoms reported by parents and/or teachers, or some other behavioral features, in combination with other measures such as, EEG (n = 2), MRI (n = 1), MRS + DTI (n = 1), and eye-tracking (n = 1).

Regarding learning disabilities, apart from cognitive processes mentioned above, the included studies explored: kinematic features extracted from graphomotor tests for detection of dysgraphia (Devillaine, 2021; Drotár and Dobeš, 2020), postural control in dyslexia (Ramezani, 2021), as well as emotional, cognitive, and behavioral symptoms associated with learning disabilities (Pérez-Elvira et al., 2021). Also, Appadurai and colleagues (Appadurai and Bhargavi, 2021) proposed a set of significant eye movement features that can be used for building a predictive model of dyslexia.

Furthermore, all studies on DCD population focused on treatment and targeted motor abilities. For instance, EbrahimiSani and associates (EbrahimiSani, 2020) found positive impact of virtual reality training on predictive motor control functions in this population, and Grohs and colleagues (Grohs, 2020) showed that motor cortex transcranial direct current stimulation did not enhance motor learning in children with DCD, as seen in other populations. Moreover, results of the study by Neto and co-writers (Neto, 2021) indicated that training with Nintendo Wii Console and both the Wiimote control and Wii Balance Board accessories, elicited improvements in motor learning (measured by the change in obtained game scores over time).

Also, the intellectual disability studies focused entirely on treatment. One of them successfully utilized smart speakers for improving speech intelligibility of adults for phrases related to device use, as well as unrelated words (Smith, 2021). Another one investigated the effect of virtual reality and computer game-based cognitive therapy on visual-motor integration (Ahn, 2021). A pre-post study design was used and the scores on The Bruininks-Oseretsky Test of Motor Proficiency-2 (BOT-2) (Bruininks and Bruininks, 2005) significantly improved after the intervention.

On the other hand, all 3 studies on specific language impairment/ language delay/disorder focused on diagnosis. Results of one of them, that used machine learning, indicated that being a boy, having a lower socioeconomic status, being older in age, and having poorer parent- and teacher-reported functional communication and literacy skills have a strong discriminatory value in distinguishing between children with and without clinically impaired language skills (Justice et al., 2019). In another study researchers built a predictive model of low language outcomes by applying machine learning and network science approaches to early language skills parental reports (Borovsky et al., 2021). Furthermore, Sharma and Singh (Sharma and Singh, 2022) derived audio features from raw speech signals and achieved an accuracy of 100 % in discriminating between individuals with and without specific language impairment.

Both Tourette syndrome studies aimed at lowering the number of tics in the affected individuals. Dyke and colleagues (Dyke, 2019) investigated a potential positive effect of a single-session cathodal transcranial direct current stimulation on occurrence of these symptoms. The research revealed significantly lower tic impairment scores (assessed using video data) post-cathodal stimulation compared to post-sham stimulation but the interaction between time (pre/post) and stimulation (cathodal/sham) turned out to be not significant. Results of the second study showed that a neuronavigated robotic bilateral repetitive transcranial magnetic stimulation of the supplementary motor area is feasible in children with Tourette syndrome and reduces their tic severity (Kahl, 2021).

Furthermore, one of the intervention studies (Fabio, 2022) targeted intensity of stereotypies in Rett syndrome. The authors compared the use of a basic telerehabilitation and advanced telerehabilitation system equipped with eye-tracking tools so that the therapist could monitor a patient's interaction with it during cognitive sessions. The advanced intervention also consisted of motor rehabilitation sessions that provided a 3D reconstruction of a patient's skeleton superimposed on the video in real-time, which allowed for better observation of the participants' potential movement improvements. The results revealed more marked reduction in stereotypies in the group using the advanced telerehabilitation system compared to the basic one.

3.2.3. Other features

Taking into consideration that only 4.1 % of the studies (n = 9) included in this systematic review covered other features than those related to brain structure or activity, typical NDD symptoms, or difficulties related to them, we decided to describe them altogether within one section.

One of the approaches was to look for distinctive audio markers that could help differentiate between ASD cases and controls (n = 2). Khozaei and colleagues (Khozaei, 2020) used high-quality voice recording devices and typical smartphones to collect cry samples of subjects with and without autism between 18 and 53 months. After pre-processing of the data, they trained a classifier and achieved sensitivity, specificity, and precision of 85.71 %, 100 %, and 92.85 % respectively, on male dataset, and 71.42 %, 100 %, and 85.71 %, on female dataset. Furthermore, Asgari and collaborators (Asgari et al., 2021) applied machine learning to speech features extracted from ADOS-2 conversational activities and achieved a maximum AUC of around 83 % when differentiating between ASD and TD participants.

Moreover, heart rate variability (HRV) was investigated in one diagnostic study of ASD, and one treatment study of ADHD. Frasch and colleagues (Frasch, 2021) collected ECG data from school-age children with ASD, age-matched TD controls, and subjects with other psychiatric conditions characterized by altered HRV such as conduct disorder or depression. The researchers identified ASD specific features from time, frequency, and geometric signal-analytical domains that enabled discriminating autistic participants from their peers, with AUC equal to 0.89. The ADHD study was conducted by Groeneveld and associates (Groeneveld, 2019), who explored the impact of combined Z-score NF and HRV biofeedback on severity of ADHD problems, HRV and breathing parameters, as well as quantitative EEG parameters.

Other ideas included ASD detection by analysing children's head turns in response to their names (Perochon, 2021), or skin temperature in various regions of the face while evoking emotions such as happiness, anger, or sadness (Ganesh et al., 2021). Also, Ruan and co-writers (Ruan, 2021) attempted to classify photos as taken either by individuals with or without autism. In this case, the feature of interest was a saliency map from an input photo taken either of people, indoors, or outdoors. As it turned out, pictures taken by participants with autism, contained less salient objects, especially in the central visual field, and the discrimination between the two groups of subjects was quite successful (the model reached an accuracy of 81.3 % when classifying photos of people). In another study, conducted by Zhao and colleagues (Zhao, 2021), children with ASD and controls were asked to answer ten yes or no questions. They were also encouraged to nod/shake their heads while doing so. The authors managed to distinguish between the ASD and TD groups with 92.11 % accuracy using the head rotation range in the nodding direction, and the amount of rotation per minute in the head-shaking direction as features fed to a decision tree classifier. The last study utilized ultrasound and biological measurements of babies to predict later ASD diagnosis (Caly, 2021). When minimizing the false positive rate, 96 % of TD and 41 % of ASD babies were identified with a positive predictive value of 77 %.

3.3. Number and type of studies during the COVID-19 pandemic

Fig. 2. shows the number of included interventional and non-interventional studies from each year. It can be observed that even though the systematic review covered only 5 months of research in 2019, there were only 8 publications less included from this year than the whole year 2020. This initial drop in the number of studies was followed by 3.2 times more included records from the year 2021 (n = 128).

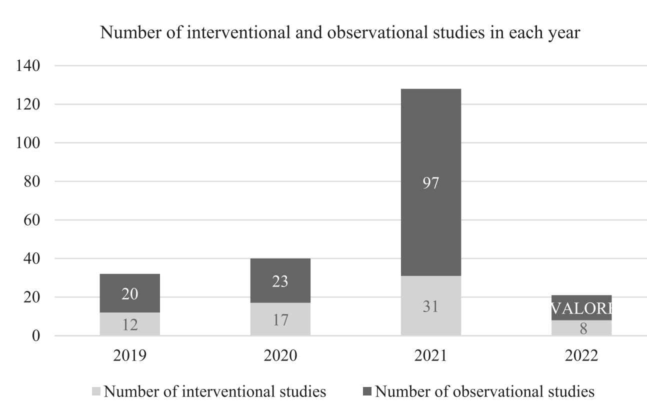

Fig. 2. Numbers of the included interventional and observational studies from each year.

4. Discussion

The purpose of this systematic review was to synthesize the current trends regarding technology application in NDDs diagnosis and/or treatment. Such overview of the latest achievements can be a source of help not only for clinicians, and therapists working directly with individuals with NDDs, but also for researchers deciding their future study directions. 3717 records were screened and the number of included publications reached 221 even though the review covered only 2 years and 7 months of research. This shows a large interest in utilizing technology as support for treatment and diagnosis of NDDs.

The studies included in this review are very heterogeneous. Not only do they cover a wide range of technologies (such as machine learning, fMRI, EEG, MRI, eye-tracking, mobile apps/tablets, neurofeedback, virtual reality, robots, transcranial magnetic stimulation, transcranial current stimulation, mixed reality, and others) but also, various NDDs, outcome measures, study designs, and population characteristics. Also, the investigated (bio)markers and symptoms vary across the included studies. What stands out is a large interest in applying machine learning algorithms to EEG, fMRI, or MRI data, especially for ASD and ADHD diagnosis. In fact, most of the included papers covered these two conditions (ASD n = 135, ADHD n = 55), which was also observed in the previous systematic review conducted by Valentine and colleagues (Valentine, 2020). The reason for the increased interest in utilizing technology for treatment of individuals with ASD may lie in its potential to overcome communication difficulties that are common in this population (Prelock and Nelson, 2012). Moreover, it could mitigate stress or anxiety potentially experienced by these individuals during a traditional face-to-face therapy (Goodwin, 2008). Many researchers are also interested in alternatives to pharmacological treatment of ADHD symptoms (e.g., methylphenidate) which can be associated with side effects (Schachar, 1997). Neurofeedback training seems to be a promising and dominating solution but the included studies report inconsistent results regarding its effectiveness. For instance, in a study by Wang and co-authors (Wang, 2021) parents reported fewer ADHD symptoms in their children after EEG neurofeedback training. Moreover, following the intervention, the topological properties and flow gain in participating individuals became close to those of healthy controls. On the other hand, Purper-Ouakil and colleagues (Purper-Ouakil, 2022) failed to demonstrate its non-inferiority compared to methylphenidate. Also, a study by Arnold and associates (Arnold, 2021) did not support a specific effect of deliberate theta/beta-ratio neurofeedback at either treatment end or at 13-month follow-up.

Most of the studies covered in this review focused on detecting a specific NDD, rather than treating symptoms and difficulties related to it. Data used for diagnostic research often overlapped among the publications, as it frequently came from the same open-source datasets containing individuals' brain structure and activity information. What differed, was the developed algorithms and approaches for its processing and analysis that led to obtaining different results. Applying machine learning algorithms to brain data turned out to be the most dominating approach within the included studies. It is a promising way to overcome potential bias in the diagnostic process. Other investigated markers included eye-gaze features (e.g., gaze preference patterns, pupillometric variation during a visuospatial working memory task), motor skills, vocal features, behavioral features from home videos, or language skills. It can be observed, that in most of the studies, covered in this review, researchers trained models that could successfully differentiate between cases and controls, confirming a big potential of technology use in NDD diagnosis.

The biggest advantage of using technology for NDD detection is that it may be objective and less dependent on the experience or knowledge of a clinician, as well as less prone to mistakes. As shown by Washington and colleagues (Washington, 2021), machine learning classification based on features extracted by a non-expert crowd achieves high performance in ASD detection using natural home videos of the child at risk. Moreover, it maintains high sensitivity when privacy-preserving mechanisms are applied. This gives promise for a cost-effective, rapid, and mobile diagnosis in the future. Objectivity and automation can also be achieved when data gathered by technologies such as MRI, EEG, eye-trackers, cameras, or graphic tablets is analysed by machine learning algorithms rather than humans. Nevertheless, this comes with a cost. Technology-free behavioral assessment conducted by clinicians is controlled by them, which was not always possible within the research reported in this systematic review. A part of the machine learning studies, in which models capable of distinguishing between individuals with and without an NDD diagnosis were trained, did not identify specific markers that led to these decisions. For instance, brain imaging data would be fed to a classifier, but the successful classification of cases and controls would not be explained in terms of any specific brain regions that contributed to the algorithm's performance. Therefore, no matter the reported classification accuracy, this might be a source of skepticism among clinicians who would not know what led to a specific diagnostic decision. Moreover, some authors report the ability of their developed algorithms to detect ASD based on only one marker, such as e.g., head turning in response to name. While this is a scalable idea for autism detection, giving a diagnosis to an individual comes with a responsibility and should be well understood and backed-up with enough observation. It is needed to find balance between automation and simplicity of a diagnostic process, and its reliability. Especially, given that most of the studies only consider differences between an NDD and TD population, omitting the fact that in real-world settings there are also many other existing conditions that could influence the obtained results. Finally, many researchers used fMRI for NDD diagnosis but to capture clear images, this kind of scanning requires staying still, which might be challenging in population of interest – according to a study by Yerys and co-authors (Yerys, 2009) less amount of interpretable data is obtained in ASD and ADHD than in TD population.

Regarding the technology-based treatment, promising results were obtained. The included research targeted a wide range of symptoms such as, inattention, hyperactivity, executive functions, working memory, motor skills, and conduct problems in ADHD, emotion recognition and comprehension, anxiety, as well as social and communication deficits in ASD, reading skills, visual spatial attention, and verbal working memory in dyslexia, motor skills in DCD, speech intelligibility and visual-motor integration in intellectual disability, tics in Tourette syndrome, or intensity of stereotypies in Rett syndrome. Most of the technology-based interventions covered in this review achieved significant improvements on the targeted symptoms. Furthermore, treatment introduced in a form of a virtual reality game, or a therapy with a social robot, especially when designed for children and adolescents, might seem more attractive to the population of interest and can potentially result in more engagement during an intervention, which is crucial for its effectiveness (Georgeson, 2020). Another advantage of technology use in NDD population is its potential to provide a side-effect-free, at-home treatment. For instance, interventions in a form of a game on a tablet that can be accessed from anywhere can be a fun, cheap, and effective way to improve individual's functioning and increase the treatment accessibility. Nevertheless, not all of the included studies use a technology that is cheap and easy to access. For instance, the use of fMRI is relatively expensive and currently the access to it is limited in some regions. Therefore, the reported studies that utilize this technology do not necessarily improve the often-discussed accessibility to treatment or diagnosis of NDDs.

It can be noticed, that technology that has been commonly used within the included studies is not necessarily innovative and has already been available for some time, e.g., the EEG was first recorded in 1924 (Tudor et al., 2005), fMRI has been widely employed in thousands of studies since 1990 (Glover, 2011), and the idea of the very commonly applied machine learning classifier, namely Support Vector Machine, was already published back in 1964 (Chervonenkis, 2013). The potential of technology-supported treatment and diagnosis is clear but its usefulness and successful application depends on many factors, such as conditions in which the data was gathered (e.g., in resting state, or during a specific task), methods of data pre-processing, or targeted population's age and its other characteristics. For instance, transcranial direct current stimulation that is known to augment motor learning in children with cerebral palsy (Grohs et al., 2019) did not have a positive impact on motor function in children 8–12 years with DCD (Ebrahimi-Sani, 2020). Also, awareness, cognition, communication, social motivation, and autistic mannerism did not improve in 6–12-year-old children with ASD after an intervention that utilized a robot with cartoon facial expressions and a tablet (Li, 2019) but significant improvements in joint attention initiations and functional play behaviors were found, when a social robot was used with ASD children aged 4–6 years (So, 2020). Similar variety can be observed in diagnostic studies that utilized the same technologies, such as fMRI or EEG but obtained different results.

From a research perspective, most of the approaches presented in the included studies still need more evidence to be integrated into health systems. The studies should be replicated and tested on bigger and more representative groups. There is a need to include more female participants, adults with NDDs, as well as individuals with commonly occurring comorbidities. Moreover, the variety of included protocols makes it very hard to conduct a meta-analysis that could lead to more direct, clinical implications. Therefore, in order to be able to draw conclusions about the efficacy of a particular technology and improve the outcomes' interpretability, a large number of studies with similar protocols should be conducted. From a clinical perspective, the use of technology for a faster, cheaper, and more objective diagnosis, or fun, engaging, and side-effect free treatment is tempting and may help professionals in their clinical practice, but should be treated with caution until more studies are conducted. Several evidence-based interventions that target symptoms and difficulties associated with NDDs, are already available and the evidence of their efficacy is far more robust in comparison to those available for the new technologies. Nevertheless, since social robots, tablets, as well as other introduced technologies are considered safe, and in the worst-case scenario simply ineffective or unpleasant (e.g., the transcranial magnetic stimulation), they could be potentially added to the already existing standards. Also, machine learning introduced into a diagnostic process could be used as help or assistance to the clinicians but is far from replacing them. Not only because of the poor quality of many studies, which makes the results less trustable, but also due to the fact that researchers often do not present ready diagnostic systems that could actually be shown to and used by the specialists. To investigate the real impact of technologies on users and families, research should start moving from the labs to the clinical context and the real-world settings. Studies that investigate the actual use of the presented technologies from the perspective of their cost and possibility of inclusion in clinical protocols, still need to be conducted. The potential cost savings for the families and/or health systems should be further explored. Moreover, the acceptability of the presented technologies needs to be investigated from the perspective of their potential users (individuals with NDDs, carers, professionals), which was often missed in the included studies.

What can be observed in this review is a smaller number of included studies from 2020 (n = 40) which might be a result of the COVID-19 pandemic that interrupted data collection of many researchers. Nevertheless, after the initial adjustment period, when the scientists often had to reorganize their work, a peak of newly published studies could be observed in 2021 (n = 128). This might be a result of the lockdowns all over the world and researchers spending more time on writing papers rather than collecting data. It is also not surprising that the open-source datasets such as ABIDE, or ADHD-200 were widely used in the light of the face-to-face interaction limitations. Applying machine learning algorithms to the already existing data allowed scientists to develop automatic diagnostic models for ASD and ADHD detection.

4.1. Limitations

42.1 % of the included studies were conducted either in the USA (n = 50) or China (n = 43). Research was scarce especially in Africa (n = 3), where two studies came from Egypt and one from South Africa. According to a report about the technology and science state in Africa, these are the two countries that produced above 50 % of the whole continent's publications in the years 2000–2004 (Pouris and Pouris, 2009). Future research should seek to balance these inequalities. Moreover, one of the biggest limitations of the included studies is their low quality and a high risk of bias. For instance, only 1 out of 38 included RCTs had a low risk of bias, 11 raised some concerns, and 26 were rated as having a high risk of bias. Some studies did not take into consideration participants who dropped out before the end of an intervention, and many did not include enough information about the studied population characteristics such as age and gender, or the used methodology. A frequently occurring issue was analyzing only a part of an available open-source dataset and not providing a rationale for it. Other problems included missing inclusion and exclusion criteria or outcome assessment methods descriptions. Furthermore, most of the studies lacked a pre-specified statistical analysis plan which automatically raised bias concerns. Also, 68.3 % (n = 151) of the studies did not state who the operator of the applied technology was and 41.6 % (n = 92) did not describe the setting in which it was used. The representativeness of the participants also raised concerns in many cases. One of the common issues was a lack of female subjects who were widely underrepresented in the included studies. Also, the research that focused on diagnosis often excluded participants with various comorbidities that are common in the NDD population. This limits the usefulness of the developed tools for clinical practice. Moreover, many of the included technology-based intervention studies were conducted on small groups of individuals. Taking the above into consideration, it is clear that more high-quality research is needed involving large, representative, and well-described samples. In order to reduce the risk of bias, it is crucial that the researchers pre-register their analysis intentions and report the used methodology in more detail. Also, missing outcome data should not be ignored and appropriate analysis methods should be used. Furthermore, when a certain technological intervention can be conducted at home, it is important to verify whether it was implemented according to the protocol. It is worth noting, that in some cases, the high risk of bias might also be a result of poor reporting of the conducted study rather than wrong methodology.

A limitation of the present systematic review is the already mentioned heterogeneity of the included research that makes it difficult to compare the obtained results and draw common conclusions regarding the effectiveness or utility of a specific technology for a treatment or diagnosis of NDDs. Multiple meta-analyses with more strict inclusion criteria need to be conducted so that technology-based intervention and diagnosis can be moved from the field of research to an actual clinical practice.

5. Conclusions

The current systematic review offers a picture of the rapidly spreading use of technology in NDD diagnosis and treatment. It presents findings from a large variety of both interventional and observational studies published between years 2019 and 2022, showing a great research interest in this field. This is, to our knowledge, the most updated systematic review in this field. Even though drawing conclusions regarding the efficacy and utility of a specific technology for an NDD assessment or treatment is difficult based on this review, many scientists present promising results that are worth further exploration. The proposed approaches might become a part of clinical practice in the future and a source of inspiration for further research. Nevertheless, if new technological approaches were to gain trust of clinicians and be used in real-world settings, more high-quality studies are needed that would provide reliable results, generalizable to the entire heterogeneous NDD population.[1]

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Declaration of competing interest

None.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2022.105021.

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