Automated detection of ADHD: current trends and future perspective

Hui Wen Loh[1], Chui Ping Ooi[1], Prabal Datta Barua[2,3], Elizabeth E Palmer[4,5], Filippo Molinari[6], U Rajendra Acharya[1,3,7,8,9,*]

[1] School of Science and Technology, Singapore University of Social Sciences, Singapore
[2] Faculty of Engineering and Information Technology, University of Technology Sydney, Australia
[3] School of Business (Information Systems), Faculty of Business, Education, Law & Arts, University of Southern Queensland, Australia
[4] Centre of Clinical Genetics, Sydney Children's Hospitals Network, Randwick, 2031, Australia
[5] Discipline of Paediatrics and Child Health, Faculty of Health and Medicine,, University of New South Wales, Randwick, 2031, Australia
[6] Department of Electronics and Telecommunications, Politecnico di Torino, Italy
[7] School of Engineering, Ngee Ann Polytechnic, Singapore
[8] Department of Bioinformatics and Medical Engineering, Asia University, Taiwan
[9] Research Organization for Advanced Science and Technology (IROAST) Kumamoto University, Kumamoto, Japan
* Corresponding author at: School of Engineering, Ngee Ann Polytechnic, 535 Clementi Road, 599489, Singapore.
E-mail address: aru@np.edu.sg (U.R. Acharya).

Abstract

Attention deficit hyperactivity disorder (ADHD) is a heterogenous disorder that has a detrimental impact on the neurodevelopment of the brain. ADHD patients exhibit combinations of inattention, impulsiveness, and hyperactivity. With early treatment and diagnosis, there is potential to modify neuronal connections and improve symptoms. However, the heterogeneous nature of ADHD, combined with its comorbidities and a global shortage of diagnostic clinicians, means diagnosis of ADHD is often delayed. Hence, it is important to consider other pathways to improve the efficiency of early diagnosis, including the role of artificial intelligence. In this study, we reviewed the current literature on machine learning and deep learning studies on ADHD diagnosis and identified the various diagnostic tools used. Subsequently, we categorized these studies according to their diagnostic tool as brain magnetic resonance imaging (MRI), physiological signals, questionnaires, game simulator and performance test, and motion data. We identified research gaps include the paucity of publicly available database for all modalities in ADHD assessment other than MRI, as well as a lack of focus on using data from wearable devices for ADHD diagnosis, such as ECG, PPG, and motion data. We hope that this review will inspire future work to create more publicly available datasets and conduct research for other modes of ADHD diagnosis and monitoring. Ultimately, we hope that

artificial intelligence can be extended to multiple ADHD diagnostic tools, allowing for the development of a powerful clinical decision support pathway that can be used both in and out of the hospital.

Keywords Attention deficit hyperactivity disorder (ADHD) · Deep learning · Machine learning · PRISMA · MRI · EEG · ECG · HRV · Questionnaires · CPT · RST · Accelerometer · Actigraphy · Pupillometric · Genetic · Social media · Artificial intelligence

1. Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is a common childhood-onset neurodevelopmental condition. According to a 2016 World Health Organization-World Mental Health Survey for ten countries, the global prevalence rate of adult ADHD was found to be 2.8%, with a higher proportion in high-income countries and a significant association with low education and male gender [1]. Children and adults with ADHD frequently exhibit three key symptoms: inattention, impulsivity, and hyperactivity, although symptoms are heterogeneous and individuals may display more or less of these individual symptoms, for example being classified as having inattention, hyperactivity/ impulsivity, or combined subtypes of ADHD [2]. ADHD inattentive (ADHD-I) is distinguished by distractibility and inattentiveness in the absence of hyperactivity symptoms, whereas ADHD hyperactive (ADHD-H) is distinguished by hyperactivity and impulsivity without inattention. The final ADHD combined (ADHD-C) type is defined by the presence of all symptoms of inattention and hyperactivity [3].

There is increasing evidence that there are distinct differences in the structure and function of the brain in individuals clinically diagnosed with ADHD: in particular changes in neuronal connections between the specific brain regions, often accompanied by changes in brain volume on neuroimaging [4], [5] (Figure 1). These neuroanatomical differences have been linked to changes in an individual's cognitive function, regulation of motivation, and attention [6]. The brain's reward system, which predominantly uses the neurotransmitter dopamine, is altered in individuals with ADHD [7]. For example, the prefrontal cortex of an ADHD patient, in particular, was discovered to have abnormally low presynaptic dopamine storage [8], [9]; critically impairing the individual's attention function, cognitive process, and working memory. [8], [10].

This reward deficit syndrome has been linked to individuals with a diagnosis of ADHD being more prone to engage in behaviors that promote the production of dopamine in the brain, such as alcoholism, drug addiction, and even aggressive conduct [2]. Individuals with ADHD are, for example, twice as likely to have Substance Use Disorder (SUD) than those without [11]–[14]. For those individuals with comorbid conduct disorder, the risk of SUD is even higher - four times the rate in the general population [11].

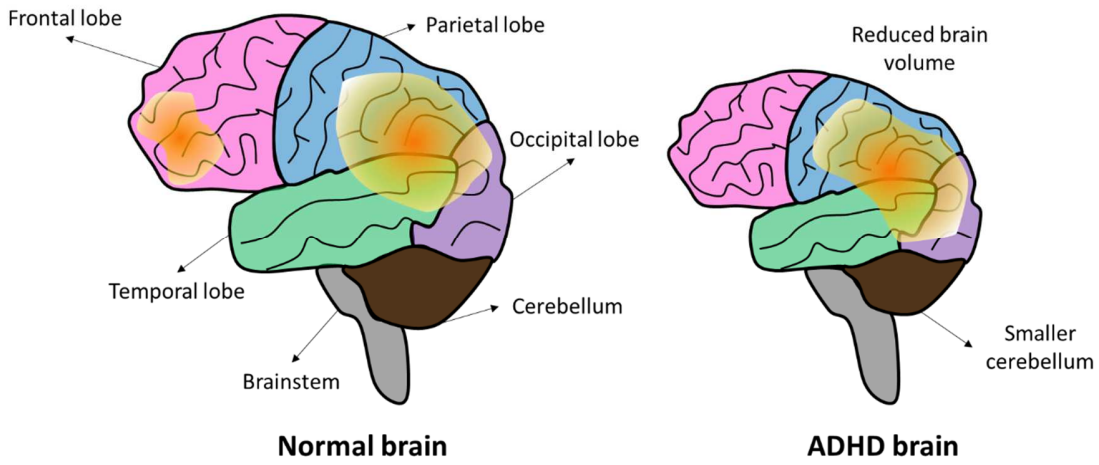

Figure 1. Schematic drawing of brains in neurotypical individuals and those diagnosed with ADHD. Yellow glowing regions represent regions of brain functional connectivity; individuals with ADHD have less neuronal connections to the prefrontal cortex as compared to normal brain.

Encouragingly, there is growing evidence that the neuroanatomical and functional changes may not be static. With appropriate early identification and treatment of ADHD symptoms, the neuroanatomy and function may resemble neurotypical individuals. For example, Mattfeld et al. [4] found that adults who had previously recovered from ADHD had restored normal brain connectivity while their minds were at rest, compared to adults who remained symptomatic with ADHD (Figure 1). Successful ADHD management can result in a significant improvement in quality of life and improved societal integration. Therefore, it is critical that ADHD is identified as early as possible, and management is evidence-based, to optimize long-term outcomes [15].

Currently, the diagnosis of ADHD is primarily a clinical one. An expert in ADHD diagnosis, typically a psychiatrist or specialist pediatricians, will conduct a series of clinical assessments to determine if an individual has five or more symptoms of inattention or impulsivity/hyperactivity and fulfil the DSM-5 diagnostic criteria [16]. However, clinical assessment by specialists takes a minimum of an hour, and there is a global shortage of trained specialists, meaning that diagnoses after often delayed [17]. For instance, Whitney et al. [18] reported that in Michigan, USA, there are only 11 trained psychiatrists to attend to over 100,000 children with likely mental health diagnoses. The ratio of psychiatrist-to-population is 11:100,000 for the United Kingdom and 14:100,000 for Australia [19].

There is also evidence that adjunctive data may be helpful in diagnosing the full spectrum of individuals with ADHD, who may be overlooked or underrecognized by current clinical assessments [16]. For example, numerous studies have attempted to diagnose ADHD via neuroimaging modalities like Magnetic Resonance Imaging (MRI) [20], [21], physiological signals like an electroencephalogram (EEG) [22], [23], and PPG

(ECG) [24], and other modalities like accelerometers [25] and game simulators [26]. These studies aim to reduce the workload of clinical diagnosticians by proposing artificial intelligence (AI) techniques, namely machine learning (ML) and deep learning (DL), for faster and more cost-effective ADHD diagnoses.

Only two review studies on ADHD identification using machine learning techniques have been published to date, and both studies have only reviewed ML studies that specifically used MRI for ADHD detection [27], [28]. In this review, we aim to uncover all the different modalities adopted by previous studies on automated ADHD diagnosis using both ML or DL techniques. Machine learning is not a fully automated technique as feature extraction of the input information (e.g. MRI images, EEG, ECG, etc.) must be carried out manually, followed by feature selection of the most significant features which will ultimately be used to train the ML classifiers for automated diagnosis of ADHD [29], [30]. The DL model, on the other hand, is a fully automated process where input information can be analyzed in its original format. Hence, feature extraction and selection procedures are not mandatory in DL models [30].

2. Methods

The PRISMA guideline 2020 [31] was used in this systematic review to analyze the most relevant studies on ADHD diagnosis using either the ML or DL approach. Using the following Boolean search strings as shown in Table 1, all publications were systematically searched through PubMed, Google Scholar, IEEE, and Science Direct. All publications up to December 2021 were included in the first identification phase of the PRISMA flowchart, as illustrated in Figure 2. As a result, we began with 467 publications which were reduced to 298 after removing 165 publications with duplicated titles. Subsequently, we screened the title and abstract of the publications. We removed 165 articles: animal studies, conference papers, non-AI studies, non-English articles, books, review papers, and non-journal articles. We were left with 133 articles, which were downloaded and read thoroughly to assess their eligibility for this review study. Upon detailed screening of the article, we further removed more conference papers, non-journal articles, non-AI studies, review papers, and irrelevant articles. We also removed articles that did not provide model accuracy results and articles to which we had no access to. Finally, 92 journal articles were found eligible for inclusion in this review.

Table 1. Boolean search string used for all journal article databases.

	Boolean search string	
Database	**[Title]**	**AND [Title/Abstract]**
PubMed Google Scholar IEEE	"ADHD" OR "attention deficit hyperactivity disorder"	“Machine learning” OR “deep learning” OR “artificial intelligence

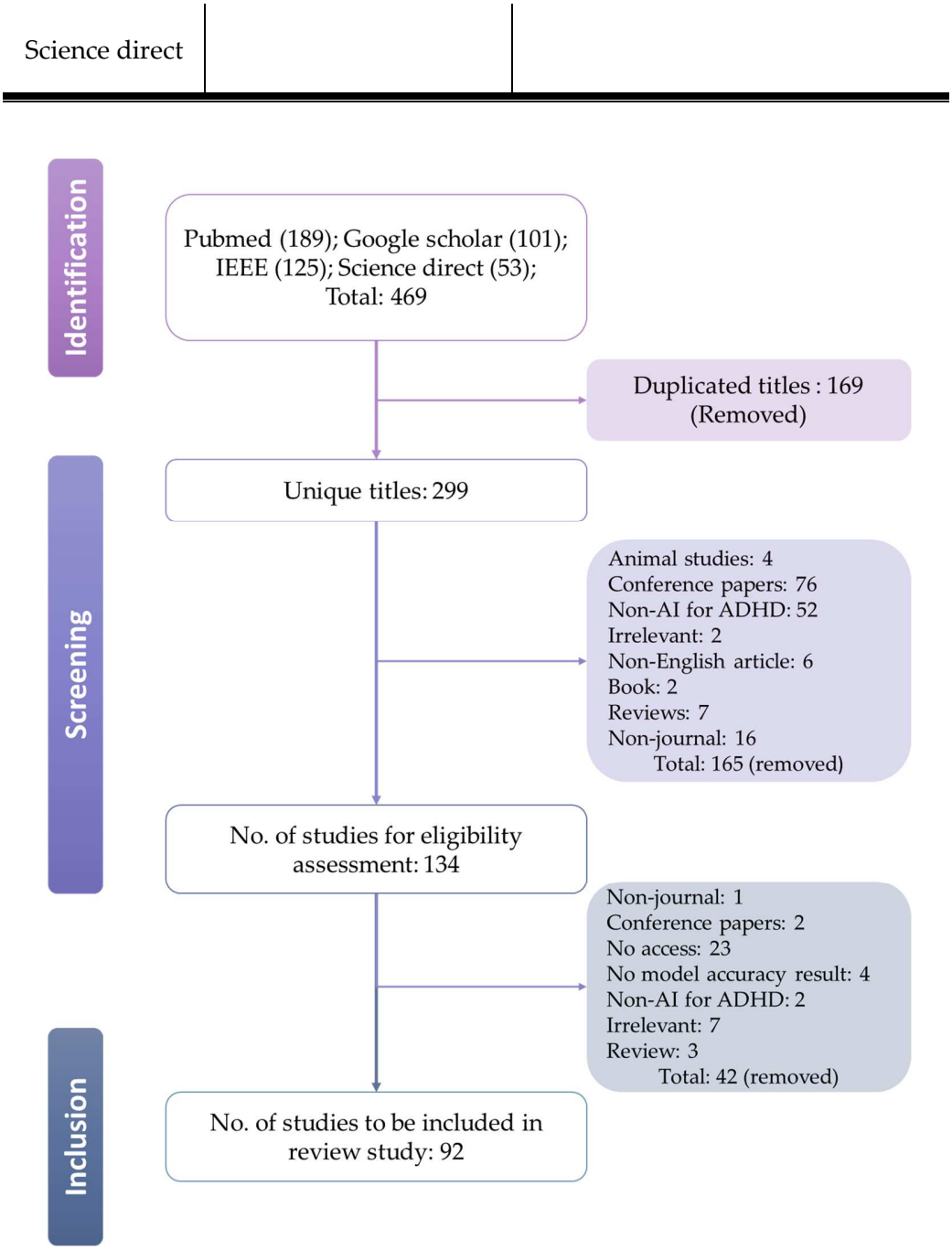

Figure 2. PRISMA flow diagram for systematic filtering of articles.

3. Results

In total, there were seven types of ADHD diagnostic tools utilized to develop AI models (Figure 3). These are discussed in the following results sections: MRI in subsection 3.1, physiological

signals in subsection 3.2, questionnaire data in subsection 3.3, game simulation and performance tests in subsection 3.4, motion data in subsection 3.5, and all other studies in subsection 3.6.

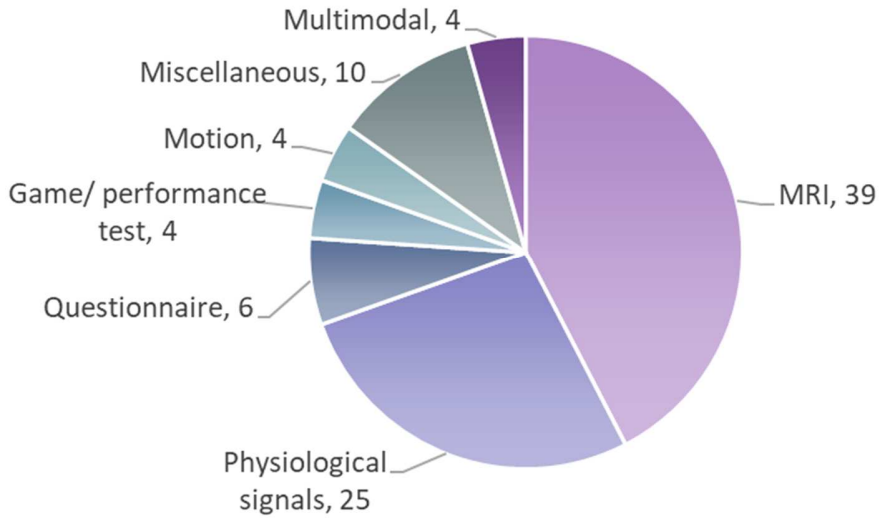

Figure 3. Pie chart representation of the ADHD assessment tools used in AI studies.

3.1 MRI

Brain MRI is the most widely studied modality for automated ADHD diagnosis, with 39 out of the 92 studies analyzing brain MRI images of ADHD patients and normal control (Table A.1). Most of the studies obtained their MRI images from one public database: the Neuro Bureau ADHD-200 Preprocessed repository (ADHD-200) [32] (Figure 4). ADHD-200 is a consortium that had collected structural and resting-state functional MRI images from 585 controls and 362 ADHD children and adolescents. Eight international imaging sites were involved in the data collection of ADHD-200. However, two out of the eight sites only provided MRI images of controls and not the ADHD individuals (Table 2). Hence, imaging data from these two sites are usually excluded from the studies. In this review, a total of 32 out of 39 MRI studies had used MRI images from ADHD-200 (Figure 4).

Table 2. Summary of number of subjects across different study sites in ADHD-200 database.

Imaging site	ADHD	Controls
Kennedy Krieger Institute	25	69
NeuroIMAGE sample	36	37
New York University Child Study Center	151	111
Oregon Health Sciences University	43	70
Peking University	102	143
University of Pittsburgh	4	94

Bradley Hospital/ Brown University	-	26
Washington University at Saint Louis	-	61
Total	***361***	***611***

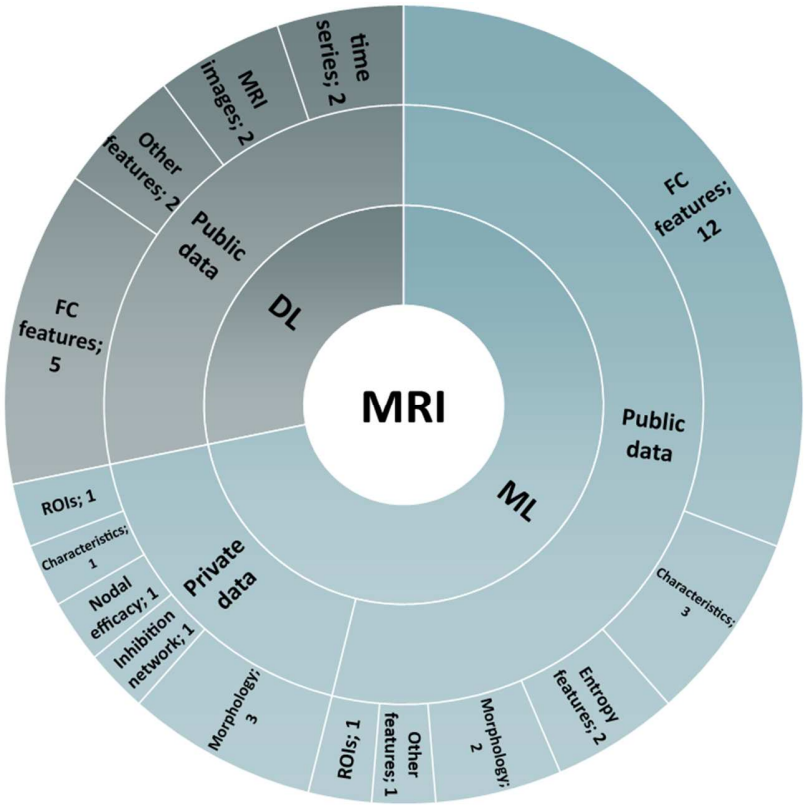

Figure 4. Sunburst plot of AI studies using MRI data. First level indicates type of AI studies, second level indicates type of dataset used, and third-level indicates type of features used to train the AI models.

It is also evident in Figure 4 that ML occupied a bigger proportion than DL in the MRI analysis for ADHD; where 28 out of 39 studies had implemented ML techniques. In addition, brain functional connectivity is the most common input feature for ADHD diagnosis; 12 ML studies and 5 DL studies had utilized function connectivity (FC) features for their studies (Figure 4, Table A.1). Functional connectivity of the brain is presented in the form of a matrix, illustrating the connection between different areas of the brain [33]. Pearson correlation coefficient is commonly employed to measure a strong correlation between the different brain regions, resulting in a heatmap where strong and weak FC between the brain regions is evident [33].

3.2 Physiological signals

Twenty-four studies utilized physiological signals to detect ADHD, most commonly electroencephalogram (EEG: 23 studies) and electrocardiogram (ECG: 1 study) (Figure 5, Table A.2). We also observed that studies using physiological signals for the detection of ADHD had high model performances; all models had accuracy results above 80% for ML and DL (Table A.2). Only one [34] out of the 24 studies had used a public EEG database: the National Brain Mapping Laboratory of Iran [35]. The rest had used their own private datasets.

As for the type of feature most extracted from EEG signals, seven ML and three DL studies had attempted to obtain power spectral features (Figure 5). Spectral analysis of EEG involves decomposing the signal into medically established frequency sub-bands, namely, alpha rhythm (8–13 Hz), beta rhythm (13–30 Hz), delta rhythm (1–4 Hz), theta rhythm (4–8 Hz), and gamma rhythm (30–80 Hz) [36]. These frequency sub-bands are evidently different between children with ADHD and controls. A study by Kamida et al. [37] discovered that children with ADHD have higher beta activity in all brain regions except for the occipital region. Another study [38] investigating the power spectral differences between ADHD of the inattentive type and the combined type, found higher theta and alpha activities in the combined type, while higher theta/beta ratio was observed in the inattentive type.

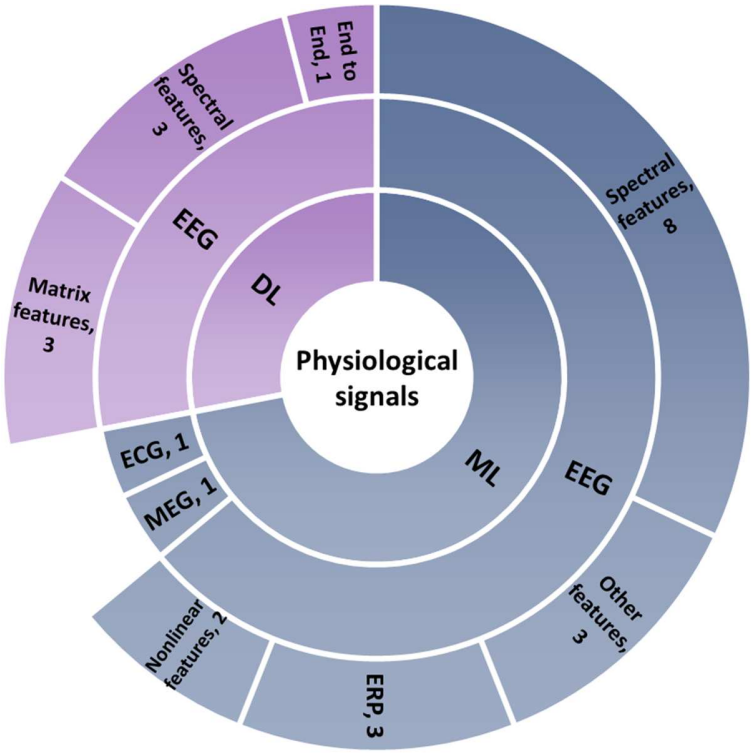

Figure 5. Sunburst plot of AI studies using physiological signals. First level indicates type of AI studies, second level indicates type of physiological signal, and the third level indicates type of feature used to train the AI models.

There is only one study that utilized ECG signals (Figure 5). Even though ECG does not provide direct information on brain activity, the autonomic nervous system links the brain to body interaction, causing fluctuations in physiological signals like ECG when an individual senses danger. For instance, an individual under acute stress will have a significant increase in the heart rate (ECG), and the same phenomenon was also observed in ADHD individuals [24], [39]. Koh et al. [24] proposed an ensemble ML classifier with entropy features extracted from ECG signals and detected ADHD individuals with high classification accuracy of 87.2%.

Another niche modality that can be utilized to identify ADHD is magnetoencephalography (MEG). To date, Hamedi et al. [40] and another multimodal study by Muthuraman et al. [41], are the only two ML studies that have employed MEG signals to identify ADHD. Unlike EEG, which records the electrical activities of the brain, MEG records the magnetic activities of the brain, which are unaffected by the tissue conductivity in the skull and cerebrospinal fluid [42]. MEG, when combined with MRI, results in magnetic source imaging (MSI), which is used to pinpoint the seizure focus in epilepsy surgery [42]. As a neuroimaging machine, MEG can potentially be used to distinguish between ADHD and controls. As such, [43], [44] discovered that MEG activity in ADHD patients are lower than in the controls. In the study by Hamedi et al. [40], they had obtained their MEG data from a public database, the open MEG archive (OMEGA) [45].

3.3 Questionnaires/ rating scales

There are various questionnaires or rating scales that medical professionals use to diagnose ADHD. In this section, there are only six studies that analyzed questionnaire/ rating scales data and only ML models were proposed (Table 3). It can also be seen in table 3 that decision tree (DT) classifiers, including random forest classifiers, are commonly proposed to analyze questionnaire data. We will only cover the questionnaires that studies have utilized to develop their best performing models (Table 3).

- **Conners' Rating Scales** are widely implemented to assess the social impact of ADHD, for example an individual's behavior in school or work [46]. Conners' parent rating scales (CPRS) used by Bledsoe et al. [47] is a parentally completed report, while Conners' adult ADHD rating scales (CAARS) used by Christiansen et al. [48], is a self-reported questionnaire.

- **Diagnostic Interview for ADHD in adults (DIVA)** [49], adopted by Tachmazidis et al. [50], is a semi-structured interview constructed based on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for ADHD diagnosis. The interview aims to assess the symptom of ADHD in five aspects of daily life: social contact, hobbies; self-confidence; relationships; work, and education.

- **Behavior Rating Inventory of Executive Function – Preschool version (BRIEF-P)** is a 63-item questionnaire for parents or teacher to rate the child's executive functions such as emotions control, working memory, organization, and planning skills [51]. This questionnaire was utilized by Öztekin et al. [52] to develop their ML model.

- **Adult ADHD Self-Report Scale (ASRS)** used by Kim et al. [53] is created by the World Health Organization, and it consists of 18 items based on the DSM-IV criteria. ASRS is a symptoms checklist for individuals to self-evaluate if they exhibit any symptoms relating to ADHD [54].

- **Minnesota Multiphasic Personality Inventory-2 (MMPI-2)** is a 567-item questionnaire where individuals are only required to answer 'true' or 'false' [55]. MMPI-2 is also used by Kim et al. [53], alongside ASRS to develop their ML model. It is widely implemented to assess various mental health problems apart from ADHD, such as depression, anxiety, and psychopathy [55].

- **Social Responsiveness Scale (SRS)** is a 65-item questionnaire that attempts to measure the social ability of individuals between ages of 4 to 18 years [56]. This questionnaire is adopted by Duda et al. [57] to differentiate ADHD individuals from patient with Autistic Spectrum Disorder (ASD).

Table 3. Summary of AI studies that used questionnaire data to develop AI model.

Author [ref]	Private datasets	Questionnaires	ML model	Validation approach	Accuracy
Bledsoe et al. [47], 2016	23 ADHD 12 normal	CPRS	SVM +DT	leave-one-out cross-validation (LOOCV)	100
Tachmazidis et al. [50], 2020	45 ADHD male 24 ADHD female	DIVA	DT + knowledge	LOOCV	95.7
Kim et al. [53], 2021	5726 college students	MMPI+ASRS	Random forest	(Hold-out) 80% training 20% test	93.6
Öztekin et al. [52], 2021	87 ADHD 75 normal	BRIEF-P	SVM	5-fold cross validation (CV)	92.6
Duda et al. [57], 2016	174 ADHD 248 ASD	SRS	ENet and LDA	3-fold CV	82.0
Christiansen et al. [48], 2020	385 ADHD 135 Obesity	CAARS	DT (lightGB	(Hold-out) 70% training	80.0

	517 problematic gambling 592 normal		M)	30% test	

3.4 Game simulation and performance tests

This section discusses conventional performance tests and game simulations to diagnose ADHD. There are two ML studies each, which utilized performance tests and game simulation respectively, to train their model (Table 4). Continuous Performance Test (CPT) and Reverse Stroop task (RST) are neuropsychological tests to evaluate the selective and sustained attention of an individual [58], [59]. The CPT is a computerized test which requires participants to react correctly to a specific stimulus [26]. For instance, participants are told to press the spacebar for all letters except for 'O'. In the traditional Stroop task, participants are given words, for example, 'Blue', which can be presented in different colors: '**Blue**' (incongruent color red), '**Blue**' (congruent color blue), and '**Blue**' (neutral color black). Participants are then required to provide the color of the word instead of the meaning of the word. Hence, in RST, the task is reversed where participants have to read out the meaning of the word regardless of the color it is printed in [60].

As for game simulations, its main purpose is to create an interactive environment that is customizable to best suit the user's needs [26], [61]. Yeh et al. [61] created a virtual reality (VR) classroom and incorporated a series of tests, including CPT, for ADHD diagnosis. In their VR system, some 'distractions' such as 'teacher standing up', 'door open', or 'thunder shower', were also included. They then recorded the test results, reaction time, and focus time for the user to complete the test. On the other hand, Heller et al. [26] utilized a videogame known as 'Groundskeeper' that is specially developed by CogCubed [62] for early ADHD detection. They extracted 33 game data variables and trained four different ML classifiers: random forest, AdaBoost, J48, and JRip. However, they did not specify which classifier provided the best performance result.

Table 4. Summary of list of AI studies that used standard performance tests or game simulation data to develop their model.

Author [ref]	Private datasets	Mode	Tests	ML models	Validation approach	Accuracy
Slobodin et al. [63], 2020	213 ADHD 245 normal	Performance	CPT	Random Forest	100-fold CV	87.0
Yasumura	108 ADHD	Performance	RST	SVM	-	86.3

et al. [64], 2013	108 normal					
Yeh et al. [61], 2020	37 ADHD 31 normal	Game	VR system	SVM	5-fold CV	83.2
Heller et al. [26], 2017	26 ADHD 26 normal	Game	Groundskeeper (CogCubed)	-	3-fold CV	78.0

3.5 Motion data (actigraphy & accelerometer)

Motion activity can also be a diagnostic marker for ADHD. In this section, two types of motion activity measure - actigraphy and accelerometer - are covered along with the four studies that utilized these motion data as listed in Table 5. Both actigraphy and accelerometer data are recorded via an accelerometer device that is usually worn on the wrist of the dominant arm and ankle of the dominant leg [65], [66]. The difference between the studies that analyzed the two types of motion data is the type of activity the subject is doing; actigraphy studies the subject's sleep efficiency [65], whereas accelerometer analyzes the subject's motion during normal daily activities [66]. As such, there are some studies that reported ADHD patients exhibited more movement than the controls during sleep [67] which correlates to increased daytime sleepiness [68]. This demonstrates that increased activity level is a well-known feature of ADHD, which is also reflected in their daily routine and can be easily monitored with wrist-worn accelerometer devices [69], [70].

In either case, the accelerometer device used to record the motion data is designed to be unobtrusive, allowing the participants to be natural in their own environment. This would not be possible with EEG or polysomnography recording procedures because data collection takes place in a laboratory that the participants are unfamiliar with. They are also required to attach a large number of electrodes, which can be very uncomfortable [71]. This, in turn, may have an impact on the quality of data collected.

Table 5. Summary of AI studies that used actigraphy or accelerometer data.

Author [ref]	Private datasets	Mode	Features	Models	Validation approach	Accuracy
Faedda et al. [65], 2016	44 ADHD 21 ADHD+ depression 48 bipolar 42 controls	Actigraphy	28 metrics	ML (SVM)	4-fold CV	83.1
Amado-Caballero et al. [66], 2020	73 ADHD 75 normal	Accelerometer	end-to-end	DL (CNN)	10-fold CV	98.6

O'Mahony et al. [25], 2014	24 ADHD 19 normal	Accelerometer	inertial measurement units	ML (SVM)	LOOCV	95.1
Muñoz-Organero et al. [72], 2018	11 ADHD 11 normal	Accelerometer	Acceleration image	DL (CNN)	LOOCV	93.8

3.8 Miscellaneous (pupillometric, twitter, MEG, and genetic)

In this section, we cover the least common modalities of ADHD diagnosis that ML studies have used. Two ML studies had utilized pupillometric data, while only one study had analyzed Twitter data (Table 6).

Interestingly, studies have shown that the brain norepinephrine system which is associated to pupil-size dynamics, is found to be impaired in ADHD patients [73]. Another study has also demonstrated that ADHD patients (off-medication) have decreased pupil diameter when performing visuo-spatial working memory tasks as compared to the controls [74]. This could be due to the difficulty in suppressing saccadic eye movements in ADHD patients who need to fixate [75]. Hence, uncontrollable eye movement in ADHD patients can be a potential biomarker for diagnosis, as Varela Casal et al. [75] and Das et al. [73] have implemented in their ML studies.

With the rise of social media, Twitter has become a potential platform of ADHD detection among Twitter users [76]. A majority of the mentally ill are reluctant to seek help from mental health care professionals, which results in the gradual accumulation of suicidal thoughts in the absence of professional help [77]. Hence, social media platform like Twitter, has become a source of comfort for these individuals to discuss mental health issues openly, as they seek connection and support from people of the same community [78]. Therefore, social media platform can be utilized for early detection of various mental illnesses and intervene suicidal actions [78]. In the study by Guntuku et al. [79], they identified highly correlated topics in Twitter and used it as a learning feature for their support vector machine (SVM) classifier (with 76% accuracy).

Table 6. Summary of AI studies that used pupillometric or Twitter data to develop their model.

Author [ref]	Datasets	Modality	Feature	ML model	Validation approach	Accuracy
Varela Casal et al. [75], 2018	21 ADHD 21 normal (private)	Pupillometric	Eye Vergence	SVM	30-fold CV	96.3
Das et al. [73], 2021	28 ADHD 22 normal	Pupillometric	pupil-size dilation	SVM	Nested 10-fold CV	76.1

	(private)		velocity and acceleration feature			
Guntuku et al. [79], 2017	1032 ADHD 1029 normal (private)	Twitter	Topic	SVM	5-fold CV	76.0

There is a known genetic influence on the likelihood that an individual will be diagnosed with ADHD [80], [81]. Numerous twin studies have reported a high heritability estimate of approximately 80% for both monozygotic and dizygotic twins [82]. ML and DL have recently been applied in seven studies to help identify ADHD genetic biomarkers. A summary on the four ML and three DL studies for ADHD are listed in Table 7. However, it is important to note that the genetic biomarkers identified [83]–[87] in Table 7 did not follow the standard genome-wide association studies (GWAS), which identify risk genetic variants via their significant P-values (i.e. not be lower than 5×10^{-8}) [84].

Table 7. Summary of AI studies that used genetic data to develop their model and identify ADHD genetic variants.

Author [ref]	Dataset	Model	Validation approach	Findings
Sokolova et al. [83], 2015	87 ADHD 77 normal	ML (Bayesian Constraint-based Causal Discovery algorithm)	-	DAT1 risk haplotype only has direct influence on the ADHD inattentive type.
Liu et al. [84], 2021	1033 ADHD 950 normal	DL (CNN)	(Hold-out) 75% training 5% validation 20% test	EPHA5 is identified as a potential risk gene of ADHD. Model diagnostic accuracy = 90.2%
Liu et al. [85], 2021	116 ADHD 408 normal	DL (MLP)	(Hold-out) 60% training 40% test	GRM1 and GRM8 genes are identified to have the highest weight in ADHD

				diagnosis Model diagnostic accuracy = 78.0%
Esteller-Cucala et al. [88], 2020	20,000 ADHD 35,000 normal	DL (Approximate Bayesian Computation coupled + deep learning framework)	-	Frequency of ADHD-risk alleles decreased since ancient time and have become maladaptive in today's society.
Cervantes-Henríquez et al. [86], 2021	408 ADHD	ML (ensemble)	(Hold-out) 70% training 30% test	The proposed model identifies ADGRL3, DRD4, and SNAP25 genes as contributing to the severity of ADHD.
Sudre et al. [89], 2021	362 ADHD	ML (Random Forest)	(Hold-out) -	Participants with the highest polygenic risk score for ADHD usually have worsening symptoms.
Jung et al. [87], 2019	39 ADHD 34 normal	ML (SVM)	10-fold CV	The proposed model identified the COMT gene as having an impact on the abnormal development of the frontal cortex in ADHD patients.

4. Discussion

The 'gold standard' to diagnose ADHD usually relies on a combination of neuropsychological tests, rating scales, behavioral observations, examinations, and evaluation of the impact of treatment trials [90]. This is time-consuming and limited by the number of trained diagnostic

specialists globally. We reviewed the accuracy of the application of ML and DL to a range of well-established diagnostic tools, such as questionnaires/ rating scales, as well as more innovative diagnostic tools, including MRI and EEG, as summarized in Table 8. All but three ML studies adopted single modality approach for ADHD diagnosis, however a multimodal approach may be well suited to ADHD due to its heterogeneous clinical nature.

Table 8. Summary of AI studies using multiple modalities to develop their model.

Author [ref]	Private datasets	Modality	Feature	ML model	Validation approach	Accuracy
Muthuraman et al. [41], 2019	11 ADHD 11 normal	EEG+MEG	Spectral features	SVM	10-fold CV	98.0
Yoo et al. [91], 2019	191 ADHD 78 normal	fMRI+genetic	cortical thickness and volume features	RF	10-fold CV	85.1
Kautzky et al. [92], 2020	16 ADHD 22 normal	Genes+PET+MRI	SNPS+ROI	RF	5-fold CV	82.0
Crippa et al. [93], 2017	22 ADHD 22 normal	blood+EEG+cognitive test	neuropsychological, FA profiles, and deoxygenated-hemoglobin features	SVM	Nested 10-fold CV	81.0

It is estimated that 60 to 100% of ADHD children will develop one or more comorbid mental health or behavioral disorders as they reach adulthood [94], [95], including conduct disorder, depression, autism spectrum disorder (ASD), and bipolar disorder. The presence of comorbidities can make accurate diagnosis even more challenging [96]. An accurate diagnosis is required in order to tailor appropriate therapies. The preliminary evidence reviewed in this study suggests that AI can play a helpful role in diagnosing individuals with ADHD with and without comorbidities. There are nine ML studies in this review that have attempted to differentiate ADHD from other mental disorders or diagnose ADHD in individuals with a range of comorbidities (Table 9).

Table 9. Summary of AI studies that had considered other comorbidities of ADHD.

Author [ref]	Dataset	Modality	Comorbid condition	ML Model	Validation approach	Accuracy (%)
Tor et al. [97], 2021	45 ADHD 62 ADHD+CD 16 CD	EEG	Conduct disorder	kNN	10-fold CV	97.88
Vaidya et al. [98], 2019	307 ADHD 240 ASD 465 Control	MRI	ASD	SVM	(Hold-out) 50% training 50% test	88.9
Koh et al. [24], 2021	45 ADHD 62 ADHD+CD 16 CD	ECG	Conduct disorder	bagged tree classifier	10-fold CV	87.2
Jun et al. [99], 2018	86 ASD 83 ADHD 125 normal	MRI	ASD	SVM	10-fold CV	84.1
Faedda et al. [65], 2016	44 ADHD 21 ADHD+depression 48 bipolar 42 controls	Actigraphy	Bipolar depression	SVM	4-fold CV	83.1
Duda et al. [57], 2016	174 ADHD 248 ASD	Questionnaire	ASD	ENet and LDA	3-fold CV	82.0
Christiansen et al. [48], 2020	385 ADHD 135 Obesity 517 problematic gambling 592 normal	Questionnaire	Obesity, problematic gambling	DT (lightGBM)	(Hold-out) 70% training 30% test	80.0
Heller et al. [26], 2013	26 ADHD 26 normal	Game	Depression, ASD, anxiety, disruptive behavior disorder	-	3-fold CV	78.0
Guntuku et al. [79], 2017	1032 ADHD 1029 normal	Twitter	Depression Bipolar Anxiety	SVM	5-fold CV	76.0

In total, we report on 69 ML studies and 23 DL studies for ADHD diagnosis. SVM is the most commonly used classifier in ML research, while convolutional neural network (CNN) is the most commonly proposed model in DL research (Figure 6). This is not to say that SVM or CNN are superior to other ML or DL models. The suitability of an ML or DL model is determined by the type of dataset and feature used to train the classifier, while the practicality of the ML or DL

model is determined by a well-structured clinical trial in which their models are tested in real clinical settings with direct interaction with ADHD patients [30].

The various validation approach adopted by the AI studies is presented in Figure 7. The top three validation adopted by AI studies for model evaluation is the hold-out validation (20 studies), 10-fold cross-validation (CV) (20 studies), and leave-one-out cross-validation (LOOCV) (18 studies). Hold-out validation is appropriate for big datasets and requires segmenting the data into training, validation, and test sets; the training set trains the model, the validation set tunes the model, and the test sets evaluate the model's performance [100]. The K-fold CV method is a robust validation method that divides datasets into k number of folds. The model's performance will be evaluated using one fold, while the remaining fold will be utilized to train the model. The K-fold CV iterates k times to confirm that all of the folds were employed to train and test the model [101]. The LOOCV is a type of k-fold CV where k is the number of samples in the dataset. Hence, it can only be implemented for small datasets due to its large computational cost [101]. However, we would like to call to attention Hamedi et al. [40]'s use of the leave-one-subject-out CV (LOSOCV) in this review. LOSOCV is a subject-based validation that ensures the AI model can predict the condition of each subject based on the data provided by the other subjects. Hence, we recommend that LOSOCV be used to evaluate the clinical relevance of the AI model since it provides a significant association between the training and test subjects [100], [102].

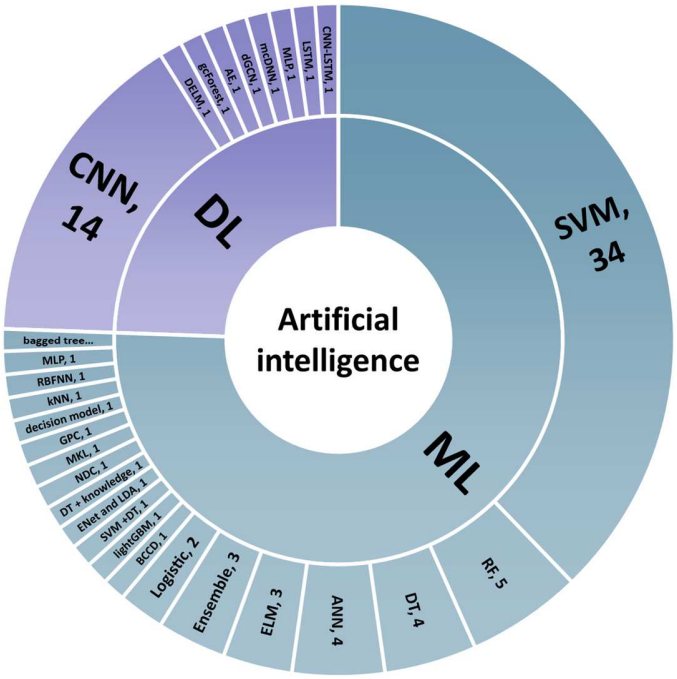

Figure 6. Sunburst plot of AI studies analyzed in this review. First level indicates type of AI studies, and second level indicates type of classifier proposed by AI studies.

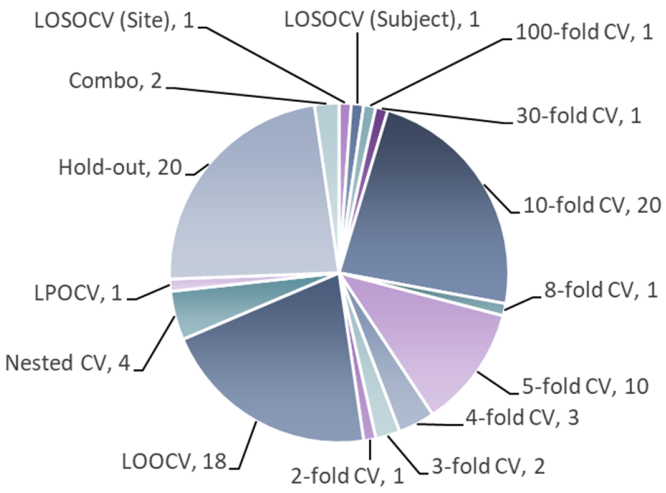

Figure 7. Pie chart representation of the validation approach used by the AI studies in ADHD detection.

There is definitely scope for improvement with AI methodology for ADHD diagnosis before it can be considered for clinical use. From Figure 8, we can see that DL research started only in 2017 and has yet to reach maturity in its technological advancement, whereas the percentage of ML studies has declined with the rise of DL research. This is not surprising given a large number of ML studies in ADHD diagnosis, which has made it extremely competitive and difficult for new studies to outperform previous ones. The average model accuracy reported by these ML and DL studies has remained stable between 80 and 90% since 2013. Nonetheless, the rapid increase in AI studies in recent years, as technology advances, indicates that computer-aided ADHD diagnosis is improving. As such, we hope to encourage more DL studies in ADHD diagnosis so that its feasibility can be demonstrated and a clinical trial can be conducted.

However, despite the vast quantity of AI research in MRI and EEG for ADHD diagnosis revealed in this review, neither diagnostic technology is currently employed in routine clinical settings by psychiatrists or pediatricians to diagnose ADHD [28], [103]. As both diagnostic tools can only be used in hospital settings or laboratories, gathering data from individuals with a diagnosis of ADHD is a time-consuming and expensive process [28], [104]. MRI requires patients to be still, which can be particularly challenging for people with ADHD, resulting in a higher chance of motion artifacts that render interpretation very difficult [105], [106]. Questionnaires, which are commonly used to assess ADHD, have the potential to be biased and subjective in their interpretation. Wearable devices, on the other hand, may be able to give objective measurements that can help with the diagnosis of ADHD. Therefore, wearable devices such as photoplethysmography (PPG) or accelerometers may be better suited as data acquisition devices for ADHD patients and should be investigated further for future AI studies.

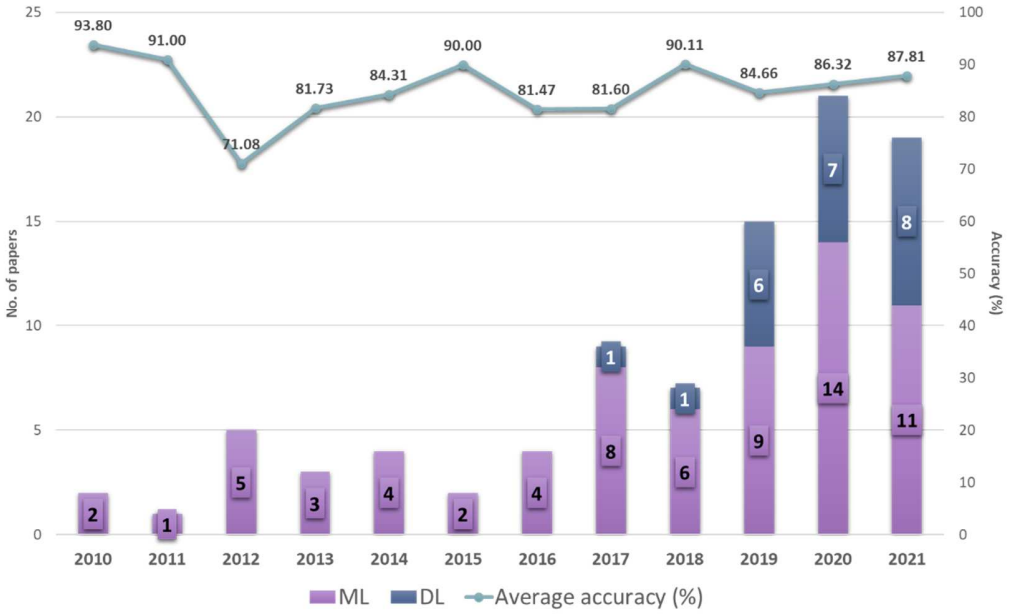

Figure 8. Bar chart representation of the number of AI studies in ADHD diagnosis published across the years from 2010 to 2021. Line graph represents the average model accuracy of AI studies across the years.

In summary, the significance of this review is as follows:

- We have gathered 92 AI studies for this review and categorized them according to the type of modality or dataset used to train their model for ADHD diagnosis. Namely, MRI, physiological signals, questionnaires, game simulation, performance test, motion data, and miscellaneous, including pupillometric, twitter, and genetic data.
- MRI and EEG signals are the two most widely used modalities in the ML and DL models for ADHD diagnosis. For these two modalities, we have identified the most commonly used features for ADHD diagnosis: functional connectivity features and power spectral features for MRI and EEG, respectively.
- For studies that have used questionnaire/ rating scales data, we have listed the standard ADHD assessment questionnaires that have successfully helped ML models to achieve high diagnostic performance.
- We have also charted the rising trend in the number of research for ADHD diagnosis over the years, in particular the DL models, which have been increasingly popular in recent years.
- Numerous validation methods employed by the ML and DL studies were also identified, and the most prevalent validation approaches used by the ML and DL research were found to be hold-out validation and 10-fold CV.

This review also has some limitations:

- Apart from the popular ADHD-200 MRI database, the scarcity of large publicly available ADHD databases for the rest of the modality category caused the majority of the studies in this review to use private datasets.
- The number of subjects and the methods used to collect data varied greatly for private datasets.
- For MRI studies that had used the ADHD-200 database, the number of subjects included varied greatly.
- It is difficult to compare the results of ADHD studies as different datasets were used, and there was a great variation in the number of subjects, data acquisition methods, and validation methods used.

5. Future direction for AI in ADHD diagnosis.

There are several future research pathways that could be followed to further explore the use of AI as a clinical decision support tool for ADHD. Ultimately, we hope to encourage the development of a cloud system, as depicted in Figure 9, that has unified data covering all ADHD diagnostic tools. As a result, clinicians could have ready access to all the information needed to confirm a diagnosis. For example, parents, teachers, or ADHD patients could complete the questionnaires on their own and have the AI models in the cloud system analyze the questionnaire data for psychiatrists or pediatricians. Hence, there is also scope for researchers to apply AI as part of a diagnostic pathway and as a precision medicine clinical decision support system to help with tailoring and monitoring treatments. However, in order to implement the cloud system depicted in Figure 9, further work will need to focus on the three primary aspects listed below.

Firstly, more publicly accessible ADHD databases need to be created. Other than the publicly available MRI ADHD-200 database used by 32 studies in this review, other studies needed to utilize private datasets. Since ADHD is a heterogenous disorder, it is important that databases of different types of ADHD diagnostic tools are available. In particular physiological signals (ECG) and motion data (accelerometer), would be highly desirable, as these were the biological tools that have shown more effectiveness in representing the inattentiveness, impulsiveness, and hyperactivity symptoms of individuals during their daily routines.

Secondly, the efficacy and usability of wearable technologies for ADHD diagnosis must be investigated and justified. Very few AI studies have attempted to use these data to diagnose ADHD; only one study used ECG signals, while four studies used motion data. There is also another study that had used heart rate variability (HRV) for ADHD diagnosis, but no accuracy data was reported hence this study was not included in this review [107]. Nonetheless, this shows that HRV is also another possible parameter for ADHD diagnosis. Another parameter that could be explored is PPG signals which can easily be acquired from smartwatches, smartphones and oximeters [108]. An advantage of PPG signals is that they have low bandwidth requirements, which do not deplete battery's capacity excessively [109], making

them excellent candidates for signals stored in a cloud system, as shown in Figure 9. The ambulatory signal collection is also very helpful in telehealth situations, which has been increasingly being used clinically since the COVID-19 pandemic.

Finally, future work should enforce the explainability of ML and DL models. AI methodologies like ML and DL can suffer from poor interpretability [110], [111]. Because of the complicated algorithm used to derive the result, DL models are referred to as a "black box", and clinicians find it hard to understand their outputs. The poor interpretability of AI algorithms has hampered their adoption in healthcare as a clinical decision support tool [112]. Therefore, future work for DL models should focus on the explainability of the model. For instance, a few techniques such as LIME, SHAP or integrated gradients that can improve the interpretability of ML or DL models [113]. We hope to encourage the development of a practical AI model for ADHD diagnosis and monitoring, which will be an important component of the cloud system depicted in Figure 9.

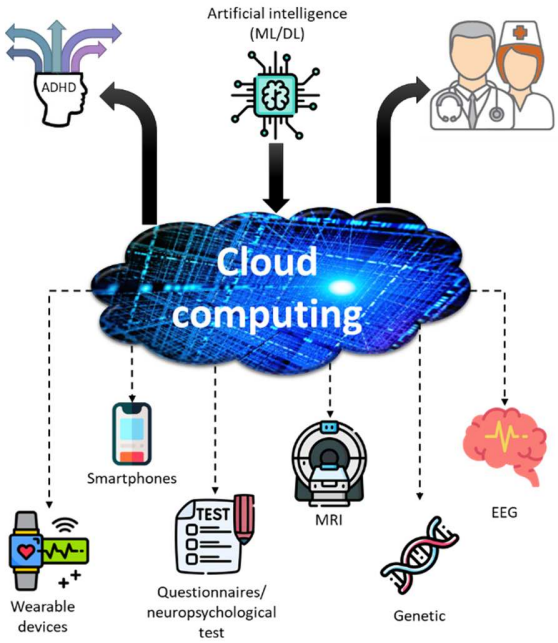

Figure 9. Cloud system designed for ADHD diagnosis and monitoring.

6. Conclusion

This review surveyed various ADHD diagnostic tools and included studies that used ML and DL AI techniques to perform the diagnosis. Ninety-one studies were determined to be eligible for this review, and they were further subdivided into their respective modalities for critical analysis. As a result, we notice that the majority of the studies were inclined toward hospital settings modalities like MRI and EEG, while the rest of the modalities were reported by very few studies. In addition, there was lack of publicly available datasets for the majority of the modalities except for MRI. There were limited studies using data acquired from wearable

devices like ECG and accelerometer, and no studies attempted to use PPG signals. Therefore, we propose that future research focus on developing more publicly available datasets for the other modalities in ADHD assessment and developing AI models that utilize data from wearable devices for ADHD diagnosis and monitoring. We also suggest future AI studies in ADHD to improve the interpretability of their models to encourage adoption in healthcare. With more robust research in AI techniques, a cloud system capable of reaching out to various ADHD diagnostic tools could become a reality and serve as an indispensable clinical decision support tool for clinicians.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix table A.1. Summary of list of AI studies that used MRI data to develop their model.

Author	Dataset	Subjects	Feature extracted	Classifier	Validation approach	Accuracy (%)
Deep learning (DL)						
Zhang et al. [114], 2020	public (Neuro Bureau ADHD-200 dataset)	422 ADHD 597 normal	time-series signals	CNN	LOSOCV (site-based)	54.1
Zou et al. [115], 2017	public (Neuro Bureau ADHD-200 dataset)	285 ADHD 491 normal	functional connectivity + morphology feature	CNN	4-fold CV	69.2
Mao et al. [116], 2019	public (Neuro Bureau ADHD-200 dataset)	359 ADHD 429 normal	preprocessed fMRI scans	CNN	(Hold-out) 54.3% training 54.9% test	71.3
Zhao et al. [117], 2021	public (Neuro Bureau ADHD-200	260 ADHD 343 normal	functional connectivity features	dGCN	10-fold CV	72.0

	dataset)					
Peng et al. [118], 2021	public (Neuro Bureau ADHD-200 dataset)	351 ADHD 430 normal	functional connectivity features	CNN	5-fold CV	72.9
Riaz et al. [119], 2020	public (Neuro Bureau ADHD-200 dataset)	351 ADHD 430 normal	fMRI time-series signals	CNN	(Hold-out) NA	73.1
Chen et al. [120], 2019	public (Neuro Bureau ADHD-200 dataset)	362 ADHD children 585 normal children	combination of imaging and personal characteristic data	mcDNN	5-fold CV	78.3
Shao et al. [121], 2019	public (Neuro Bureau ADHD-200 dataset)	310 ADHD 359 normal	functional connectivity features	gcForest	(Hold-out) NA	82.7
Khullar et al. [122], 2021	public (Neuro Bureau ADHD-200 dataset)	351 ADHD 430 normal	Raw images	CNN-LSTM	NA	98.2
Preetha et al. [123], 2021	public (Neuro Bureau ADHD-200 dataset)	260 ADHD-C children 173 ADHD-I children 744 normal children	-	DELM	NA	98.2
Tang et al. [21], 2021	public (Neuro Bureau ADHD-200 dataset)	-	functional connectivity features	AE	LOOCV	99.6
Machine learning (ML)						
Colby et al. [124], 2012	public (Neuro Bureau ADHD-200 dataset)	285 ADHD 491 normal	functional connectivity features, Structural and morphological features	SVM-RBF	10-fold CV	55.0

Qureshi et al. [125], 2016	public (Neuro Bureau ADHD-200 dataset)	67 ADHD-C children 67 ADHD-I children 67 normal children	Cortical Thickness and volume features	ELM	(Hold-out) 70% training 30% test	60.8
Brown et al. [126], 2012	public (Neuro Bureau ADHD-200 dataset)	192 ADHD-C children 124 ADHD-I children 523 normal children	characteristic data	Logistic	10-fold CV	62.5
Zhou et al. [127], 2021	Private	116 ADHD 116 normal	macrostructural property, Morphometric measures, Image intensity measures	MKL	Nested 5-fold CV	64.3
Itani et al. [128], 2019	public (Neuro Bureau ADHD-200 dataset)	146 ADHD 105 normal	gender and 26 ROI	DT	LOOCV	66.6
Anderson et al. [129], 2014	public (Neuro Bureau ADHD-200 dataset)	276 ADHD 472 normal	Phenotypic, Independent Components, motion, structural, functional connectivity features	DT	10-fold CV	66.8
Sato et al. [130], 2012	public (Neuro Bureau ADHD-200 dataset)	249 ADHD 122 ADHD-I	functional connectivity features	Logistic	LOOCV & k-fold CV	67.0
Tan et al. [131], 2017	public (Neuro Bureau ADHD-200 dataset)	117 ADHD 98 normal	FV and demographic variables	SVM	10-fold CV	68.6
Sidhu et al. [132], 2012	public (Neuro Bureau ADHD-200 dataset)	141 ADHD-C children 98 ADHD-I children 429 normal	phenotypic + imaging data	SVM	10-fold CV	72.9

		children				
Chaim-Avancini et al. [133], 2017	Private	52 ADHD 44 normal	ROIs	SVM	10-fold CV	73.8
Wang et al. [134], 2018	private	36 ADHD 35 normal	interregional morphological patterns	SVM-RFE	LOOCV	74.6
Liu et al. [135], 2020	public (Neuro Bureau ADHD-200 dataset)	351 ADHD 430 normal	Deep learning model extracted features	AdaDT	(Hold-out) 77% training 23% test	75.6
Luo et al. [136], 2020	Private	36 ADHD 36 normal	Features of nodal efficiency	Ensemble	5-fold CV	76.6
Hart et al. [137], 2013	Private	30 ADHD 30 normal	inhibition networks	GPC	LOOCV	77.0
Khan et al. [138], 2021	public (Neuro Bureau ADHD-200 dataset)	295 ADHD 364 normal	functional connectivity features	SVM	(Hold-out) 75% training 25% test	81.0
Miao et al. [139], 2019	public (Neuro Bureau ADHD-200 dataset)	308 ADHD 361 normal	Principle Components and Entropy-Based Features	DT	(Hold-out) 79% training 21% test	81.8
Jun et al. [99], 2018	public (ABIDE and ADHD200 dataset)	86 ASD 83 ADHD 125 normal	ROI-to-ROI functional connectivity feature	SVM	10-fold CV	84.1
Sun et al. [140], 2020	public (Neuro Bureau ADHD-200 dataset)	351 ADHD 430 normal	functional connectivity features	SVM	LOOCV	85.3
Shao et al. [141], 2020	public (Neuro Bureau ADHD-200 dataset)	35 ADHD 32 normal	Principle Components and Entropy-Based Features	T-R-SVM	(Hold-out) 60% training 20% validation 20% test	86.4

Riaz et al. [142], 2017	public (Neuro Bureau ADHD-200 dataset)	59 ADHD 93 normal	functional connectivity features	SVM	LOOCV	86.8
Chen et al. [143], 2020	public (Neuro Bureau ADHD-200 dataset)	272 ADHD 361 normal	functional connectivity features	SVM	LOOCV	88.1
Vaidya et al. [98], 2019	private	307 ADHD 240 ASD 465 Control	3 behavioral profiles	SVM	(Hold-out) 50% training 50% test	88.9
Deshpande et al. [144], 2015	public (Neuro Bureau ADHD-200 dataset)	260 ADHD-C children 173 ADHD-I children 744 normal children	linear/nonlinear directional/nondirectional functional connectivity features	FCC ANN	LOOCV	90.0
Peng et al. [145], 2013	public (Neuro Bureau ADHD-200 dataset)	59 ADHD 93 normal	brain structure features	ELM	LOOCV	90.2
Qureshi et al. [146], 2017	public (Neuro Bureau ADHD-200 dataset)	67 ADHD-C children 67 ADHD-I children 67 normal children	functional connectivity features	ELM	(Hold-out) 79% training 21% test	92.9
Johnston et al. [147], 2014	private	34 ADHD 34 control	white matter images (m)	SVM	LOOCV	93.0
Tang et al. [148], 2020	public (Neuro Bureau ADHD-200 dataset)	59 ADHD 93 normal	functional connectivity features	Decision model	LOOCV	97.6
Bohland et al. [20], 2012	public (Neuro Bureau ADHD-200 dataset)	-	Gender, Non-Imaging Phenotypic, Anatomical, and functional connectivity features	SVM	2-fold CV	98.0

*NA= Not available

Appendix table A.2. Summary of list of AI studies that used physiological signals to develop their model.

Author	Dataset	Subjects	Feature extracted	Sampling frequency	Classifier	Validation approach	Accuracy (%)
EEG- Deep learning (DL)							
Vahid et al. [149], 2019	private	48 ADHD 44 normal	end-to-end	500	CNN	LOOCV	83.0
Dubreuil-Vall et al. [150], 2020	private	20 ADHD 20 normal	EEG spectrograms	500	CNN	Leave-pair-out CV (LPOCV)	88.0
Chen et al. [151], 2019	private	50 ADHD 57 normal	Grad-CAM	1000	CNN	8-fold CV & (Hold-out 8:1)	90.3
Tosun et al. [152], 2021	private	1088 ADHD sample 1088 normal sample	Power spectral features	500	LSTM	(Hold-out) 80% training 20% test	92.2
Chen et al. [153], 2019	private	50 ADHD children 51 normal children	connectivity matrix	1000	CNN	10-fold CV	94.7
Moghaddari et al. [34], 2020	public (National brain mapping laboratory of Iran)	31 ADHD 30 normal	Power spectral band separation Making RGB images	128	CNN	5-fold CV	98.5
Ahmadi et al. [23], 2020	private	13 ADHD-C children 12 ADHD-I children 14 normal children	spatial and power spectral features	250	CNN	5-fold CV	99.5
EEG-Machine learning (ML)							
Müller et al. [154], 2019	private	181 ADHD 147 normal	Power spectral features, ERP peak	500	SVM	Nested 10-fold CV	80.0

			amplitudes and latencies				
Kim et al. [155], 2021	Private	34 ADHD 45 normal	MMN source activity features	1000	SVM	LOOCV	81.0
Tenev et al. [156], 2014	private	67 ADHD 50 normal	eye close, eye open, ECPT and VCPT	256	Ensemble	10-fold CV	82.3
Khoshnoud et al. [157], 2018	private	12 ADHD 12 normal	nonlinear power spectral features	256	SVM	4-fold CV	83.3
Chen et al. [158], 2019	private	50 ADHD 58 normal	Power spectral features	1000	SVM	10-fold CV	84.6
Mueller et al. [159], 2011	private	75 ADHD 75 normal	ERP components	250	SVM	10-fold CV	91.0
Altınkaynak et al. [160], 2020	private	23 ADHD 23 normal	Morphological, nonlinear, and wavelet features	2500	MLP	LOOCV	91.3
Mueller et al. [161], 2010	private	74 ADHD 74 control	ERP components	-	SVM	10-fold CV	92.0
Ahmadlou et al. [162], 2010	private	40 ADHD 7 normal	Power spectral features	256	RBFNN	(Hold-out) 90% training 10% test	95.6
Tor et al. [97], 2021	private	45 ADHD 62 ADHD+CD 16 CD	nonlinear features	500	kNN	10-fold CV	97.9
Guney et al. [163], 2021	private	27 ADHD 38 normal	event-related potentials (ERPs)	1000	ANN	10-fold CV	98.4
Rezaeezadeh et al. [164], 2020	private	12 ADHD children 12 normal children	non-linear power spectral features	256	SVM (RBF)	10-fold CV	99.6
Joy et al. [165], 2021	private	5 ADHD 5 normal	nonlinear power spectral	256	ANN	-	99.8

			features				
Kaur et al. [166], 2019	Private	47 ADHD 50 normal	PSR-PSO	256	NDC	(Hold-out) 69% training 31% test	100.0
Bashiri et al. [167], 2018	private	15 ADHD-HI 30 ADHD-I	Power spectral features	250	ANN	(Hold-out) 70% training 15% validation 15% test	100.0
Öztoprak et al. [22], 2017	private	70 ADHD 38 normal	Power spectral features	1000	SVM-RFE	5-fold-CV	100.0
ECG-Machine learning (ML)							
Koh et al. [24], 2021	private	45 ADHD 62 ADHD+CD 16 CD	entropy features	500	Ensemble	10-fold CV	87.2
MEG-Machine learning (ML)							
Hamedi et al. [40], 2021	public-OMEGA	25 ADHD 25 normal	Coherence	2400	SVM	LOSOCV	92.7

*NA= Not available

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