Effectiveness of Virtual/Augmented Reality-based therapeutic interventions on individuals with autism spectrum disorder: A comprehensive meta-analysis

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Abstract

In recent years, the application of Virtual Reality (VR) technology for therapeutic purposes has escalated dramatically. Favorable properties of VR for engaging patients with autism, in particular, have motivated an enormous body of investigations targeting autism-related disabilities with this technology. This study aims to provide a comprehensive meta-analysis for evaluating the effectiveness of Virtual Reality (VR) on the rehabilitation and training of individuals diagnosed with an autism spectrum disorder. Accordingly, we conducted a systematic search of related databases and after screening for inclusion criteria, reviewed 33 studies for more detailed analysis. Results revealed that individuals undergoing VR training have remarkable improvements with a relatively large effect size with Hedges g of 0.74. Furthermore, the results of the analysis of different skills indicated diverse effectiveness. The strongest effect was observed for daily living skills ($g=1.15$). This effect was moderate for other skills: $g=0.45$ for Cognitive skills, $g=0.46$ for Emotion regulation and recognition skills, and $g=0.69$ for social and communication skills. Moreover, five studies that had used augmented reality also showed promising efficacy ($g=0.92$) that calls for more research on this tool. In conclusion, the application of VR-based settings in clinical practice is highly encouraged, though their standardization and customization need more research.

Keywords: Autism spectrum disorder, Virtual Reality, Augmented reality, Rehabilitation

1. Introduction

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder characterized by impairments in social communication and social interaction in conjunction with restricted, repetitive patterns of behavior, interests or activities ([American Psychiatric Association, 2013](#)). Affecting 1 in 68, ASD is the most prevalent psychological childhood disorder with sustained long term effects on the quality of life of these patients ([Baio, 2014](#)).

Although at present there is no particular accepted treatment for ASD, there is a growing consensus that appropriately targeted individualized behavioral and educational intervention programs (e.g. Treatment and Education of Autistic and Related Communication Handicapped Children (TEACCH) program, Early Intensive Behavioral program, Applied Behavior Analytic (ABA) program, Denver model, etc.) have the potential to positively impact the lives of individuals and their families ([Virues-Ortega, Julio, & Pastor-Barriuso, 2013](#), [Eldevik et al., 2009](#), [Makrygianni, Gena, Katoudi, & Galanis, 2018](#), [Dawson et al., 2010](#), [Weitlauf et al., 2014](#)). The increasing number of individuals with ASD together with the substantial achievements have been made thus far by this behavioral rehabilitation programs have ignited a line of research aimed at developing several technologies with the focus on improving these programs. ([H. L. Miller & Bugnariu, 2016](#)). Some examples include robotics ([Billard, Robins, Nadel, & Dautenhahn, 2007](#); [Dautenhahn, 2003](#); [M. Moghadas & H. Moradi, 2018](#)), interactive video modeling ([Aldi et al., 2016](#); [Golan et al., 2010](#); [Macpherson, Charlop, & Miltenberger, 2015](#)), mobile and touchpad devices ([Burckley, Tincani, & Guld Fisher, 2015](#); [Cihak, Wright, & Ayres, 2010](#); [El Zein et al., 2016](#)), wearable training systems on google glass ([Kinsella, Chow, & Kushki, 2017](#)) and virtual reality ([Parsons & Cobb, 2011](#); [Parsons & Mitchell, 2002](#)). Interestingly, individuals with ASD have shown special interest and adherence to computerized programs ([Moore & Calvert, 2000](#)) and learning through it ([Bernard-Opitz, Sriram, & Nakhoda-Sapuan, 2001](#); [Williams, Wright, Callaghan, & Coughlan, 2002](#)). Moreover, the burden of many hours of training by a therapist can be alleviated by using technology-based training at home.

Among these technologies, virtual reality (VR) has been one of the most promising tools to address the psychological needs of people with ASD in various settings. Almost two decades ago, VR has been introduced as an effective tool in neurocognitive rehabilitation of patients with

ASD (Cheryl G. Trepagnier, 1999). This effectiveness has been approved by a decade of research afterward practicing different types of VR configurations on patients with different levels of disorder (Bellani, Fornasari, Chittaro, & Brambilla, 2011, Georgescu, Kuzmanovic, Roth, Bente, & Vogeley, 2014). Besides, some efforts that have focused on elaborating VR-based intervention by proposing consideration of psychological theories in task design (Rajendran, 2013) and highlighting particular features of VR configurations and human-VR interactions (Parsons, 2016) could have possibly resulted in the improved application of this technology in the recent works. Virtual reality reduces the social pressure on the patient and provides a realistic environment for more effective training and possibly reduces the needed training hours. Current studies cover a great range of training interventions, including training of social adaptation and communication skills (Kurniawan, 2018; Manju, Padmavathi, & Tamilselvi, 2018; Zhao, Swanson, Weitlauf, Warren, & Sarkar, 2018), emotional skills (Esubalew Bekele et al., 2014; Ip et al., 2018; Lorenzo, Lledo, Pomares, & Roig, 2016), daily living skills such as shopping (Adjorlu, Høeg, Mangano, & Serafin, 2017; Lamash, Klinger, & Josman, 2017), driving (Ross et al., 2018; Wade et al., 2015, 2016) and street crossing (Josman, Ben-Chaim, Friedrich, & Weiss, 2008; Saiano et al., 2015) and cognitive functions (Didehbandi, Allen, Kandalaft, Krawczyk, & Chapman, 2016; Nubia, Fabián, Wilson, & Wilmer, 2015; Vahabzadeh, Keshav, Salisbury, & Sahin, 2018).

VR is a Human-computer interface which by using computer graphics generates a multidimensional environment with multiple sensory channels that allow individuals to explore the virtual environment (VE) through visual, auditory, tactile and sometimes even olfactory perception, creating an interactive and immersive experience for the user (Burdea & Coiffet, 2003; Self, Scudder, Weheba, & Crumrine, 2007a). VR can be implemented in Head-mounted visual display systems (HMDs), head and body tracking, CAVE automatic virtual environments or room-like displays and other technologies. They can be used to create a realistic sense of "presence" within a computer-generated environment (Mishkind, Norr, Katz, & Reger, 2017). Augmented Reality (AR), which can be considered as another type of VR, is a real-time view of an existing world that is superimposed by some virtual data. Unlike VR technology that fully submerges people in an artificial environment avoiding the existing world, AR technology enhances the feeling by overlaying the computer-generated things over the real world (Raaja, ., ., & Vijayabhas, 2014).

VR training offers several advantages, maybe the most important one is providing safe access to realistic environments that would be considered dangerous in the real world along with active participation in the virtual world. Furthermore, by providing flexibility in controlling the task complexity, reinforcement through repetition and real-time visual and auditory feedback, VR enhances enjoyment and thus improves learning quality through it. These favorable properties of VR have made it a viable tool to be used in training and rehabilitation (Holden, 2005; Weiss, Kizony, Feintuch, & Katz, 2006).

In the past decade, VR has served as an effective new treatment tool in different areas such as rehabilitation in post-stroke patients (Iruthayarajah, McIntyre, Cotoi, Macaluso, & Teasell, 2017; Li, Han, Sheng, & Ma, 2016), pain management (Luo, Cao, Zhong, Chen, & Cen, 2019), phobias, post-traumatic stress disorders, obsessive-compulsive disorders, anxiety and stress disorders (Kampmann, Emmelkamp, & Morina, 2016), depression (Fodor et al., 2018), ADHD (Bashiri, Ghazisaeedi, & Shahmoradi, 2017), Cerebral palsy (Y.-P. Chen, Lee, & Howard, 2014) and, of course, ASD.

Although during recent years, several systematic reviews have been conducted to evaluate the efficacy of technology application on training and teaching different skills such as communication and social skills (DiGennaro Reed, Hyman, & Hirst, 2011; Wainer & Ingersoll, 2011), academic skills (Pennington, 2010), or information processing (Den & Sterkenburg, 2015), only the contribution of Patricia Mesa-Gresa et al. in 2018 (Mesa-Gresa, Gil-Gómez, Lozano-Quilis, & Gil-Gómez, 2018) was focused on VR and autism as an evidence-based systematic review including both clinical and technical databases about the effectiveness of VR-based intervention in ASD. However, their study did not provide a statistical analysis of outcomes for different clinical targets, besides the included population in their study was limited to children and adolescence.

To date of this study, there is just one meta-analysis on technology-based intervention including computer games, interactive DVDs, shared active surfaces, and virtual reality in the patients with autism (Grynszpan, Weiss, Perez-Diaz, & Gal, 2014). Their study presented a comprehensive meta-analysis on the technology-based intervention used in ASD people, however, the type of technology used in their included studies was mostly based on computer gaming software, with 18

studies employing desktop computers out of 21; while the number of studies applying VR technology for training patients with autism have witnessed a dramatic surge during recent years.

Hence, we have tried to conduct a comprehensive meta-analysis focused on the effectiveness of VR technology per se in the training and rehabilitation of patients with autism. To achieve this goal, we performed a systematic search for studies assessing this type of intervention on the ASD population and evaluated the effectiveness of VR training on different skills including social and communication, emotion regulation, daily living, and cognitive skills. We evaluated and compared the effect sizes of different skills' improvement to appraise the most influenced clinical targets.

2. Methods

2.1. Study identification and selection

We systematically searched the Clinical and technical databases including PubMed, ERIC, web of science, PsycINFO and IEEE following a comprehensive search strategy with the main search terms of *virtual reality, augmented reality, artificial reality, computer-simulated reality, virtual environment, virtual world, computer-simulated environment, mediated reality, mixed reality* for intervention and the search terms of *autism spectrum disorder, pervasive children developmental disorder and Asperger* for disorder, considering adjusted queries for each database. The detailed search strategy and search queries for each database can be seen in supplemental data. The initial search yielded a total number of 1204 articles. There was no limit on the publication date and the search is updated until 19 October 2019.

After removing duplicate records 915 articles remained for the preliminarily screening of titles and abstracts. Those studies presenting original work and discussed virtual or artificial realities for rehabilitation and training of the ASD population which was published in a peer-reviewed journal or peer-edited conference proceeding books were selected. Case reports, review articles, records that only contained an abstract and records in non-English languages have been discarded. The

remained articles were 52 randomized clinical trials, cohort studies, and case series. The full text of these articles was retrieved for more detailed consideration.

A full-text detailed review was done using the PICO process. The criteria for including studies in our meta-analysis were: 1) participants of any age were diagnosed with autism spectrum disorder with a formal diagnostic tool, 2) intervention was conducted on an interactive virtual reality-based setting, 3) the designed intervention aimed at improving skills related to the core symptoms or deficits of ASD, 4) the same measured data was available on a control group as for intervention group that measurements performed on the intervention group before undertaking the goal intervention or on a control group which did not receive the goal intervention and 5) intervention outcomes were assessed by a quantitative measure which was similar for the intervention and control conditions. The studies which did not comply with these criteria were excluded. Along with those, 9 records which were containing incomplete and/or inaccurate outcome reports in its text or figures, were contacted for further information ([Adjorlu et al., 2017](#); [E. Bekele et al., 2016](#); [Bozgeyikli et al., 2017](#); [Cox et al., 2017](#); [Dickinson & Place, 2016](#); [Escobedo, Tentori, Quintana, Favela, & Garcia-Rosas, 2014](#); [Lorenzo et al., 2016](#); [Lorenzo, Pomares, & Lledo, 2013](#)). One of them responded ([Saiano et al., 2015](#)) and thus included in the study. Besides that, 5 other articles were excluded for a very small sample size (less than 3) ([C.-H. Chen, Lee, & Lin, 2015](#); [Cheng, Huang, & Yang, 2015](#); [Ke & Im, 2013](#); [Lorenzo et al., 2016](#); [Wang & Reid, 2013](#)) and 3 others for an unfavorable design of the experiment (e.g. single case reports) ([Esubalew Bekele et al., 2014](#); [Kim et al., 2015](#); [Parsons, 2015](#)). In the end, 33 studies were proved to be eligible for entering the meta-analysis. The flow diagram of study selection process is presented in Fig. 1.

All the studies were coded for the following items: definite diagnosis of disease, diagnostic tool, mean and standard deviation of age of participants, number of participants assigned and completed the course of intervention in the target and control group, contributing factors and modalities that experimenters controlled for inclusion of study population, concomitant comorbidities with ASD in participants, Type of intervention technology (VR or AR), technical details of intervention, experiment properties and intensity of intervention, design of experiment (uncontrolled or case-control), purpose of experiment, outcome measures and their descriptions.

Fig. 1 flow diagram of study selection and identification process.

2.2. Coding and defining variables

Autism spectrum disorder is a very heterogeneous disorder that different patients may vary hugely in levels of deficit in different aspects of cognitive functionalities, thus most of the studies had attempted measuring multiple outcomes for assessment of therapeutic effectiveness. Dealing with this variability in study outcomes, we categorized them into four major categories: Social and communication skills (SCS; e.g. social adaptation and interaction, communication, social reciprocity, social responsiveness, negotiation skills, theory of mind), Emotion recognition and regulation skills (ERS; e.g. emotion expression, affect recognition, stress and anxiety management), Daily Living Skills (DLS; e.g. driving, shopping, street crossing, job interview skills) and Cognitive Skills (CS; e.g. attention and concentration, reasoning and problem solving, executive function, language and meta-cognition). By this means, we were able not only to determine the general effectiveness of VR training but also to distinguish different aspects of ASD-related disabilities in terms of benefit they receive from intervention.

There was a considerable number of trials in which outcomes were assessed by a measure that was mostly intuitive and specifically designed for that experiment (e.g. number of greeting with a friend in virtual environment or subject performance in a face detection task, driving, cross

walking, shopping task or construction play task) rather than measures that are widely used in the field (e.g. SRS score of social awareness, PEP-3 score Affective expressions, ABAS score of leisure, etc.). We classified these two types of measures as non-formal and formal and considered it as a possible moderator of measured training effectiveness for each trial. Another presumed moderator was the type of technology used for intervention, namely VR or AR, which are characteristically different in terms of design and application. To scrutinize the effectiveness of the intervention at any age, we assumed four age categories of 4 to 8, 8 to 12, 12 to 16 and above 16 years old. Each trial fell into one of these categories based on their participant's mean age. In a considerable number of trials, patients had some concomitant comorbidity along with their main disorder, ASD. To see how much this comorbidity affected the results of the intervention, we considered the presence or absence of comorbidity as another moderator and compared the results of interventions when having or not having concomitant comorbidity. These four categorical moderators were defined for further subgroup meta-analysis. The trials in which full information regarding any of these moderators was not available were excluded from analysis for that moderator.

Subgroup meta-regression was also applied to three continuous moderator variables: number of intervention sessions, sex, and publication date. These variables were defined as the number of separate sessions or visits in which intervention was applied, male ratio (number male subjects divided by the total number of subjects) and the year of publication of the study, respectively.

2.3. Statistical procedure

Similar to the majority of studies in the literature of training effectiveness, the pool of studies in our meta-analysis included a mixture of two major types of experiment designs, namely controlled and uncontrolled designs. In controlled or independent-groups design, one group receives the training and the other group serves as a control. The difference between the groups on the outcome measure is used as an estimate of the treatment effect. On the other hand, in uncontrolled or single-group pre-test: post-test design, each individual is measured before and after treatment and the difference between the individual's scores before and after it is used as an estimate of the treatment effect.

As the characteristic distinction between these two types of designs can lead to a significant difference in estimated effect size and its precision, we opted for design-specific estimations

proposed by (Morris & DeShon, 2002) for each study. For uncontrolled studies, the repeated measure effect size was calculated as the mean of change from pre to post-test scores divided by its standard deviation which is equivalent to the t-statistic of paired t-test between two pre and post-test data. Then, the SMD for these trials was calculated with:

$$\text{Eq.1 } SMD (\text{uncontrolled}) = \frac{t}{\sqrt{n}}$$

Where t represents t-statistic and n represents the number of participants. We used the t-stats values provided in the contents of articles whenever possible or calculated them from the exact pre and post-test scores.

For controlled studies, the SMD at the post-test was calculated by:

$$\text{Eq.2 } SMD (\text{controlled}) = \frac{\mu_c - \mu_i}{SD_{pool}}$$

Where μ_c represents mean of the control group, μ_i represents mean of the intervention group and SD_{pool} is calculated as:

$$\text{Eq.3 } SD_{pool} = \sqrt{\frac{(N_i - 1) * SD_i^2 + (N_c - 1) * SD_c^2}{N_i + N_c - 2}}$$

Where N_i is the size of the intervention group, N_c is the size of the control group, SD_i is the standard deviation of the intervention group and SD_c is the standard deviation of the control group at post-test.

For two controlled studies in which pre-test data were available for both intervention and control groups, SMD was calculated as:

$$\text{Eq.4 } SMD (\text{prepost controlled}) = \frac{(\mu_{post_i} - \mu_{pre_i}) - (\mu_{post_c} - \mu_{pre_c})}{SD_{pre}}$$

Where μ_{post_i} represents the mean of intervention group scores at post-test, μ_{pre_i} the mean of intervention group scores at pre-test, μ_{post_c} the mean of control group scores at post-test, μ_{pre_c} the mean of control group scores at pre-test and SD_{pre} is again calculated with the following equation:

$$\text{Eq.5 } SD_{pre} = \sqrt{\frac{(N_i - 1) * SD_{pre_i}^2 + (N_c - 1) * SD_{pre_c}^2}{N_i + N_c - 2}}$$

Where SD_{prei} and SD_{prec} represents the standard deviation of intervention and control group scores at the pre-test respectively (Morris, 2008). All of the above-mentioned calculations of SMDs were done in a way that assures the highest precision in the estimation of each experiment's effect size by the available information.

The final effect size indicator, Hedges g , then defined as the product of the output SMD and small sample correction factor $C = \frac{3}{4*df+1}$ where df is degree of freedom. Effect sizes were calculated and reported so that a positive sign represents an improvement in the target skill.

After the computation of effect sizes for each of the trials, we found out that most of them reporting more than one estimated value which is called dependent nested effect sizes in the literature of meta-analysis. Assuming independence between estimated values for multiple outcomes in each study is usually trivial and thus, obtaining a study-level effect size by averaging the values within studies might lead to some useful information loss. Handling the dependency among effect size estimates, three main methods have been proposed to date: Multivariate meta-analysis, Three-level meta-analysis and Robust Variance Estimation (RVE) (Moeyaert et al., 2017). Multivariate meta-analysis is applied when one or multiple outcomes are measured in each study are from a set of known and fixed outcomes across studies. The measured outcomes in our meta-analysis were highly variable from study to study so, we could not apply Multivariate analysis. Due to the small sample size of controlled trials, some of the estimated results of the three-level analysis were underpowered and unreliable, which would question drawn conclusions based on them. So, we opted for the third introduced method, Robust Variance Estimation. It's shown that this method accommodates well the dependence arising from multiple sources simultaneously, including multiple measures and multiple treatment groups (Moeyaert et al., 2017) and thus can be a felicitous choice for our study. Further detail on the application of the RVE method on our data is described in Results.

According to the guidelines of (Cohen, 1988), an absolute effect size of 0.2 to 0.3 is regarded as a small effect, around 0.5 as a medium effect and from 0.8 on as a large effect.

Heterogeneity was assessed by Cochran's Q , I^2 and τ^2 statistics. I^2 describes the percentage of variation in studies. The smaller the I^2 , the lower the level of heterogeneity among estimated values. τ^2 statistic is also a measure of between-study variance of effect sizes. When Q statistic is

very small, the estimated I^2 is not accurate in capturing the real heterogeneity (Borenstein, Higgins, Hedges, & Rothstein, 2017). In these cases, τ^2 is more informative specifically when comparing among subgroups with low heterogeneity.

Publication bias was investigated by visual inspection of funnel plots looking for any clue of asymmetry plus Eggers intercept test (Egger, Smith, Schneider, & Minder, 1997) to validate the conclusions.

All the analyses in the main text were done using customized scripts in MATLAB Mathworks. Three-level meta-analysis was performed in R using (Cheung, 2015).

3. Results

3.1. Description of studies

Thirty three studies complied with the inclusion and exclusion criteria (see methods) and entered into the meta-analysis. From them, 7, 24 and 2 of studies recruited only controlled, only uncontrolled and mixed design of experiments respectively. For the 2 mixed ones (Lamash et al., 2017; Yuan & Ip, 2018), as each of the designs had belonged to the different uncorrelated phases of the experiment, we treated each of them as a separate trial which led to 35 trials in aggregate (26 uncontrolled and 9 controlled). There was an overall number of 540 participants, 360 of them pertaining to uncontrolled and 180 to the intervention group of controlled studies. There were also other 156 ASD participants served as the control group who received no intervention at all.

For all of the two types of studies, pre and post-intervention data were defined with precision. In controlled trials, the evaluation of subjects was done after completion of the training phase (post-intervention) and the resultant data were compared between intervention and control groups. Only four out of these nine controlled trials (Ip et al., 2018; Smith et al., 2014) performed the same measurements of outcomes for baseline before-training phase of the study (pre-intervention) as for the post-intervention phase. Four of uncontrolled trials, applied ABC measurement strategy in a way that outcomes were measured in three temporal phases of the first session, last session and a while after completion (follow-up) of intervention (C.-H. Chen, Lee, & Lin, 2016; Kurniawan, 2018; Vahabzadeh et al., 2018). In these trials, we ascribed measured data in the first and last

sessions to be pre and post-intervention data respectively. Again in one another uncontrolled (Nubia et al., 2015) and one controlled (Zhang, Warren, Swanson, Weitlauf, & Sarkar, 2018a) trial measurement once was done after non-VR traditional training and it was repeated after targeted VR training which measured data in the first condition labeled pre and in the latter labeled post-intervention. In the other remaining trials, measurements were done just before and after the execution of VR training (pre and post).

Diagnosis of ASD in (C.-H. Chen et al., 2016, (Morag Maskey, Rodgers, Grahame, et al., 2019a) was confirmed by DSM-IV, in (Didehbani et al., 2016; Kandalaft, Didehbani, Krawczyk, Allen, & Chapman, 2013; Stichter, Laffey, Galyen, & Herzog, 2014; Wade et al., 2016) by ADOS, in (M. Maskey, Lowry, Rodgers, McConachie, & Parr, 2014) by SCQ, in (Smith et al., 2015, 2014) by SRS-II, in (Saiano et al., 2015; Simoes, Bernardes, Barros, & Castelo-Branco, 2018; Yang et al., 2017, (F. Chen, Wang, Peng, Yan, & Pan, 2019a) (Zhang et al., 2018a) by DSM_V and finally in (Josman et al., 2008) by CARS. The diagnostic tool in the other twenty trials was not mentioned. Participants in trials (Smith et al., 2015; Yang et al., 2017, (Ke & Moon, 2018a) were High-Functioning Autism Spectrum Disorder (HFASD), in (F. Chen et al., 2019a) were Low-Functioning Autism Spectrum Disorder (LFASD), in (Kandalaft et al., 2013; Zhao et al., 2018) were Asperger or Pervasive developmental disorder –not otherwise specified (PDD-NOS) , in (Milne, Luerssen, Lewis, Leibbrandt, & Powers, 2010; Strickland, Coles, & Southern, 2013) were HFASD or Asperger and in (Bai, Blackwell, & Coulouris, 2015) were Asperger. The level of disease in other twenty six trials was not specified. Several trials had considered controlling some contributing factors in the population of their study that could potentially impact the outcome of the intervention. For example, (C.-H. Chen et al., 2016; Didehbani et al., 2016; Ip et al., 2016, 2018; Manju et al., 2018; Saiano et al., 2015; Stichter et al., 2014; Yang et al., 2017, (Ke & Moon, 2018a) controlled the participants for IQ score, (Vahabzadeh et al., 2018, (Morag Maskey, Rodgers, Grahame, et al., 2019a) for SCQ score, (Wade et al., 2016) for SRS-II score, (F. Chen et al., 2019a) for PEP-3 score of language and motor skills and (Zhang et al., 2018a) for ASI score. In six uncontrolled and three controlled trials, patients had another concomitant comorbidity or disorder alongside their main disorder, ASD. Examples include trials (Didehbani et al., 2016; Vahabzadeh et al., 2018) that some of the patients had a diagnosis of ADHD, (M. Maskey et al., 2014, (Morag Maskey, Rodgers, Grahame, et al., 2019a) that some patients had phobia and (Josman et al., 2008; Saiano et al., 2015; Simoes et al., 2018, (F. Chen et al., 2019a) (Zhang et al.,

2018a) that some of them had an intellectual disability or language disorder. More details of included studies for uncontrolled and controlled trials are provided in Table 1 and Table 2 respectively.

1.1.Meta-analysis

In the 35 trials entailed in our meta-analysis, Effect Sizes (ES) Hedges g were computed for 167 total number of outcome measures which 122 of them pertaining to uncontrolled and 45 pertaining to controlled trials. As ESs in two groups were significantly different from each other ($p=0.0003$, unpaired t -test), we were not allowed to combine them into one group and so we have done all further analysis separately for each of them.

To compute the study-level effect sizes, its variance and also between-study variance, we followed the procedure described in (Hedges, Tipton, & Johnson, 2010) . Based on this procedure, an estimate of within-study correlation (ρ) is needed to compute other statistics. As this estimate could not be extracted from most of our included studies, we ran a sensitivity analysis by choosing various values for ρ ranging from 0 to 1 and then computed other statistics based on the chosen value. The results of sensitivity analysis are given in supplementary Table 1. By this analysis, we inferred that the value study-level computed ES estimates are sensitive to the choice of ρ but it was an ascending function of ρ (the larger the ρ , the larger the estimated study-level ESs). Therefore, to avoid any overestimation in computing summary effect sizes, we fixed the value of ρ at 0 and performed the analysis with this value. It's noteworthy here to say that the procedure that we applied in this study is the most parsimonious one avoiding any overstatement of results, but in a realistic situation, the observed effectiveness might be larger as assuming the existence of some level of correlation between study outcomes seems to be a rationale assumption. For each trial, we first computed study-level effect sizes for all of the outcomes irrespective of their category applying RVE procedure which gave us overall ES of each study. Then we repeated this procedure on estimated ESs of outcomes in each category of each study to obtain category based effect sizes of that study.

Table 1 characteristics of included studies, uncontrolled trials

Trial ID	age	N	Type	Methodic details	Application details	Study purpose	Outcome Measure				
	mean(sd)						Name	Details	Skill	g	SEg
(Manju et al., 2018)	4.6(0.9)	5	VR	VE with scenes presented on wall	N/S	social skills and attention	Likert score	attention grasping	CS	2.39	2.07
							Likert score	social interaction	SCS	1.6	1.47
Overall										1.99	1.82
(Kurniawan, 2018)	N/M	12	AR	PECS-AR	N/S	communication ability	communication ability score	teacher's assessment	SCS	1.26	0.47
Overall										1.26	0.58
(C.-H. Chen et al., 2016)	11.5	6	AR	ARVMS	7 sessions	facial expressions and emotions of others in social situations	performance	instructor assessment	ERS	4.81	2.94
Overall										4.81	2.96
(Didehbani et al., 2016)	11.4(2.7)	30	VR	social scenarios in customized Second Life™ VE	10, 1-h sessions	enhance emotion recognition, social attribution, attention and executive function	NEPSY-2 affect recognition	facial affect recognition	ERS	0.66	0.23
							EKMAN 60	recognition of basic emotions		0.46	0.31
							triangle total	understanding of social intentionality	SCS	0.38	0.22
							triangle intentionality			0.45	0.23
							fluid reasoning	selective attention and concentration	CS	0.52	0.27
Overall										0.44	0.41
(Ip et al., 2016)	8.7	33	VR	school related social scenarios in 4-side CAVE	28 sessions	enhance social skills and coping skills while avoid unnecessary embarrassment	Eyes Test	emotion recognition	ERS	0.53	0.29
							affective expression			0.68	0.31
							social reciprocity	social reciprocity	SCS	0.6	0.3
							PEP-3 overall	social functioning and communication		0.76	0.32
Overall										0.64	0.45
(Maskey et al., 2014)	11.2(2)	9	VR	exposure to fearful stimuli in VE	4, 20 to 30-min sessions	reduction or treating specific phobia	SCAS-P	Children’s Anxiety Scale parent score	ERS	0.62	0.46
							SCAS-C	Children’s Anxiety Scale child score		0.66	0.45
Overall										0.64	0.56
(Stichter et al., 2014)	12.6(0.7)	11	VR	social competence tasks in computer-generated 3D VE	31 sessions over four month period	enhance social competence	SRS total parent score	Social Responsiveness Scale	SCS	1.04	0.46
							SRS social awareness parent score			0.47	0.36
							SRS social cognition parent score			1.15	0.48
							SRS social communication parent score			1.26	0.51
							SRS social motivation parent score			0.75	0.41
							SRS total teacher score			0.53	0.37
							SRS social awareness teacher score			0.34	0.35
							SRS social cognition teacher score			-0.12	0.34
							SRS social communication teacher score			0.6	0.38

							SRS social motivation teacher score			0.34	0.35
							BRIEF global executive parent score	Behavior Rating Inventory of Executive Function	CS	0.68	0.39
							BRIEF behavioral regulation parent score			0.45	0.36
							BRIEF metacognition parent score			0.64	0.39
							BRIEF global executive teacher score			0.5	0.37
							BRIEF behavioral regulation teacher score			0.14	0.34
							BRIEF metacognition teacher score			0.33	0.35
							reading in mind's Eye			students performance	ERS
							Faux pas stories	-0.35	0.35		
							Strange stories	0.25	0.35		
							DANVA	child facial expressions analysis	0.44	0.36	
							trail making: number letter switching	D-KEFS Delis–Kaplan executive functioning system	CS	0.17	0.34
							design fluency: switching designs			0.62	0.38
							design fluency: total correct designs			1.06	0.46
							color-word interface: inhibition task			-0.03	0.34
							color-word interface: inhibit/switch			0.16	0.34
							CPT-2 overall omission errors	continuous performance test-II (CPT-II)		0.09	0.34
							CPT-2 overall commission errors			0.15	0.34
Overall										0.44	0.5
(Bernardini, Porayska-Pomsta, & Sampath, 2014)	N/M	19	VR	playing game with VA	several 10 to 20-min sessions in a week for 8 weeks	help children acquire social communication skills	response to social partner	SCERTS Assessment Protocol (SAP) to assess socio-emotional abilities of autistics	SCS	0.07	0.42
							initiation to social partner			0.02	0.42
							social behavior			0.02	0.42
							sequences of social behaviors			-0.25	0.43
							speech toward social partner			0.06	0.42
							missed opportunities			0.81	0.54
Overall										0.12	0.55
(Milne et al., 2010)	10.5	14	VR	interacting with VA	N/S	teaching social skills and how to cope with bullying	Conservation skills	performance in social scenarios measured by evaluators scoring	DLS	0.67	0.33
							Dealing with bully skills			1.09	0.39
Overall										0.88	0.49
(Wade et al., 2015)	15.9 (1.3)	6	VR	driving simulation in VE	6 visits of 3 driving sessions in 24 trials	improve safe driving skills	performance based failures	subject's performance	DLS	1.98	1.30
Overall										1.98	1.34
	6	5	AR		N/S		attention process		CS	0.53	0.3

(Nubia et al., 2015)				pictogram recognition task		improve attention process and appearance of verbal language	emergence of language	number of children successfully finished the attention task		0.55	0.31
										0.54	0.45
(Vahabzadeh et al., 2018)	15(3.4)	8	AR	maintain gaze toward faces by AR smart glasses	1 session	improving gaze duration to faces and reducing ADHD symptoms	ABC-H score	measure of ADHD symptoms	CS	0.72	0.51
Overall										0.72	0.61
(Yuan & Ip, 2018)	9(1.1)	36	VR	social scenarios in 4-sided CAVE	1,1-h session	train emotional and social skills	PEP-3 Affective expressions	emotion expression and regulation	ERS	0.35	0.18
							PEP-3 social reciprocity	social interaction and adaptation	SCS	0.64	0.19
Overall										0.5	0.38
(Bai et al., 2015)	6.8	12	AR	playing with augmented toys in mirror AR display	N/S	improve and learn pretend play and representation of pretense	pretend play frequency	Play Observation Scale	CS	0.7	0.42
							pretend play duration			0.94	0.47
							constructive play frequency			1.42	0.59
							constructive play duration			1.01	0.49
Overall										1.02	0.6
(Lamash et al., 2017)	14.6(1.8)	33	VR	shopping training in VAP-S software	5 sessions	shopping skills, Executive cognitive and meta-cognitive skills	WebNeuro attention component	evaluation of cognitive and meta-cognitive functions	CS	0.58	0.2
							WebNeuro executive function component			0.58	0.2
							WebNeuro verbal component			-0.38	0.19
							TOGGS accuracy	Test of Grocery Shopping Skills, performance in shopping	DLS	1.5	0.27
							TOGGS time			0.62	0.2
							TOGGS redundancy			0.93	0.22
							TOGGS strategy usage			1.85	0.31
Overall										0.81	0.4
(Wade et al., 2016)	15.3(1.6)	8	VR	3D game driving simulator	6, 75-min sessions	enhancing driving skills	duration time	performance	DLS	0.73	0.51
							number of failures			1.27	0.67
								Overall		1	0.7
(Yang et al., 2017)	22.5(3.9)	17	VR	VR-SCT computer program	10, 1-h sessions	emotion recognition training and theory of mind or socio-cognitive skills improvement	ACS-SP emotion recognition	Social Perception	ERS	0.89	0.56
							ToM triangle test	theory of mind	SCS	1.08	0.61
Overall										0.99	0.67
(Kandalaft et al., 2013)	21.2(2.7)	8	VR	interacting with VA in Second LifeTM software	10 sessions	enhancing social skills, social cognition, and social functioning	SP-total	Verbal and Non-Verbal Emotion Recognition by ACS-SP	ERS	0.89	0.56
							SP-affect			0.39	0.45
							SP-prosody			1.03	0.59
							SP-pair			0.59	0.48
							EKMAN 60	theory of mind (ToM)	SCS	1.25	0.66

							triangle			1.08	0.61
							SSPA	conversation skills		0.32	0.44
Overall										0.79	0.64
(Saiano et al., 2015)	24(10)	6	VR	street crossing and path following in VE representing a city	10, 45-min sessions	teaching of street crossing and path following skills	care givers score	Likert Scores questionnaire	DLS	1.85	1.23
							parent score			0.92	0.76
							speed			subject performance in city surveying and street crossing	1.71
							composite index	0.45			0.59
							figural distance	0.75			0.69
							path length taken	0.48			0.6
							Overall				
(Ross et al., 2018)	18	46	VR	driving simulation in VE	8-12 sessions	improve attitude toward driving	DAS-PR positive attitude	Driving Attitude Scale Parent-Report	DLS	1.74	0.25
							DAS-PR negative attitude			1.07	0.19
Overall										1.41	0.4
(Josman et al., 2008)	13.2(3)	6	VR	street crossing in VE computer program	8,10 to 30-min sessions	teach street crossing skill	N of left looking at first crosswalk	participant performance in VR software	DLS	1.72	1.16
							N of right looking at first crosswalk			0.58	0.63
							N of left looking at second crosswalk			0	0.53
							N of right looking at second crosswalk			0.37	0.57
							total N of left looking crossing the road			1.4	0.99
							total N of right looking crossing the road			0.19	0.54
							N looked left at crosswalk with terrafic light			0.18	0.54
							N looked right at crosswalk with terrafic light			0.45	0.59
							N of accidents at the crosswalk with traffic light			0.75	0.69
Overall										0.63	0.8
(Zhao et al., 2018)	12.4(2.6)	12	VR	social games in CVE	N/S	motor skill and social interaction simultaneously	completed pieces(/min) study1	performance in puzzle game	SCS	1.07	0.83
							cooperative efficacy % study1			0.76	0.7
							total play time (s) study1			0.9	0.75
							word count of ASD subjects(/min) study1			0.34	0.57
							back-and-forth sentences(/min) study1			-0.65	0.66
							aggregate score study1			0.76	0.7
Overall										0.53	0.8
(Simoes et al., 2018)	18.8(4.5)	6	VR	street crossing and bus taking in VE presented by HMD	3, 20 to 40-min sessions	teaching bus-taking routines and effectively using bus for transformation	action accuracy	performance in bus taking	DLS	1.1	0.5
							debriefing accuracy			1.8	0.69
							global EDA	stress level	ERS	0.66	0.66
							bus EDA			0.81	0.72

							streets EDA			0.51	0.61
Overall										0.98	0.72
(Morag Maskey, Rodgers, Ingham, et al., 2019)	29.8	8	VR	Blue VR room	4, 20-min sessions of graded exposure	Treating phobia and anxiety	Anxiety BAI score	BAI	DLS	0.03	0.42
							Anxiety GAD score	GAD-7		-0.04	0.42
							Depression score	PHQ-9		0.32	0.44
							Quality of Life(QoL) physical	WHOQOL-BREF questionnaire addresses quality of life		-0.47	0.46
							QoL psychological			-0.03	0.42
							QoL social			-1.2	0.66
							QoL environmental			0.2	0.42
Overall										-0.17	0.58
(Ke & Moon, 2018b)	N/M	8	VR	3d virtual world designed by OpenSimulator	Average of 20.22 hours, over 16-31 session	Enhance social skills	Responding	Performance evaluated by instructors	SCS	0.02	0.42
							Initiation			1.26	0.67
							Negotiation			1.61	0.78
							Self-identification			0.83	0.54
							Cognitive flexibility			2.09	0.96
Overall										1.16	0.77
(I. T. Miller, Wiederhold, Miller, & Wiederhold, 2019)	5.2	5	VR	HMD, google cardboard	1 session per week for 3 weeks	Improve air travel[WU1] skills	Parent score	5-point Likert score	DLS	0.98	1.03
							Researcher score			1.1	1.11
Overall										1.04	1.12

ABC-H = aberrant behavioral checklist, ACS = advanced clinical solutions, ADHD = attention deficit hyperactivity disorder, AR = augmented reality, ARVMS = augmented reality video modeling system, BAI = Beck Anxiety Inventory, BRIEF = behavior rating inventory of executive function, CAVE = Cave automatic virtual environment, CPT = continuous performance test, CS = cognitive skills, CVE = collaborative virtual environment, DANVA = diagnostic analysis of non-verbal accuracy, DAS-PR = driving attitude scale parent report, DLS = daily living skills, EDA = electrodermal activity, ERS = emotion regulation and recognition skills, GAD-7 = Generalized Anxiety Disorder-7, N = number of participants, N/S = not specified, NEPSY = a developmental NEUROPSYchological assessment, NM = not mentioned, PECS = picture exchange communication system, PEP = psychoeducational profile, PHQ-9 = Patient Health Questionnaire-9, SAP = SCERTS assessment protocol, SCAS_C = Spence children's anxiety scale-child version, SCAS_P = Spence children's anxiety scale-parent version, SCQ = social communication questionnaire, SCS = social and communication skills, SRS = social responsiveness scale, SSPA = social skills performance assessment, TOGGS = test of grocery shopping skills, VA = virtual avatar, VE = virtual environment, VR = virtual reality, VR-SCT = virtual reality social cognition training.

Table 2 characteristics of included studies, controlled trials

Trial ID	Age	Number		Methodic details	Application details	Study Purpose	Outcome Measure				
	mean(sd)	NI	NC				Name	Details	Skill	g	SEg
(Ip et al., 2018)	13.55	36	36	social scenarios in half-CAVE	28, 30-min sessions	improving emotion recognition, emotion expression and social reciprocity, social adaptive skills	Faces Test	emotion recognition	ERS	0.26	0.24
							Eyes Test			0.14	0.24
							PEP-3 Affective expressions			emotion expression, regulation and social reciprocity	0.44
							PEP-3 social reciprocity	0.47			0.24
							ABAS communication	social adaptive skills	SCS	0.13	0.24
							ABAS community use			-0.64	0.25
							ABAS leisure			-0.24	0.24
							ABAS self-direction			-0.48	0.24
							ABAS social			-0.23	0.24
Overall									-0.05	0.34	
(Yuan & Ip, 2018)	8.97(1.1)	36	36	social scenarios in 4-sided CAVE	1,1-h session	enhancing emotional and social skills	PEP-3 Affective expressions	emotion expression and regulation	ERS	0.54	0.24
							PEP-3 social reciprocity	social interaction and adaptation	SCS	0.66	0.25
							Overall				
(Lamash et al., 2017)	14.58(1.77)	33	23	shopping training in VAP-S software	5 sessions	improving shopping skills	TOGGS accuracy	performance in shopping	DLS	1.02	0.29
Overall									1.02	0.38	
(Smith et al., 2015)	25(6.9)	15	8	being interviewed by VA in VR_JIT computer software	N/S	improving job interviewing skills	Likert score	self confidence	SCS	0.82	0.48
							weeks looking for a job			0.23	0.46
							completed interviews			0.08	0.46
Overall									0.37	0.52	
(Smith et al., 2014)	24.9(6.7)	16	10	being interviewed by VA in VR_JIT computer software	10-h	improving job interviewing and vocational skills	role-play performance total score	standardized role-plays	SCS	0.52	0.43
							job interview content score			0.39	0.43
							hard worker			0.58	0.43
							easy to work with/teamwork			0.32	0.42
							sounding professional			0.25	0.42
							negotiation skills			0.32	0.42
							interviewee performance score	training experience questionnaire (TEQ) by interviewee		0.49	0.43
							sharing things positively			0.73	0.44
							sounding honest			0	0.42
							sounding interested in job			0.26	0.42

							comfort level			0.46	0.43
							establishing overall rapport			0.35	0.42
							job interview self-confidence rating			self-confidence measure	0.61
Overall										0.4	0.48
(Strickland et al., 2013)	18.21(1.03)	11	11	being interviewed by VC in JobTIPS computer program	1 session	enhancing job finding skills	response content scale	content of the participant's responses	DLS	2.81	0.68
							response delivery scale	behaviors related to greetings and farewells		0.81	0.47
Overall										1.8	0.63
(Morag Maskey, Rodgers, Grahame, et al., 2019b)	10.8(2)	16	16	Blue room VR	4 sessions	Reduce phobia in ASD patients with Anxiety disorder	Target behavior rating	Rating of specific phobia change	ERS	1	0.39
							Total fearfulness	FSSC-R		-0.196	0.37
							Intense fears			-0.291	0.37
							Total anxiety score, parent	SCAS-P		0.21	0.37
							Total anxiety score, child	SCAS-C		-0.04	0.37
							Formal activity, diversity	CAPE: participation in a range of solitary and group voluntary activities		-0.138	0.37
							Formal activity, intensity			-0.1	0.37
							Informal activity, diversity			-0.239	0.37
							Informal activity, intensity			-0.276	0.37
Overall										0	0.44
(F. Chen, Wang, Peng, Yan, & Pan, 2019b)	4.9(1.1)	11	11	3D virtual punctuation tutor	3 sessions	Improve speech	Consonants	Rated with linguistics	CS	0.36	0.45
							Vowels			0.38	0.45
Overall										0.37	0.5
(Zhang, Warren, Swanson, Weitlauf, & Sarkar, 2018b)	4(1.21)	6	5	Quiver Vision augmented reality android app	20 weeks, 2, 15-min session per week	Enhance social skills	Social score	ASI disorder score	SCS	0.135	0.69
							Communication and language			0.14	0.69
							Anticipation and flexibility			-0.28	0.69
							symbolization			-0.2	0.69
Overall										-0.05	0.73

ABAS = adaptive behavior assessment system, CAVE = Cave automatic virtual environment, CS = cognitive skills, DLS = daily living skills, ERS = emotion regulation and recognition skills, FSSC-R = Fear Survey Schedule for Children—Revised, NC = number of participants in control group, NI = number of participants in intervention group, PEP= psychoeducational profile, SCAS_C = Spence children's anxiety scale-child version, SCAS_P = Spence children's anxiety scale-parent version, SCS = social and communication skills, TOGGS = test of grocery shopping skills, VA = virtual avatar, VAP-S = virtual action planning supermarket, VC = virtual character, VR_JIT = virtual reality job interview training.

1.1.1. Overall effectiveness of VR training

Fig. 2 forest plot of overall effectiveness of VR training for uncontrolled trials with 95% confidence interval

Fig. 3 forest plot of overall effectiveness of VR training for controlled trials with 95% confidence interval. Solid vertical lines represent strong effect size boundary ($g=-0.8$ and 0.8) and dashed vertical lines represent weak effect size boundary ($g=-0.3$ and 0.3)

In the first step, we computed the overall ES for each trial. For the 26 uncontrolled trials a large positive effect size was found ($g=0.74$, $SEg=0.17$) with low heterogeneity ($I^2=2.5\%$ and $\tau^2=0.11$). Excluding one of the potential outliers with extremely large ES ($g=4.8$) (C.-H. Chen et al., 2016) led to similar results ($g=0.736$, $SEg=0.17$) (Fig. 2).

For 9 controlled trials, summary effect size was at medium range ($g=0.45$, $SEg=0.25$) with moderate heterogeneity ($I^2=49.5\%$ and $\tau^2=0.055$). Excluding one of the potential outliers with much larger ES ($g=1.8$) (Strickland et al., 2013) led to a bit smaller summary ES but it was still at the medium

range of effectiveness ($g=0.38$, $SEg=0.2$) (Fig. 3). We have

interpreted the results for overall effectiveness of studies with random effect model of meta-analysis relying more on controlled trials due to their more robust experimental design.

1.1.2. Skill based effectiveness of VR training

Fig. 4 forest plot of skill-based training effectiveness for uncontrolled trials with 95% confidence interval

Fig. 5 forest plot of skill-based training effectiveness for controlled trials with 95% confidence interval

Further, ESs were computed for each skill category (defined in methods). In uncontrolled trials, Social and communication skills (SCS) had been addressed in 11 trials, Emotion regulation and recognition skills (ERS) in 10 trials, Daily living skills (DLS) in 9 trials and Cognitive skills (CS) in 7 trials. VR training led to medium to strong effectiveness in SCS ($g=0.68$, $SEg=0.08$, $\tau^2=0.13$), medium effectiveness in ERS ($g=0.46$, $SEg=0.05$, $\tau^2=0.07$), strong effectiveness in DLS ($g=1.16$, $SEg=0.09$, $\tau^2=0.48$) and medium effectiveness in CS ($g=0.45$, $SEg=0.02$, $\tau^2=0.03$) (Fig. 4).

In controlled trials, SCS was addressed in 5 trials, ERS in 3 trials and DLS in 2 trials and CS in one trial. The effectiveness of VR training was weak for SCS ($g=0.2$, $SEg=0.23$, $\tau^2=0.03$), weak to moderate for ERS ($g=0.34$, $SEg=0.06$, $\tau^2=0.02$) and again very strong in DLS ($g=1.37$, $SEg=0.18$, $\tau^2=1.12$). The single trial which addressed CS revealed weak to moderate effectiveness ($g=0.37$, $SEg=0.002$). Regarding heterogeneity in these estimated summary ESs, a considerably large amount of between-study variance (τ^2) was observed in DLS category in both design groups but, it was relatively small for SCS, ERS and CS but it was small for ERS (compare the τ^2 values presented above) (Fig. 5).

So while in other skills, we observe promising

effectiveness, the Daily Living Skills is proven to be the most affected area as its strong effectiveness was consistent among both controlled and uncontrolled trials.

1.1.3. Analysis of confounding factors

Since a sizable number of trials had not used any legitimate criteria for screening the participants undergoing intervention (e.g. IQ score, social responsiveness score, disease severity, etc.), we recomputed overall effect sizes for those trials which screened their population applying this kind of criteria to see how much our results would be biased by this potential confounding factor. In the population screened trials, the results for uncontrolled trials were $g=0.72$, $SEg=0.05$, $k=12$ and $\tau^2=0.04$ and for controlled trials were $g=0.25$, $SEg=0.1$, $k=7$ and $\tau^2=0.01$. These results in unscreened trials were $g=0.73$, $SEg=0.2$, $k=14$ and $\tau^2=0.18$ for uncontrolled and $g=0.8$, $SEg=0.05$, $k=2$ and $\tau^2=0.35$ for controlled trials.

Comparing these effect sizes among two screen groups, the results were not meaningfully different from each other in uncontrolled trials unlike substantial decline from unscreened to screened trials in controlled interventions. Due to very small sample size of unscreened controlled trials, the results derived from them seems less reliable. Although, more cautions should be devoted to screening population before intervention.

1.2. Subgroup meta-analysis

Results of subgroup analysis for controlled trials would be underpowered and misleading because of its small sample size, so the conclusions of subgroup meta-analysis and meta-regression are limited to the data of uncontrolled trials.

We performed a subgroup meta-analysis for the categorical moderators described in methods. Results showed that the overall effect sizes had been computed based on the data obtained from non-formal measures were somehow larger than those obtained from formal measures ($g=0.93$, $k=11$ and $\tau^2=0.2$ for non-formal and $g=0.66$, $k=15$ and $\tau^2=0.09$ for formal trials). This can be due to the customized measurements that suit the intervention design, less validity of measures and susceptibility to the rater bias. Regarding the frequency of each measure's application for

Table 3 subgroup meta-analysis results for type of measure, type of technology and age moderators

Subgroup	Category	N	g	SEg	Q	τ^2
formal measure	Overall	15	0.665	0.181	19.7	0.096
	SCS	8	0.604	0.044	3.3	0.107
	ERS	8	0.439	0.052	4.35	0.063
	DLS	4	1.236	0.04	0.701	0.552
	CS	5	0.366	0.007	1.716	0.017
non-formal measure	Overall	11	0.931	0.097	5.192	0.203
	SCS	3	1.027	0.221	0.773	0.277
	ERS	2	0.957	0.101	1.916	0.241
	DLS	5	1.059	0.156	1.535	0.283
	CS	2	0.719	0.048	0.705	0.141
AR	overall	5	0.912	0.097	3.975	0.304
	CS	3	0.72	0.039	0.705	0.151
VR	Overall	21	0.715	0.178	21.72	0.099
	SCS	10	0.627	0.047	4.024	0.102
	ERS	9	0.449	0.05	4.481	0.061
	DLS	9	1.155	0.093	3.242	0.477
	CS	4	0.334	0.004	1.173	0.013
age: 4-8	Overall	4	0.797	0.059	1.405	0.137
	CS	3	0.775	0.055	1.436	0.149
age: 8-12	Overall	7	0.572	0.024	3.457	0.045
	SCS	4	0.582	0.013	0.747	0.12
	ERS	6	0.462	0.028	3.969	0.089
	CS	2	0.377	0.001	0.000	0.012
age: 12-16	Overall	7	0.847	0.06	1.406	0.091
	SCS	2	0.848	0.156	0.402	0.059
	DLS	4	1.11	0.1	1.129	0.295
	CS	2	0.339	0.008	0.704	0.021
age: >16	Overall	6	0.854	0.345	11.19	0.356
	SCS	2	0.982	0.041	0.055	0.299
	ERS	4	0.462	0.24	2.752	0.028
	DLS	3	1.331	0.039	0.284	0.825
Comorbidity present	Overall	6	0.608	0.019	1.104	0.033
	ERS	3	0.599	0.002	0.038	0.095
	DLS	3	1.077	0.361	0.771	0.16
	CS	2	0.455	0.011	0.387	0.043
Comorbidity absent or not reported	Overall	20	0.77	0.195	23.67	0.132
	SCS	10	0.744	0.101	4.763	0.143
	ERS	7	0.404	0.06	6.036	0.062
	DLS	6	1.193	0.059	2.208	0.553
	CS	5	0.45	0.03	3.252	0.03

AR = augmented reality, CS = cognitive skills, DLS = daily living skills, ERS = emotion regulation and recognition skills, g = Hedges' g, N=number of trials, Q = cochrane's Q stat, SCS = social and communication skills, SEg = standard error of g, VR = virtual reality

categories, most of them had applied formal measures unless DLS which application of non-formal measures was more frequent. In DLS, the summary effect size was a bit larger for formal measures, although it was derived from only 3 trials ($g=1.24$, $k=4$, $\tau^2=0.55$ for formal and $g=1.06$, $k=5$, $\tau^2=0.28$ for non-formal measures). For the type of technology (VR or AR), AR interventions led to a larger overall summary effect size ($g=0.91$, $k=5$, $\tau^2=0.3$ for AR and $g=0.71$, $k=21$, $\tau^2=0.1$ for VR). The most of AR interventions were applied for CS that showed more effective training in this skill than VR ($g=0.72$, $k=3$, $\tau^2=0.15$ for AR and $g=0.33$, $k=4$, $\tau^2=0.01$ for VR). Regarding intervention effectiveness for age categories, results showed that skill acquiring, in general, got better as the participants got older ($g=0.8$, $k=4$, $\tau^2=0.13$ for age 4-8, $g=0.57$, $k=7$, $\tau^2=0.04$ for age 8-12, $g=0.84$, $k=7$, $\tau^2=0.09$ for age 12-16 and $g=0.85$, $k=6$, $\tau^2=0.36$ for age >16). Skill categories followed the same trend as the strongest effectiveness observed in the ages above 16 for all of them ($g=0.98$, $k=2$, $\tau^2=0.3$ for SCS, $g=0.46$, $k=4$, $\tau^2=0.03$ for ERS and $g=1.33$, $k=3$, $\tau^2=0.82$ for DLS, for other age groups, see Table 3). It is also noteworthy to say that effectiveness was relatively strong for CS in participants aged 4-8 y/o which was the major outcome addressed by our included trials in this age group ($g=0.77$ $k=3$, $\tau^2=0.15$). These results point to a more favorable effect of VR interventions for older patients. Subgroup analysis for comorbidity revealed considerable decline in training effectiveness on ASD patients with concomitant comorbidity as $g=0.77$ in 20 trials with $\tau^2=0.13$ in which patients didn't have any specified comorbidity dropped to $g=0.6$ in 6 trials with $\tau^2=0.03$ in which patients had some type of comorbidity alongside with their main disease. This effect was even more sophisticated in controlled trials so that $g=0.57$ in 6 trials with $\tau^2=0.08$ without specified comorbidity reduced to $g=0.11$ in 3 trials with $\tau^2=0.03$ in which a comorbidity was diagnosed.

The full details of the results for this part can be seen in Table 3.

1.3. Meta-regression

To see if there is any significant interaction between continuous moderators (number of sessions, sex and publication date) and effectiveness of the intervention, we opted for univariate linear regression on weighted effect sizes as a function of each of these moderators for all designs and skill categories (Table 4). Significant relationship was found in publication date for overall ($N=122$, $\beta_1=0.4$, $p=0.02$) and DLS ($N=30$, $\beta_1=0.95$, $p=0.006$) which show that over time, intervention qualities has been likely to be improved as the technology has been advancing; there

Table 4 meta-regression results for number of sessions, sex and publication date moderators

Moderator	Skill	N	Slope	p
number of sessions	Overall	122	-0.035	0.4912
	SCS	38	0.0086	0.8766
	ERS	27	0.0297	0.6552
	DLS	30	0.5425	0.3548
	CS	27	-0.148	0.188
gender	Overall	122	4.5146	0.2318
	SCS	38	-2.162	0.8148
	ERS	27	6.6054	0.0935
	DLS	30	-0.25	0.9892
	CS	27	-18.7	0.1484
publication date	Overall*	122	0.4021	0.0219*
	SCS	38	0.212	0.5024
	ERS	27	-0.237	0.4484
	DLS*	30	0.9515	0.0067*
	CS	27	0.7987	0.2738

* denotes significant values with $p < 0.05$. CS = cognitive skills, DLS = daily living skills, ERS = emotion regulation and recognition skills, N = number of outcomes in each group, SCS = social and communication skills.

was no significant association between the number of sessions or gender and computed effect sizes in any of outcome categories.

1.4.Publication bias

Visual inspection of the funnel plot (Fig. 6) for both controlled and uncontrolled overall effect sizes pointed to a symmetrical funnel for both trials. To validate this conclusion statistically, we applied Egger's regression intercept test. The test results corroborated the visual inspection by revealing no significant bias for uncontrolled and controlled trials (intercept= 0.27, $p=0.24$ for uncontrolled and intercept= 0.1, $p=0.88$ for controlled trials). This implies that drawn conclusions are robust and reliable.

Fig. 6 funnel plot for VR training effectiveness of both uncontrolled and controlled trials with pseudo 95% confidence interval.

Filled and empty circles represent Hedges g value of uncontrolled and controlled trials respectively. Solid lines represent g with 95 % confidence interval of uncontrolled trials and dashed lines represent g with 95 % confidence interval of controlled trials

Comparing effectiveness of VR training with some of conventional behavioral programs that was addressed by three meta-analysis studies, we observed a comparable moderate effectiveness of our study with the most of clinical targets appraised by them. One exception was effectiveness of early intensive behavioral intervention on full scale IQ of patients with ASD which was proved to be strong ($g=1.1$ of 9 controlled studies). The other interesting finding was that TEACCH and ABA programs were not effective in improving daily living skills ($g=0.34$ from 6 and $g=0.14$ from 29 studies respectively), while, the effectiveness of VR training on this clinical target was very strong as it's observed in this study. For full results on this part, see Table 5.

Table 5 characteristics and effectiveness of three of the conventional rehabilitation programs

study ID	intervention	publication year	number of studies	case number	study design	outcome measure	ES statistic	ES
(Virues-Ortega et al., 2013)	TEACCH	2013	13	172	uncontrolled	overall	cohen d	0.47
			6	93		eye-hand coordination		0.26
						motor functioning		0.36
						gross motor function		0.58
						imitation		0.41
						perception		0.4
			5	74		communication skills		0.34
			6	81		daily living skills		0.32
			5	74		social functioning		0.64
			5	43		cognitive functioning		0.41
			9	121		verbal skills		0.36
			4	44		maladaptive behaviors		-0.92
(Eldevik et al., 2009)	Early Intensive behavioral	2013	9	153/105(control)	controlled	full scale IQ	hedges g	1.1
						adaptive behavior		0.66
(Makrygianni et al., 2018)	Applied Behavior Analytic interventions (ABA)	2018	29	831	uncontrolled	intellectual abilities	hedges g	0.74
						communication skills		0.65
						expressive-language skills		0.742
						receptive- language skills		0.597
						non-verbal IQ		0.463
						adaptive behavior		0.422
						socialization		0.444
						daily living skills		0.138

ES = Effect Size estimate, TEACCH = Treatment and Education of Autistic and Related Communication Handicapped Children

2. Discussion

We performed a systematic review and meta-analysis on the effectiveness of applying virtual reality-based therapeutic interventions on the alleviation of deficits in ASD patients. Based on the results of 26 uncontrolled and 9 controlled trials, we concluded that VR technology can be a viable

tool for designing interventions aimed at enhancing and improving different skills in people suffering from ASD at any age. To our knowledge, this is the first meta-analysis focusing exclusively on the effectiveness of VR-based interventions for training ASD patients. Although there are some meta-analysis studies available on the same topic with various types of new technologies that may (Grynszpan et al., 2014; Self, Scudder, Weheba, & Crumrine, 2007b) or may not (Hong et al., 2016, 2017; Wilkinson & Hennig, 2007) include VR, the number of trials that methodologically focused on VR was not large enough to draw rigorous conclusions around their efficacy. The increase in the number of VR interventions has been conducted recently besides its public availability has justified the need for this study. Overall moderate effectiveness of VR interventions that we observed in this study is in line with the results of previously mentioned studies. Moderate to high and moderate effectiveness was found for uncontrolled and controlled trials respectively. Low heterogeneity in uncontrolled trials would provide further support for the conclusion drawn from these trials. Moderate heterogeneity in controlled trials cast doubts on interpretation of their results that could be explained by their relative small sample size (only 9 trials comparing to 26 uncontrolled trials) and also the heterogeneity of control groups.

Further analysis of entailed categories of skills revealed relatively same moderate effectiveness of intervention for social and communication skills, emotion recognition and regulation skills and cognitive skills unless daily living skills that outperformed other categories with promising large effectiveness in both design groups. This effect was proven to be consistent across different trials with different designs as heterogeneity was low for both of them. This finding can be specifically of interest because of the more reflective nature of DL skills which means that they are gained and generalized in later stages of cognitive development and ASD subjects are required to be trained for it similar to their neurotypical counterparts. Unlike reflective skills, communication or emotional skills are more intuitive in the sense that they are generally gained in the early stages of development without any specific effort. It is also possible that observed large effect is originated from the larger mean age of participants in this outcome category comparing to other categories which have given them superiority and dexterity in learning and practicing skills. But anyway, significantly larger effectiveness of VR training for DLS compared to the others is persuasive enough for us to put forward the hypothesis that reflective skills hold more potential toward improvement by training than intuitive skills. Here we may have corroborated this hypothesis for VR-based training. On the other hand, medium effectiveness for communication, emotion and

cognitive skills may be due to the complex mental nature of these skills. As it is reflected in the recent systematic review ([Mesa-Gresa et al., 2018](#)), although these skills have been the center of attention in most studies, just partial improvements have been made. Knowing this, in future efforts, a more elaborated intervention design seems necessary to ascertain the effectiveness of VR training on these types of skills. Taken together, we encourage psychiatrists and educators of people with ASD to practice this type of technology with more focus on Daily living skills.

Results of our subgroup analysis are merely discussed on overall outcomes of uncontrolled trials. The small sample size of other subgroups precluded us from drawing a strong conclusion for them. The effectiveness of an intervention based on formal and non-formal measures was roughly similar and around moderate range which indicates that our results might not be affected with the existence of non-formal assessments. By the way, cautious interpretation of informal measures should be considered and it is possible that defined informal measures could be biased. The effectiveness of AR was similar and even a little larger than VR interventions. Although the sample size of the AR subgroup was relatively small, considering its low heterogeneity, the resultant conclusion on this subgroup can be reliable. This is particularly important because AR interventions can be conducted by the means of AR-enabled mobile phones which is ubiquitous nowadays providing more controlled interventions for larger populations of patients with ASD. The superiority of AR can be assigned to its simplicity in design and convenience in using compared to VR in which tasks are designed and applied in more complex environments with more parameters to understand and deal with. This simplicity can lead to a sooner and better engagement of participants in the task specifically for younger children.

Results of subgroup analysis for age categories revealed that performance improves as the age gets larger. Particularly, it's important to note that this improvement is happening not only in daily living skills, which are reflective skills and later in development but also in other intuitive areas, such as social skills and emotion recognition skills. This phenomenon may be induced by two factors. First, patients with autism presumably develop a kind of mechanism to overcome the deficits primarily caused by ASD and so they assimilate to their milieu as they age. Second, older patients may have the advantage that they understand the task and VR environment better and so they interact with it more efficiently, resulting in improved performance. In the first age category (4-8 y/o), a notable relatively strong effectiveness was observed in cognitive skills which were the

only addressed area in this age group. Despite the small sample size, the relatively large effect size was persuasive enough for us to consider it. This large effect may also be seen in other areas of SCS, ERS, and DLS; therefore, we encourage the scientific community to target their interventions on these areas too.

We observed a substantial decline in the effectiveness of training on patients who suffered from some sort of concomitant comorbidity along with ASD. This phenomenon was particularly interesting in controlled trials as observed moderate effectiveness of training on ASD patients without other comorbidity was completely vanished when concomitant comorbidity was taken into account. This alarms the future practitioners who are trying to improve skills in patients with ASD by the means of VR interventions to carefully screen their target patients for having other concomitant comorbidity.

The effectiveness of training for High Function ASD patients was moderate to large which was equivalent to its overall value regardless of the level of the disorder. Most of the studies whether comprised of a combination of low-functioning and high-functioning autism spectrum disorder (LFASD and HFASD) participants or the level of disease were not specified, so direct association between level of disease and effectiveness of intervention could not be derived. For this reason, we call for papers with more focus on defining the level and functionality of disease in included participants for better characterizing the target population of intervention.

Results of meta-regression revealed a significant correlation between publication date and VR training effectiveness which can be interpreted under improvement in the design and conduction of VR interventions over time. Surprisingly, effectiveness was not influenced by the total number of intervention sessions. It's important to mind that, the session's duration and its distribution over the course of intervention were unreported or highly heterogeneous among the trials and therefore, the net number of sessions might not be a good representative for intensity and quality of intervention. For this reason, hesitant interpretations warrant caution and more controlled interventions in terms of design, duration and longevity are needed for more conclusive interpretations on this matter. The sex of participants was not a significant moderator of the results in our study as it is not seen in other studies of this kind.

Unlike conventional behavioral rehabilitation programs, the strong effectiveness for daily living skills that was achieved by VR-based training programs was persuasive enough for us to assert

using VR technology in the design of rehabilitation programs targeted on daily living skills in clinical practice. In the other clinical targets, more studies and further improvement in the design or application of VR technology is still needed before its use in practice.

2.1.Limitations and recommendations for future research

Most of our included studies were uncontrolled pre-posttest trials. It has been argued that these types of trials should be avoided in meta-analysis as the pre-test and post-test scores are not independent of each other and thus accurate calculation of SMDs requires knowledge of correlation value between these two scores which is not provided in most of the studies (Cuijpers, Weitz, Cristea, & Twisk, 2017). By the way, maybe due to differing epistemological bases of research being carried out in this broad domain, most of the studies have adopted this type of design for their intervention which makes considering this massive body of data for analysis inevitable. Here, we have done all the calculations with the premise of independent pre and post-test scores (zero correlation) which is subsequently leading to the largest pooled variance and thus the smallest possible value of computed effect size. For this reason, we claim that our applied method is the most parsimonious one avoiding any overestimation in computing the effect sizes.

The number of participants in most studies was rather low and so their estimations would not be adequately powered but its effect might be compensated by a considerably large number of included trials. There were a considerable number of trials that did not screen participants for important contributing factors that could affect the result of the intervention. This issue seemed to be a challenge for our results. However, later analysis relieved this issue by showing that the summary effect size of those trials which screened included population in intervention on participants did not encounter any meaningful change comparing to the ones which screened their population.

The type of VR technology that has been applied by studies was various enough to prevent us from establishing any systematic relationship between the type of VR and its effectiveness, thus more studies are needed to explore the existence of such a link. To our surprise, restricted and repetitive behaviors, which is one of the core symptoms of ASD, was not addressed by any of studies, so more experiments are encouraged to be targeted in this area in the future works. Follow-up assessment of participants was performed in an only limited number of trials, therefore, the maintenance of treatment effects, although important, but could not be assessed by our study.

3. Conclusion

In conclusion, the current findings support the effectiveness of VR training to improve ASD-related disabilities. The strong observed effectiveness for daily living skills could justify the application of VR interventions in clinical practice. For future research, the designed experiments need to be more controlled in terms of selection of participants, type and duration of intervention and choice of a measurement tool and finally, more efforts should be devoted to follow-up assessments carried out weeks or months after the end of the intervention to ensure that the effects of training are consolidated and maintained.

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Statement of competing interests

The authors have no competing interests to declare.

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