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Use of virtual reality in bipolar disorder: a systematic review

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Abstract

Virtual reality (VR) is a technology that allows to interact with recreated digital environments and situations with enhanced realism. VR has shown good acceptability and promise in different mental health conditions. No systematic review has evaluated the use of VR in Bipolar Disorder (BD). This PRISMA-compliant systematic review searched PubMed and Web of Science databases (PROSPERO: CRD42023467737) to identify studies conducted in individuals with BD in which VR was used. Results were systematically synthesized around four categories (cognitive and functional evaluation, clinical assessment, response to VR and safety/acceptability). Eleven studies were included (267 individuals, mean age = 36.6 years, 60.7% females). Six studies using VR to carry out a cognitive evaluation detected impairments in neuropsychological performance and delayed reaction times. VR was used to assess emotional regulation. No differences in well-being between VR-based and physical calm rooms were found. A VR-based stress management program reduced subjective stress, depression, and anxiety levels. VR-based cognitive remediation improved cognition, depressive symptoms, and emotional awareness. 48.7% of the individuals with BD considered VR-based cognitive remediation 'excellent', whereas 28.2% considered it 'great'. 87.2% of individuals did not report any side effects. 81.8% of studies received a global quality rating of moderate. Emerging data point towards a promising use of VR in BD as an acceptable assessment/intervention tool. However, multiple unstudied domains as comorbidity, relapse and prodromal symptoms should be investigated. Research on children and adolescents is also recommended. Further research and replication of findings are required to disentangle which VR-interventions for which populations and outcomes are effective.

Introduction

Bipolar disorder (BD) is a chronic, recurrent, and debilitating illness (Skjelstad, Malt, & Holte, 2010) that is characterized by fluctuations in mood states and energy (Grande, Berk, Birmaher, & Vieta, 2016). BD significantly affects psychosocial functioning and quality of life (Carlson & Pataki, 2016; Salazar de Pablo et al., 2020) and is the second most common mental disorder affecting days out of role functioning in young people (Alonso et al., 2011). A recent large-scale meta-analysis estimated that the global peak age at onset of BD is 19.5 years (Solmi et al., 2021). Despite such an early onset, and despite different diagnostic strategies having been used for the detection of BD and the difficulties associated, the BD diagnosis is typically delayed by as long as 5–10 years after the occurrence of early symptomatology (Berk et al., 2007). Furthermore, a significant number of individuals with BD do not receive any treatment, and there is a significant gap in their treatment provision. For instance, an epidemiological survey found that 80% of adolescents meeting the criteria for a bipolar spectrum disorder were not on any treatment (Merikangas et al., 2010).

Different interventions have been evaluated or piloted to ameliorate the negative consequences of BD. Mood-stabilizing agents, such as lithium, have shown antimanic, antidepressant, and anti-suicidal effects (McIntyre et al., 2020; Salazar de Pablo & Young, 2024) but are associated with significant side effects. Psychosocial interventions, including psychotherapy,

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when added to medication for the treatment of BD, consistently show advantages over medication alone, particularly for individuals with bipolar depression (Swartz & Swanson, 2014). However, even in bipolar depression, psychotherapy is often not available and is underused (Linden, 2013). Besides, limited insight and awareness, may result in difficulties to engage in therapy, particularly present in individuals with a recent onset of illness (Özdel, Kart, & Türkçapar, 2021). Furthermore, additional clinical challenges, such as intense fears about being outside in everyday situations, may also appear (Freeman et al., 2022).

Virtual reality (VR) is defined by the use of computer modeling and simulation, enabling a person to interact with an artificial three-dimensional (3-D) visual or other sensory environment (Lowood, 2023). VR enables researchers and clinicians to design realistic scenarios that can be used to assess the individual response to an environment and has been used in different mental health conditions (Peng, Menhas, Dai, & Younas, 2022).

In psychosis, several systematic reviews have been conducted (Chan et al., 2023; Riches et al., 2021; Rus-Calafell, Garety, Sason, Craig, & Valmaggia, 2018; Schroeder et al., 2022). Two of them have found that VR has been used as an intervention and also for the assessment of clinical symptoms and neurocognitive deficits (Chan et al., 2023; Rus-Calafell et al., 2018). Other two recent systematic reviews found that VR is a promising tool for the assessment and treatment of social functioning impairments in psychosis (Riches et al., 2021; Schroeder et al., 2022). These difficulties are often present in BD. In recent years, research has begun to evaluate the use of VR in people with BD. This approach has offered benefits such as increased ecological validity, enhanced personalization, and improved engagement (Bell, Nicholas, Alvarez-Jimenez, Thompson, & Valmaggia, 2020). Other key advantages include the possibility to use realistic scenarios as part of therapy work and rehabilitation.

However, despite its potential benefits and clinical importance, to our knowledge, there is no systematic review appraising the research findings and the relevance of the field. To address this gap, this is the first systematic review evaluating the use of VR in BD. Our aim was to evaluate VR as an assessment (either for a cognitive evaluation, functional evaluation, or clinical assessment) or an intervention for individuals with BD.

Methods

This study (protocol: PROSPERO CRD42023467737) was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) (Moher, Liberati, Tetzlaff, & Altman, 2009) (online eTables 1–2) statements.

Search strategy and selection criteria

A systematic search strategy was used to identify relevant articles, and a two-step literature search was implemented by two independent researchers (GSP, ORH). PubMed and Web of Science database (Clarivate Analytics) were searched until the 1 August 2023, the last one incorporating the Web of Science Core Collection, BIOSIS Citation Index, KCI-Korean Journal Database, MEDLINE, Russian Science Citation Index, and SciELO Citation Index, as well as Cochrane Central Register of Reviews, and Ovid/PsychINFO databases. The following search terms were applied: ('virtual reality' OR 'VR') AND ('mania' OR 'manic' OR 'bipolar disorder' OR 'bipolar'). Articles identified were screened as abstracts, and after the exclusion of those which did not meet our inclusion criteria, the texts of the remaining articles were assessed for eligibility, and decisions were made regarding their inclusion or exclusion in the review. We completed the search process by manually reviewing the references of previously published articles and extracting any additional relevant titles. We also looked for thesis and gray literature in Open Grey database.

Inclusion Criteria: (a) studies with original data, including original articles, abstracts, conference proceedings or gray literature (b) conducted in individuals with BD (children, adolescents, or adults), (c) in any language, (d) in which VR is used as a diagnostic or treatment tool. In line with previous studies, the criteria for inclusion from a VR perspective were that the studies used immersive and interactive VR environments in three-dimensional (3D) graphics presented with a head-mounted display, or that they used 2D graphics on a computer screen but were interactive, meaning that individuals could navigate through the environment using a joystick or a mouse/keyboard and they had elements or objects they could interact with (Rus-Calafell et al., 2018). Exclusion criteria were: (a) reviews, clinical cases, study protocols, or studies providing only qualitative data, (b) studies focusing on other physical health or mental health conditions, (c) studies using other treatment strategies only. As stated in our protocol, studies including individuals with mood disorders in which BD represented >50% of the individuals in a relevant group for which results are provided were included, but the corresponding authors were contacted to gather additional information on the use of VR on BD specifically.

Data extraction

Two researchers (OR, SGV) independently extracted data from included studies into a database. Discrepancies were resolved through consensus with a senior researcher (GSP). The following variables were extracted: first author and year of publication, cohort, country, sample size, design (cross-sectional, longitudinal, RCT, other clinical trial), designation of individuals (BD-I, BD-II, BD-NOS), instrument used to characterize BD (e.g. DSM, ICD), age, sex, quality assessment (see below), VR equipment (e.g. Head-mounted displays -HMD-, Cave Automatic Virtual Environment -CAVE- etc), task carried out, category (cognitive and functional evaluation; clinical assessment; response to VR as a treatment; safety/acceptability) and key findings per outcome.

Risk of bias (quality) assessment

The Evaluation of Public Health Practice Project 'Quality Assessment Tool for Quantitative Studies' (QATQ) was used to assess the quality of all the studies included in the systematic review. The QATQ rates studies across six general domains: selection bias, study design, confounders, blinding, data collection, and withdrawals. A global rating for the paper is described as follows: Strong = no weak ratings; Moderate = one weak rating; Weak = two or more weak ratings on the subscales. The QATQ has favorable content and construct validity, and inter-rater reliability (Thomas, Ciliska, Dobbins, & Micucci, 2004).

Strategy for data synthesis

Results were systematically synthesized around four categories based on previously published systematic reviews (cognitive and functional, clinical assessment, response to VR as a treatment, safety/acceptability). Categories were pre-defined, although due to the evidence available, cognitive evaluation category was

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expanded to 'cognitive and functional evaluation'. Our aim was to stratify according to the population of study (children & adolescents; adults), but because all the studies were conducted in adults, this was not possible.

Results

Sample characteristics

The literature search yielded 361 citations, which were screened, and 41 full-text articles were assessed for eligibility (Fig. 1). After excluding those not meeting the inclusion criteria, 11 studies from 10 samples were included in the systematic review.

The overall database comprised 267 individuals. The mean age of the individuals was 36.6 years and 60.7% were female. 70% of samples were involved in cross-sectional studies and 30% were clinical trials (one RCT and two other clinical trials). Three study samples were conducted in Denmark, two in South Korea, one in Iran, one in Italy, one in Singapore, one in Sweden, and one in the USA. Characteristics of the included studies can be found in Table 1, including key findings and a summary of the equipment and tasks/experiments carried out. For more details regarding equipment and tasks, please check online supplementary eTable 3. A summary of findings from clinical, functional, and cognitive evaluation can be found in Fig. 2.

Key finding by outcome category

Cognitive and functional evaluation

Six studies used VR to carry out a cognitive and functional evaluation (Gould et al., 2007; Hørlyck, Obenhausen, Jansari, Ullum, & Miskowiak, 2021; Kim et al., 2009a; Miskowiak et al., 2021; Mohammadi, Hesami, Kargar, & Shams, 2018).

One of them also carried out a neuroimaging evaluation (Kim et al., 2009a). This study compared euthymic individuals with BD and healthy controls who underwent functional MRI while performing a VR 2-D non-immersive social cognition task (Kim et al., 2009a). Individuals with BD compared to healthy controls showed delayed reaction times when presented to different conditions (angry avatar, happy avatar and neutral avatar, all $p < 0.001$) with comparable response accuracy ($p > 0.05$). Relative to healthy controls, individuals with BD showed reduced activations in the 'mirror neuron system', including the right inferior frontal cortex with the angry avatar and reduced activations in the premotor cortex and insula with the happy avatar ($p < 0.05$) (Kim et al., 2009a).

Another study assessed adults with BD, schizophrenia and healthy controls in spatial navigation (allocentric memory, egocentric memory), verbal memory and visual memory using VR. While individuals with schizophrenia appeared significantly impaired on allocentric, egocentric, visual, and verbal memory tasks ($p < 0.05$), there were no statistically significant differences between individuals with BD and healthy controls in spatial navigation ($p > 0.05$) (Mohammadi et al., 2018).

In a third study, individuals with mood disorders (unipolar/bipolar depression) found significantly fewer locations on the spatial navigation task than healthy controls ($p = 0.01$) while navigating a town using a 3-D (nonaerial) view. Among individuals with depression, cognitive deficits in spatial memory navigation correlated with the severity of depression ($r = -0.33$, $p = 0.02$). There were no differences in scores on the spatial working memory task between individuals with unipolar or bipolar depression and healthy controls ($p = 0.95$). There were no differences between individuals with and without a history of substance abuse either ($p > 0.05$) (Gould et al., 2007).

In another study, individuals with BD completed executive functions tasks in a virtual, non-immersive office environment on a computer. Individuals with unipolar disorder and BD reported significantly more functional problems in everyday life on the Functioning Assessment Short Test (FAST)- focusing on six domains (autonomy, occupational functioning, cognitive functioning, finances, interpersonal relationships and leisure activities)- than the healthy control group ($p < 0.001$). There were no differences between the groups when using another scale, the Performance-based Skills Assessment (UPSA-B), measuring financial skills and communication skills (Hørlyck et al., 2021). Lower cognitive scores were correlated with more functional disability ($r = 0.30–0.44$ depending on the scale, $p < 0.01$). No differences were found between individuals with unipolar disorder and those with BD on any clinical/functional outcome evaluated ($p > 0.05$) (Hørlyck et al., 2021).

A study comparing individuals with mood disorders (either unipolar depression or BD) showed impaired global neuropsychological performance ($p = 0.001$). Across individual domains, they exhibited impairments in verbal learning and memory ($p = 0.02$), processing speed ($p < 0.001$), working memory ($p = 0.004$) and executive functions ($p = 0.011$). They showed no impairment in sustained attention ($p = 0.59$) (Miskowiak et al., 2021). Individuals with unipolar depression and BD were not compared.

Finally, individuals with unipolar disorder and BD showed impaired performance in global cognition and executive functions compared to the healthy control group ($p < 0.01$). They showed reduced performance compared to the healthy control group on the executive function sub-composite score ($p < 0.01$), the attention sub-composite score ($p < 0.05$) and the verbal learning and memory sub-composite score ($p < 0.05$) (Hørlyck et al., 2021). In the verbal learning and memory sub-composite score, individuals with BD scored significantly lower than those with unipolar depression ($p = 0.05$) (Hørlyck et al., 2021). There were no differences between individuals with unipolar disorder and BD on other cognitive outcomes.

Clinical assessment

Three studies from two samples used VR to carry out a clinical evaluation for individuals with BD (Kim, 2008; Kim et al., 2009b; Kjærstad et al., 2022).

A study found impairments in emotional regulation in individuals with BD compared to unaffected first-degree relatives and healthy controls using a VR-based social scenarios test. Individuals with BD completed a traditional behavioral paradigm, and a novel VR-based social scenarios test called the VERA test in which they were presented with social scenarios in a fully immersive 360-degree VR environment and were instructed to either simply view the scenario or try to dampen their emotional response. The study found a decrease in emotion regulation success in negative VR social scenarios in individuals with BD ($p = 0.01$). Individuals with BD were less able to damper their emotional response than healthy controls ($p = 0.04$) and unaffected first-degree relatives ($p = 0.02$), whereas results in unaffected first-degree relatives were comparable to healthy controls ($p = 0.97$) (Kjærstad et al., 2022).

In another study which generated two publications, the mean interpersonal distance (IPD) of individuals with bipolar mania to an avatar in VR was inversely correlated with the severity of manic symptoms ($p < 0.05$) (Kim, 2008; Kim et al., 2009b).

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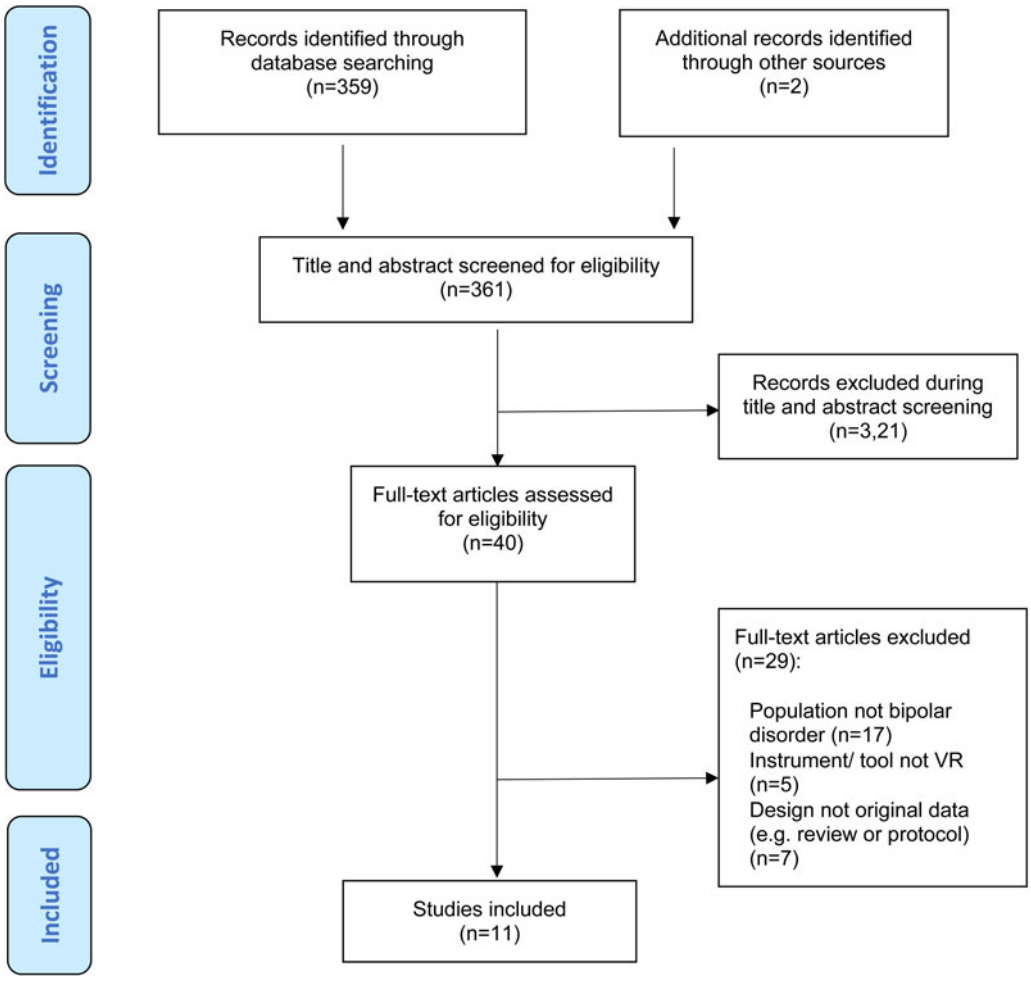


Figure 1. PRISMA flowchart outlining study selection process.

However, they demanded greater personal space ($p < 0.001$), more so in female than male participants ($p = 0.007$) (Kim, 2008; Kim et al., 2009b). Individuals with bipolar mania showed more gaze aversion ($p < 0.001$) (Kim, 2008; Kim et al., 2009b). They exhibited a reduced affective valence toward angry avatars ($p = 0.041$), heightened arousal toward neutral avatars ($p = 0.011$) and reduced arousal toward happy avatars ($p = 0.018$) compared to healthy controls (Kim, 2008). Affective valence toward angry avatars was significantly diminished in the individuals with BD compared to healthy controls ($p = 0.041$) (Kim et al., 2009b). Individuals with BD showed enhanced arousal toward neutral avatars ($p = 0.011$), but diminished arousal toward happy avatars ($p = 0.018$) (Kim et al., 2009b).

Response to virtual reality as a treatment

Three studies used VR as an intervention and measured its efficacy (Ilioudi et al., 2023; Perra et al., 2023; Shah et al., 2015).

One study used VR to provide cognitive remediation through an app – 24 sessions of 45 min, two sessions per week- (Perra et al., 2023). The app offered psychoeducation and exercises of varying difficulty, divided into three modules: memory and learning; cognitive estimates: and attention and working memory. Compared to the waitlist group, individuals with BD receiving reported a significant improvement regarding cognitive functions (memory: $p = 0.003$; attention: $p = 0.002$, verbal fluency: $p = 0.010$; executive function: $p = 0.003$), depressive symptoms ($p = 0.030$), emotional awareness ($p = 0.007$) and biological rhythms ($p = 0.029$) (Perra et al., 2023).

Another study compared the use of a VR-based and a physical calm room in a sample of individuals admitted to an inpatient psychiatric intensive care unit specialized in BD (but also accepting individuals with anxiety and depression). After the intervention, well-being improved ($p < 0.01$) and heart rate decreased ($p = 0.02$) in both present calm rooms and the VR-based calm room. No changes in blood pressure were found ($p > 0.05$) (Ilioudi et al., 2023). There were no significant differences in the efficacy of the two interventions in enhancing well-being (Ilioudi et al., 2023). No specific analyses for individuals with BD were carried out.

A feasibility study evaluated a VR-based stress management program on stress-related variables for individuals with BD ($n = 12$) and major depressive disorder ($n = 10$) (Shah et al., 2015). Following the 3-day intervention (1-h sessions administered by researchers), individuals had lowered subjective stress, depression and anxiety levels ($p < 0.001$) (Shah et al., 2015). Significant differences in skin temperature ($p < 0.001$) were found, but no differences in systolic blood pressure ($p = 0.10$), diastolic blood pressure ($p = 0.97$) and heart rate ($p = 0.14$) (Shah et al., 2015). No specific analyses for individuals with BD were carried out.

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Table 1. Characteristics of the included studies

First author, year	Country	Design; QA	Sample size (*N*) BD total: N each group in clinical trials	Designation; instrument to characterize BD	Age: mean ± S.D. (range); Sex: % females	VR equipment	VR tasks and experiments/ interventions carried out	Key findings
Gould et al. (2007)	USA	Cross-sectional; Moderate	30	BD-I, BD-II; DSM-IV, SCID	45.8 ± 11.7[b]; 43.3[b]	VR Town: 3-D (nonaerial) view.	Individuals familiarized themselves with a village and then navigated through it using a computer-generated route where they had to find several destinations and their memory was tested.	Individuals with BD ($n = 20$) or depression ($n = 10$) found fewer locations on the Spatial Navigation Task ($p = 0.01$). The number of locations found was inversely correlated with the severity of depressive symptoms ($r = -0.33$, $p = 0.02$). Individuals with BD/ depression and comparison subjects did not differ in performance on the spatial working memory test ($p = 0.95$). Performance on the navigation task was correlated with performance on the spatial working memory task ($r = -0.45$, $p = 0.007$).
Hørlyck et al. (2021)	Denmark	Cross-sectional; Moderate	11	N.a.[a]; ICD-10	37.4 ± 12.4[b]; 57.1[b]	Computer in a virtual, non-immersive office environment 2-D.	In JEF©, individuals are tasked with completing various activities within a virtual office setting, categorized into three distinct groups: (i) preparing for an upcoming meeting, (ii) handling incoming office mail, and (iii) addressing ad hoc tasks. The activity is not immersive and bears resemblance to engaging in a computer game.	Individuals with BD ($n = 11$) or UD ($n = 10$) showed impaired performance on executive functions (JEF score) and impairments on the global cognition score compared to the HC group ($p < 0.01$). The UD/BD group showed reduced performance compared to the HC group on the executive function sub-composite score ($p < 0.01$), the attention sub-composite score ($p < 0.05$) and the verbal learning and memory sub-composite score ($p < 0.05$). Lower cognitive scores were associated with more functional

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Table 1. (*Continued.*)

First author, year	Country	Design; QA	Sample size (*N*) BD total: N each group in clinical trials	Designation; instrument to characterize BD	Age: mean ± s.d. (range); Sex: % females	VR equipment	VR tasks and experiments/ interventions carried out	Key findings
								disability, as reflected by moderate correlations with higher FAST scores ($r = 0.30$, $p < 0.01$) and lower UPSA-B scores ($r = 0.44$, $p < 0.001$).
Ilioudi et al. (2023)	Sweden	Other clinical trial; Moderate	27: 20 calm room, 7 physical room.	BD-I, BD-II, BD unspecified; Clinical	39.1 ± 13.5 (21–68; 58.3)	Wireless 3-D VR HMD (Oculus Go)	Breathing exercises, mindfulness programs, and relaxing music. A variety of soothing nature environments could be tailored through (e.g. day and night scenes and dynamic weather). Unit/ward's staff received instructions on how to use the rooms.	No significant differences in the efficacy of virtual calm rooms and physical calm room in enhancing well-being were found ($p > 0.05$). In both groups state of well-being improved ($p < 0.01$) and heart rate decreased ($p = 0.02$) at the group level from before to after the intervention but no changes in blood pressure were detected ($p > 0.05$). 20% participants declined to participate. The mean duration of stay in the intervention was longer for the physical calm room group compared to the VR calm room group (25.4 *v.* 15.2 min, $p < 0.03$).
Kim (2008)	South Korea	Cross-sectional; Moderate	20	BD-I; DSM-IV-TR	30.1 ± 5.9; 50	HMD and headphones, immersive.	Individuals adjusted their distance to avatars for comfortable conversation, then they measured the angle of gaze deviation from avatar's forehead, and subjects rate emotions and excitement toward avatars using the Self-Assessment Manikin scale.	The mean interpersonal distance of individuals with bipolar mania was inversely correlated with the severity of manic symptoms ($p = 0.018$). However, individuals with bipolar mania exhibited relatively avoidant-withdrawn patterns of interpersonal behaviors when compared with healthy controls, by demanding

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Table 1. (*Continued.*)

First author, year	Country	Design; QA	Sample size (*N*) BD total: N each group in clinical trials	Designation; instrument to characterize BD	Age: mean ± s.d. (range); Sex: % females	VR equipment	VR tasks and experiments/ interventions carried out	Key findings
								greater personal space ($p < 0.001$). Females demanded greater interpersonal distance than males ($p = 0.007$). Individuals with BD also showed more gaze aversion ($p < 0.001$) and they exhibited a reduced affective valence toward angry avatars compared to the control group ($p = 0.041$); Individuals with BD demonstrated heightened arousal toward neutral avatars ($p = 0.011$) and reduced arousal toward happy avatars compared to controls ($p = 0.018$).
Kim et al. (2009a)	South Korea	Cross-sectional; Moderate	14	BD-I; DSM-IV-TR	30.4 ± 5.9; 57.1	N.a. (not 3D)	Individuals were presented with emotional avatars and asked to infer the reason for the avatar's emotion based on verbal and nonverbal cues. The task consisted of six experimental blocks and six control blocks, and each block had three phases: observation, inference, and response. The participants were asked to judge a short sentence that suggested a potential reason for the avatar's emotion by clicking a mouse button.	Individuals with BD exhibited significantly delayed reaction times across all blocks ($p = 0.005$). No significant differences were found in mean reaction time between the experimental and control blocks within either of the two groups (for individuals with BD, $p = 0.181$; for healthy subjects, $p = 0.723$). In experimental blocks, healthy controls outperformed in happy *v.* neutral (accuracy: $p = 0.022$; reaction time: $p < 0.001$), while individuals with BD showed better performance in happy reaction time alone ($p = 0.005$) but not accuracy ($p = 0.089$).

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First author, year	Country	Design; QA	Sample size (*N*) BD total: N each group in clinical trials	Designation; instrument to characterize BD	Age: mean ± s.d. (range); Sex: % females	VR equipment	VR tasks and experiments/ interventions carried out	Key findings
Kim et al. (2009b)	South Korea.	Cross-sectional; Moderate	20	BD-I; DSM-IV-TR	30.1 ± 5.9; 50	HMD and headphones, immersive.	Individuals were asked to approach an avatar and stop at a distance where they felt most comfortable to have a conversation. From that distance, subjects were to say 'hello' first and wait for the response of the avatar. The avatar would then talk about topics compatible with its facial emotion and request that the subjects introduce themselves. Individuals rated emotional feelings and excitement toward avatars using the Self-Assessment Manikin scale.	In individuals with BD, interpersonal distance was significantly greater than that of healthy controls ($p < 0.001$). Females demanded greater interpersonal distance than male individuals ($p = 0.007$). Among the individuals with BD, only IPD from the happy avatars exhibited significant differences (the smallest) compared to IPD from the neutral avatars and IPD from the angry avatars). However, within the control group, only IPD from the angry avatars demonstrated significant differences (the largest) in comparison to the distances from the other two emotional avatars. The mean interpersonal distance of individuals with BD, were inversely correlated with the severity of mania ($p = 0.023$). The overall mean of averted gaze angles of the BD group was significantly greater than that of the control group ($p < 0.001$). The between-group differences of gaze angles across the emotional types of avatars were all significant (all $p = 0.007$). Affective valence toward angry avatars was significantly diminished in the patient group relative to the control

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First author, year	Country	Design; QA	Sample size (*N*) BD total: N each group in clinical trials	Designation; instrument to characterize BD	Age: mean ± s.d. (range); Sex: % females	VR equipment	VR tasks and experiments/ interventions carried out	Key findings
								group ($p = 0.041$). Individuals with BD showed enhanced arousal toward neutral avatars ($p = 0.011$), but diminished arousal toward happy avatars ($p = 0.018$).
Kjærstad et al. (2022)	Denmark	Cross-sectional; Moderate	30	N.a. (73% BD-II); ICD-10, SCAN	33.2 ± 9.7; 76.7	Fully immersive 360-degree spherically camera-recorded equipment.	Individuals completed two paradigms to assess their emotional regulation abilities: a traditional behavioral paradigm and a novel VR-based social scenarios test called the VERA test. In the VERA test, participants were presented with social scenarios in a fully immersive 360-degree VR environment and were instructed to either simply view the scenario or try to dampen their emotional response. The scenarios were presented in a fixed order (neutral, negative, positive), and each condition concluded with a self-rated emotion rating. The traditional behavioral paradigm involved participants down-regulating emotions to descriptions of social scenarios on a computer screen.	Statistically significant differences in the main effect of group for emotion regulation success in negative VR social scenarios ($p = 0.01$) were found, driven by individuals with BD being less successful at dampening their emotional response than healthy controls ($p = 0.04$) and unaffected relatives ($p = 0.02$). No differences between unaffected relatives and healthy controls were found ($p = 0.97$).
Miskowiak et al. (2021)	Denmark	Cross-sectional; Moderate	28	N.a.[a]; ICD-10	35.3 ± 11.7[b]; 60[b]	Standalone HMD Oculus Go 32 GB portable headset, immersive.	CAVIR: The tasks included memorizing a list of ingredients and taking them out of the fridge, planning and selecting the order of sub-tasks involved in cooking a meal, placing correct	Individuals with mood disorders (BD = 28, unipolar disorder = 12) showed impaired global neuropsychological performance compared to healthy controls ($p = 0.001$). Across

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Table 1. (*Continued.*)

First author, year	Country	Design; QA	Sample size (*N*) BD total: N each group in clinical trials	Designation; instrument to characterize BD	Age: mean ± S.D. (range); Sex: % females	VR equipment	VR tasks and experiments/ interventions carried out	Key findings
							ingredients in a pot based on a key of symbols, observing and memorizing the location of cutlery and flatware in the kitchen cupboards and drawers, and repeatedly checking the lasagne in the oven in response to a specific combination of visual and auditive cues while ignoring irrelevant stimuli.	individual domains, they exhibited impaired verbal learning and memory ($p = 0.02$), processing speed ($p < 0.001$), working memory ($p = 0.004$) and executive functions ($p = 0.011$). They showed no impairment in sustained attention ($p = 0.59$). In individuals with psychosis spectrum disorders impaired global neuropsychological scores compared to healthy controls were found ($p < 0.001$), but only a non-significant trend towards impaired sustained attention ($p = 0.059$) was found.
Mohammadi et al. (2018)	Iran	Cross-sectional; Moderate	20	BD-I, BD-II; DSM-IV	31.1 ± 7.7; 65	The environments were 3-D, fully colored, textured, and presented a first-person view.	The VRNT featured 3D first-person and 2D overhead views, and individuals viewed the overhead environment (two environments – a virtual neighborhood and a virtual maze) for 60 s, followed by the 3D view, locating goals marked in the overhead view (yellow circle), recording responses and reaction times. The movements in the environment were controlled using a joystick.	There were no statistically significant differences between individuals with BD and healthy controls in spatial navigation ($p > 0.05$). In the neighborhood task individuals with schizophrenia performed significantly worse than healthy controls on the virtual neighborhood task ($p < 0.001$). Individuals with BD scored lower than healthy controls, but the differences were not significant ($p > 0.05$). In the virtual maze task, individuals with schizophrenia performed significantly worse than healthy controls

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Table 1. (*Continued.*)

First author, year	Country	Design; QA	Sample size (*N*) BD total: N each group in clinical trials	Designation; instrument to characterize BD	Age: mean ± s.d. (range); Sex: % females	VR equipment	VR tasks and experiments/ interventions carried out	Key findings
								($p < 0.05$), but no significant differences in individuals with BD were found ($p > 0.05$).
Perra et al. (2023)	Italy	RCT; Strong	75: 50 experiment room; 25 control group	N.a; DSM-IV	47.2 ± 13.5; 66.7	HMD ('Oculus Go') fully immersive 3D	The CEREBRUM app offered 52 exercises of varying difficulty, divided into three modules: Memory and Learning, Cognitive Estimates, and Attention and Working Memory. During the VR exposure, participants answered the health worker's questions while exploring the 360° scenario. The intervention consisted of 24 sessions of 45 min each, divided into two sessions per week over three months. Each session included a structured sequence of activities, including reception, psychoeducation, exercise psychoeducation, execution of the exercise in VR with positive and corrective feedback, post-exercise comments, and homework. The intervention consisted of 24 sessions of 45 min, two sessions per week.	Compared to the waitlist group, individuals with BD receiving fully immersive VR-based cognitive remediation reported a significant improvement regarding cognitive functions (memory: $p = 0.003$; attention: $p = 0.002$; verbal fluency: $p = 0.010$; executive function: $p = 0.003$), depressive symptoms ($p = 0.030$), emotional awareness ($p = 0.007$) and biological rhythms ($p = 0.029$). The intervention for individuals with BD had good acceptability and tolerability 48.7% of the individuals considered their experience of the intervention 'excellent', whereas 28.2% and 23.1% considered it 'great' and 'good', respectively. At the end of the intervention, 87.2% of individuals did not report any side effects. 5.1% reported nausea and daze. 2.5% reported feelings of emptiness/ unreality. 78% completed all the sessions.

(*Continued*)

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Table 1. (*Continued.*)

First author, year	Country	Design; QA	Sample size (*N*) BD total: N each group in clinical trials	Designation; instrument to characterize BD	Age: mean ± s.d. (range); Sex: % females	VR equipment	VR tasks and experiments/ interventions carried out	Key findings
Shah et al. (2015)	Singapore	Other clinical trial; Strong	12: 12 interventi-on group, no control.	N.a.[a]; Clinical	(21–60); 72.7[b]	A lightweight, HMD (model ITG-PCX3) was used to guide the relaxation practice.	VR DE-STRESS Program comprised psychoeducation and relaxation practice guided by VR-based relaxation videos. The program involved viewing relaxation videos showcasing three relaxation techniques: abdominal breathing, muscle relaxation, and guided imagery. The relaxation videos contained visual presentations, soothing auditory instructions (with female voice in English), and relaxing music. The participants were asked to practice the relaxation techniques while viewing the videos. The intervention consisted of three daily 1 hour sessions administered by researchers.	Following the 3-day intervention with a VR-based stress management program, individuals with BD or major depression had significantly lowered subjective stress, depression and anxiety levels ($p < 0.001$). Increased skin temperature was found ($p < 0.001$). No significant differences in systolic blood pressure ($p = 0.10$), diastolic blood pressure ($p = 0.97$) or heart rate ($p = 0.14$) across six measurement points were found. There was a significantly increased perceived relaxation across the six time points ($p < 0.001$). 84.5% agreed to engage in the study. 86.4% completed the study.

AVLT, Auditory-Verbal Learning Test; BD, Bipolar Disorder; CANTAB, Cambridge Neuropsychological Test Automated Battery; CAVE, Cave Automatic Virtual Environment; CAVIR, Cognition Assessment in Virtual Reality; DSM, Diagnostic and Statistical Manual of Mental Disorders; FAS, Functioning Assessment Short Test; HMD, Head-mounted displays; ICD, International Classification of Diseases; JEF, Jansari assessment of Executive Functions. FAST, Functioning Assessment Short Test; MMSE, Mini-Mental State Examination; QA, quality assessment; RAVLT, Rey Auditory Verbal Learning Test; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status Effort Scale; RCT, randomized clinical trial; ROCFT-R, Rey-Osterrieth Complex Figure Test (ROCFT-R); ROCFTD, Rey-Osterrieth Complex Figure Test; RVP, Rapid Visual Information Processing; SCAN, Schedules for Clinical Assessment in Neuropsychiatry; SCID, Structured Clinical Interview for DSM–IV; SWM, Spatial Working Memory; UD, unipolar depression; UPSA-B, Performance-based Skills Assessment; VRNT VR, virtual reality.: Virtual Reality Navigation Test; WAIS-III, Wechsler Adult Intelligence Scale.

[a]Mood disorders: unipolar and bipolar disorder.

[b]Data available for combined mood disorder only.

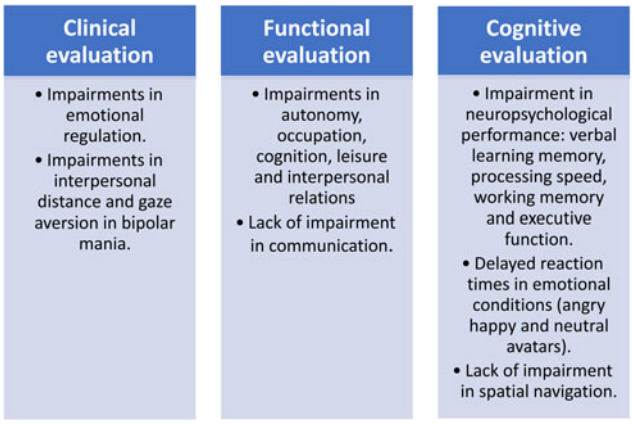


Figure 2. Summary of findings from clinical, functional, and cognitive evaluation.

Safety/acceptability

Three studies used VR as an intervention and measured directly or indirectly its safety/acceptability for the interventions detailed above (Ilioudi et al., 2023; Perra et al., 2023; Shah et al., 2015). The rest of the studies included were cross-sectional.

48.7% of the individuals with BD considered VR-based cognitive remediation 'excellent', whereas 28.2% considered it 'great' and 23.1% considered it 'good'. At the end of the intervention, 87.2% of individuals did not report any side effects (Perra et al., 2023).

Of the individuals receiving a VR-based stress management program, 86.4% completed the study. Qualitatively, participants reported that the program helped them 'be strong and determined', 'think positively', 'see things in a bigger picture', 'open mind', 'look forward to the future', 'learn to relax', 'manage insomnia', and 'cope with stress' (Shah et al., 2015), although note some of these outcomes are related to the efficacy of the intervention.

Finally, the mean duration of stay in the VR calm room was 25.4 min, while it was 15.2 min in physical calm room (Ilioudi et al., 2023). 20% participants declined to participate.

Quality of the included studies

81.8% of studies received a global rating of moderate and 18.2% received a global rating of strong. 'Data collection' was strong in all the included studies, while 81.8% were assessed as weak in quality due in the 'withdrawals and dropout' section.

Discussion

To the best of our knowledge, this is the first systematic review to evaluate the use of VR in BD. BD poses significant challenges in terms of diagnosis, delayed onset recognition, and limited treatment options. The present systematic review explores the application of VR as a diagnostic and therapeutic tool in BD, shedding light on its potential contributions to clinical, cognitive, and functional assessments, treatment interventions, and safety/acceptability.

This systematic review revealed a range of studies employing VR for cognitive evaluations in BD. There is increasing awareness of the importance of cognitive difficulties in BD, and assessments and interventions are being recommended. Our results speak to this more recent emphasis and provide a useful and potentially engaging assessment method for this group. Specifically, impairments in verbal learning, memory, processing speed, working memory, and executive function were found in adults with BD, which can lead to poor outcomes and poor functioning. The findings regarding special navigation were conflicting, as one study found impairment in BD while the other one did not. In any case, VR shows promise to carry out cognitive assessments and detect some of these difficulties. Unfortunately, cognitive assessments typically have limited ecological validity (Miskowiak et al., 2021). VR assessments can dynamically adapt to the individuals' responses in real time, which provides an interactive and personalized experience which can be beneficial when doing a cognitive evaluation. The impairments identified can also serve to develop VR-based interventions (Moreno et al., 2019).

In regard to clinical outcomes, impairments in emotional regulation were found in individuals with BD compared to unaffected first-degree relatives and healthy controls (Kjærstad et al., 2022). This offers us a useful way to assess emotional regulation performance, which can be useful for assessment and therapy. Understanding the specific challenges faced by individuals with BD in social scenarios provides a foundation for tailoring treatment strategies. For instance, positive emotion regulation interventions could be incorporated into comprehensive treatment plans (Painter et al., 2019).

Two of the interventions evaluated seemed particularly promising, both from an efficacy and from a safety/acceptability perspective: VR-based cognitive remediation for cognitive functions, depressive symptoms, emotional awareness and biological rhythms (Perra et al., 2023); and VR-based stress management program on stress-related variables, anxiety, and depression (Shah et al., 2015). The number of interventions studied is still very limited to make specific recommendations at individual level, at least compared to other mental health fields. In the psychosis field, it has been suggested that VR could be particularly helpful for individuals with intense fears about being outside in everyday situations (Freeman et al., 2022). Precision strategies should aim to assess outcomes and develop interventions that are more likely to be effective at the group or individual level (Salazar de Pablo et al., 2021). VR may not be the best tool for everyone, the same way as house exercise through VR may be a good substitute to exercising outside for some individuals but not others (Peng et al., 2022). For instance, remotely-delivered cognitive behavioral therapy (CBT) seems to be equally efficacious as face-to-face CBT, except for those individuals with higher severity of OCD symptoms at baseline, in which face-to-face CBT is more effective (Salazar de Pablo, Pascual-Sánchez, Panchal, Clark, & Krebs, 2023). Furthermore, adolescents seem to be particularly attracted to VR for its broad range of immersive activities and social engagement opportunities (Maloney, Freeman, & Robb, 2021). This may mean that the effectiveness of VR interventions could be higher. Unfortunately, none of the studies included in this review focused on this population and this remains an area needing research.

Other studies have included individuals with BD among their participants, although they were not included as they did not fulfill the inclusion criteria. For instance, an RCT evaluated a virtual screen-based stress management program on individuals admitted into the hospital with several mental disorders including schizophrenia, depression, and BD. They found a significant increase in perceived relaxation and knowledge after the intervention compared with the waiting list group (Tan, Chng, Lau, & Klainin-Yobas, 2021). Other interventions could be trialled or

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piloted in the future, including VR-based exposure therapy, which has been used for anxiety disorders (Boeldt, McMahon, McFaul, & Greenleaf, 2019) and for post-traumatic stress disorder (PTSD) (Kothgassner et al., 2019). In PTSD, VR-based exposure therapy has meta-analytically shown an improvement in PTSD symptoms and depressive symptoms (Kothgassner et al., 2019). Another example would be VR-based CBT, which has been used for anxiety and depression (Baghaei et al., 2021; Wu, Sun, Zhang, Zhou, & Ren, 2021). VR interventions could integrate real-time mood monitoring and feedback mechanisms to help individuals with BD track their emotional states and recognize early warning signs of mood episodes. Furthermore, interventions (e.g. cognitive restructuring exercises) could target maladaptive thought patterns associated with depressive symptoms or manic symptoms. Novel interventions are also being trialled. For instance, Lithium Hindsight 360 (LH360) is a VR prototype intended to help individuals with BD communicate, though alternatives to writing, such as dance and somatic movement (Kim & Crowe, 2020). There is also an ongoing study looking at retinal electrophysiological markers in individuals with BD (https://clinicaltrials.gov/study/NCT05161546?cond=Bipolar%20Disorder&intr=Virtual%20Reality&rank=4) and another looking at enhancing cognitive reserve of the offspring of individuals with BD and schizophrenia (https://clinicaltrials.gov/study/NCT03722082?cond=Bipolar%20Disorder&intr=Virtual%20Reality&rank=7).

This study has some limitations that have to be taken into consideration when interpreting its results. First, the number of included studies and the number of individuals with BD was small. Further studies, including collaborative studies with a larger sample size are recommended. Second, the predominant focus on adults limits the generalizability of the results. Future research should explore the application of VR in other populations as adolescents with BD. Third, there were methodological flaws in some of the included studies. For future studies, matching participants and adjusting groups and results is recommended. Fourth, the populations, including BD characterizations, were heterogeneous and some studies included individuals with mood disorders. Furthermore, some studies did not provide their results for individuals with BD only and combined them with data from individuals with other mood disorders. Evidence from studies focusing on participants with BD is more likely to be applicable to individuals with BD. Fifth, the VR equipment used were also heterogeneous and some studies did not provide details on the characteristics of the equipment used. These details including the degrees of immersion are important. Finally, with six studies focusing on cognitive evaluation, three on clinical evaluation and three on the efficacy and tolerability of interventions, there are many domains that have not been studied. We recommend researching other domains, including management of comorbidity, relapse or appearance of new episodes and prodromal symptoms, among others.

Conclusion

In conclusion, emerging data point towards the promising utility of VR in BD as a tool for cognitive and clinical assessments in individuals with BD. Furthermore, certain VR interventions show potential for improving cognitive functions and managing symptoms. However, multiple domains have not been investigated and studies have been limited to adults. New domains as comorbidity, relapse and prodromal symptoms should be investigated. Research on children and adolescents is also recommended. Further investigation and replication of findings are required to disentangle which VR-based interventions and for which populations and outcomes are effective. More research is also needed to explore the long-term effects of VR interventions on individuals with BD.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291724001247.

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