



Psychological Interventions for Individuals with 22q11.2 Deletion Syndrome: a Systematic Review

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Abstract

Objectives 22q11.2 deletion syndrome (22q11.2DS) is common microdeletion syndrome associated with intellectual and learning disorders, psychiatric disorders, and a complex physical phenotype. The aim of this review was to build upon a previous systematic review on this topic and identify psychological interventions attempting to address the behavioural (including cognitive and emotional) phenotype of the syndrome.

Methods Articles were reviewed and organised as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for conducting systematic reviews. The literature search identified 1124 studies, out of which nine studies met the inclusion criteria. The nine studies are summarised in terms of (a) study design and follow-up, (b) populations involved, (c) intervention characteristics, and (d) feasibility.

Results The findings indicate that it is important to consider the individual's needs, developmental stage, and the syndrome-specific behavioural phenotype when implementing (and evaluating) psychological interventions.

Conclusions The existing literature has a heavy focus on the delineation of the behavioural phenotype and associated psychiatric comorbidities but there are very few studies exploring how to adapt and implement effective interventions to support the mental health and well-being of people with 22q11.2DS. Future studies are required to evaluate the feasibility of interventions as well as the effectiveness in reducing distress, building skills, and improving quality of life.

Keywords Velo-cardio-facial syndrome · DiGeorge syndrome · Psychotherapy · Cognitive remediation · Applied behavioural analysis

22q11.2 deletion syndrome (22q11.2DS) is a genetic disorder that commonly affects individuals, with an estimated prevalence of 1 in 2148 live births and 1 in 992 pregnancies (Blagojevic et al., 2021; Grati et al., 2015). It is most commonly occurring de novo but is in some cases familial. The syndrome is caused by the deletion of approximately fifty functional genes, resulting in a variable phenotype that impacts major organs. The multisystem syndrome is associated with congenital cardiac and palatal anomalies, hypocalcemia, immunodeficiency, renal abnormalities, dysphagia,

hypocalcemia, scoliosis, and subtle dysmorphic features (McDonald-McGinn et al., 2015). In some cases, non-invasive prenatal testing or newborn screening for severe combined immunodeficiency may identify 22q11.2DS but oftentimes the diagnosis is in middle childhood or later (Óskarsdóttir et al., 2023). Early indicators may also include feeding difficulties and various structural anomalies. Because of this complex medical phenotype, many people with the syndrome are frequently unwell often requiring medical interventions and hospitalisations, particularly in early childhood. In addition, more than half of individuals require some type of surgical intervention during childhood, ranging from relatively straightforward insertions of grommets to complex cardiac and palatal repairs and reconstructions (Kobrynski & Sullivan, 2007). In early life, the focus is mostly on dealing with physical health concerns but as the child develops, and the most urgent physical needs have been addressed, the focus mostly shifts to needs associated with developmental differences that occur at significantly higher

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rates than in the typically developing population. Differences include speech and language disorders, intellectual disability, specific learning disorders, autism, and attention-deficit hyperactivity disorder (ADHD), as found by Óskarsdóttir et al., (2023). These complex, often chronic, needs can result in attachment disruptions, trauma, and stress for the whole family system with a significant impact on emotional well-being, behaviour, learning, social relationships, and overall quality of life both in the short and long term (Snihirova et al., 2022; Swillen & McDonald-McGinn, 2015). Indeed, poor mental health and psychiatric disorders are common, with anxiety and depression frequently reported amongst both children and adults with the syndrome (Schneider et al., 2014). In addition, adolescents and adults with 22q11.2DS are at an increased risk of experiencing psychotic symptoms, according to Jhavar et al. (2021) and Schneider et al. (2014). The prevalence of psychiatric conditions in this population highlights the importance of developing new and evaluating existing psychological and behavioural interventions designed for people with 22q11.2DS.

A recent survey of patient advocacy organisations highlighted that brain and behaviour, including psychiatry, early intervention, and education, were the second-highest priority for subspecialty areas of care in 22q11.2DS (Óskarsdóttir et al., 2023). It has been recognised that neuropsychological and psychiatric assessments are important parts of care for individuals with this syndrome, and the psychosocial context, including parental well-being, parental discipline, socio-economic status, negative life events, peer victimisation, and hostile close relationships, impacts on the psychological well-being and mental health of people with 22q11.2DS (Snihirova et al., 2022). However, the clinical guidelines published by Óskarsdóttir et al. (2023) and Boot et al. (2023) do not mention evidence-based psychological interventions to address these concerns. They do note, however, that cognitive behavioural therapy (CBT) may not be as effective for people with poorer language skills. Therefore, there is a need to conduct more research into the feasibility and effectiveness of alternative psychological interventions to CBT, which may be better suited to the abilities and needs of individuals with 22q11.2DS.

Psychologists can play a critical role in supporting people with 22q11.2DS by helping them, and their families, to navigate the challenges and barriers they face across the lifespan. Identifying strengths, challenges, and needs related to an often-complex biopsychosocial presentation can facilitate the development of intervention and behavioural support plans that are tailored to suit an individual's specific needs. These plans can encompass cognitive remediation programmes to address cognitive impairments, psychotherapy to help people cope with emotional issues related to their disability, and behavioural interventions to help people

learn new skills that may significantly improve their quality of life. Psychologists are also well placed to support and educate families of people with 22q11.2DS more broadly, helping them to better understand the challenges faced by the person they care for and providing them with effective tools and strategies to better support them. Buijs et al. (2018) undertook a review of non-pharmacological treatments of psychiatric disorders in 22q11.2DS, identifying a paucity of relevant studies and a need to explore the feasibility and efficacy of interventions to support this population. In Buijs et al.'s (2018) study, it was also suggested that due to the lack of research in this area, there is insufficient evidence to inform revisions to clinical guidelines on non-pharmacological treatments based upon the needs of individuals with 22q11.2DS. Hence, the current systematic review of existing studies is aimed at extending on the previous study and identifying and examining psychological and behavioural interventions targeted at improving developmental, well-being, and mental health outcomes for people with 22q11.2DS.

Method

The systematic review was completed according to the PRISMA Checklist (Moher et al., 2009). In December 2022, the systematic review was registered and approved by PROSPERO (CRD42023383996).

Literature Search Procedure

A search was conducted within the PsycINFO and MEDLINE electronic databases. The literature search process is illustrated in Fig. 1, which is a flow diagram adapted from Moher et al. (2009). There were no limits placed on the type, date, or language of publication. To identify all pieces of literature concerned with the treatment of 22q11.2 deletion syndrome, multiple search terms were generated. These terms were sorted into three categories, including population, intervention, and mental health, which reflected each aspect of the research question. Specifically, the population search terms were 22q11.2*, Digeorge*, Cayler*, velocardiofacial*, velo-cardio-facial*, conotruncal*, Shprintzen*, Opitz g*, and Sedlackova*. The intervention search terms were intervention/ or interven*, therap*, treatment/ or treatment*, cognitive therapy/ or Cognitive Behaviour Therapy/ or CBT*, mental health/ or mental health*, behavior/ or behav*, psycho*, counseling/ or counsel*, non-drug*, nondrug*, nonpharm*, non-pharm*, drugfree*, and drug-free*. The neurodevelopmental and mental health search terms were autism spectrum disorder/ or ASD*, attention deficit disorder with hyperactivity/ or ADHD*, paranoid schizophrenia/

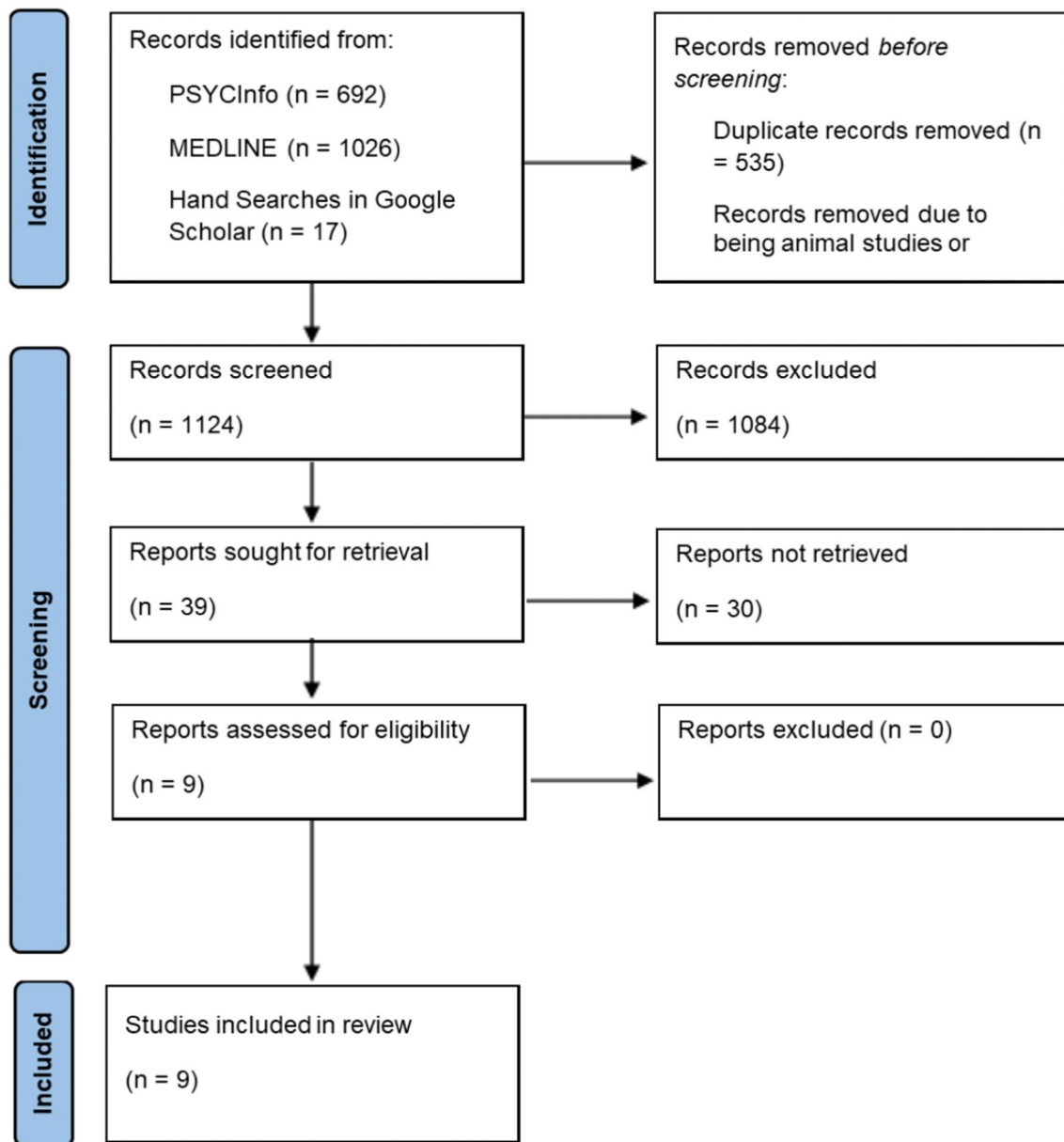


Fig. 1 Flow diagram of the systematic review process—adapted from Moher et al. (2009)

or schizophrenia*, or acute schizophrenia/ or schizophrenia/, major depression/ or depress*, anxiety/ or generalised anxiety Disorder/ or anxi*, bipolar* or bipolar disorder/ or bipolar II disorder/ or bipolar I disorder/, stress* or post-traumatic Stress/ or posttraumatic stress disorder/ or stress/, or Complex PTSD/ or PTSD*, social anhedonia/ or anhedonia/ or anhedonia*, intellectual development disorder/ or intellectual*, psychosis/ or affective psychosis/ or acute Ppychosis/ or psychosis* or childhood psychosis/, panick attack/ or panic* or panic disorder/, obsessive compulsive disorder/ or obsess*, agoraphobi* or agoraphobia/, phobi*, and psychiatri*. The search was completed in January 2023.

Study Selection

All identified studies were imported into EndNote where duplicates were removed. There were several missed duplicates after the automatic process, which were manually removed by one of the researchers. Additionally, some animal studies were manually removed in EndNote, as the systematic review was to be focused on human studies. Following this, the systematic review programme, Covidence, was utilised to screen the studies. Two researchers (CC and NG) screened the titles and abstracts of each manuscript simultaneously. When conflicts arose, they consulted the research leader (LC) to determine the suitability of the studies in the

next round of screening. Next, a full-text screening was conducted by the same two researchers. Any conflicts that arose during this screening were resolved by the lead researcher. Overall, there were 1124 studies screened in Covidence. After the two screening phases, a total of nine studies met the pre-determined inclusion criteria and were included in the systematic review.

Data Extraction and Management

The inclusion criteria for all publications included in the review were (a) the study population had a diagnosis of 22q11.2DS /DiGeorge syndrome, (b) psychological or behavioural interventions were used and evaluated, and (c) the interventions attempted to improve developmental outcomes and/or mental health of individuals in the study population. The exclusion criteria utilised to remove articles during the screening process were (a) animal studies, (b) studies without an intervention component, (c) pharmacological or drug-based interventions, (d) individuals in the study population did not have a diagnosis of 22q11.2DS /DiGeorge syndrome, (e) conference presentations or abstracts, and (f) systematic, scoping, or literature reviews.

Quality Assessment

A quality assessment based upon Joanna Briggs' critical appraisal tool checklists was conducted on each included study in the systematic review. The case study, case series, and case control assessment checklist criteria were applied to each study where applicable. These appraisal tools assessed studies based on the appropriateness of case and control matching, descriptions of participant demographics and clinical conditions, descriptions of diagnostic tests/assessments and interventions, and reporting of analyses, results, and outcomes. The quality assessment of each study is seen in Table 1.

Results

This review contains nine studies that met the inclusion criteria. Table 2 summarises all included studies. Each study is analysed according to study design, follow-up, the target population, the research aims, intervention, outcome measures, and conclusions.

Study Designs and Follow-up

The nine included studies were published between 2013 and 2022. Of the nine articles, two were case studies, one used a controlled, single-case experimental design, and the remaining six utilised a longitudinal experimental design to

obtain data on the effectiveness of the interventions. Three interventions contained follow-up assessments at 6, 8, and 12 months, respectively.

Population

A total of 127 participants were included in these studies, all with a confirmed 22q11.2DS or DiGeorge diagnosis. Two of the nine studies used control groups (Harrell et al., 2013; Shashi et al., 2015), with nineteen participants of the 127 being in the control group. All controls were age-, ethnicity-, and gender-matched individuals diagnosed with 22q11.2DS. The remaining participants were all part of the intervention groups. Most of the articles focused on adolescents specifically, including participants aged 10–18 years; four studies looked at adults with 22q11.2DS as well, with ages ranging from 19–63 years.

Research Aims and Intervention Characteristics

Three studies (Harrell et al., 2013; Mariano et al., 2015, 2018) aimed to investigate and improve the cognitive skills of adolescents with 22q11.2DS. Harrell et al. (2013) sought to determine if using an online cognitive remediation programme (BrainWorks™) which provided exercises targeting attention, working memory, and processing speed could improve general cognitive skills. The study included an age, race, and gender-matched control group in a between-group design. The participants were provided with an opportunity to demonstrate that they were able to complete the exercises independently before the trial. The intervention involved completing three games per session in four BrainWorks sessions per week, across 12 weeks and included a 10-dollar incentive for every session completed. Mariano et al. (2015) proposed a similar aim for their research to determine if cognitive skills in adolescents could be improved using a digital, cognitive remediation programme (Challenging Our Minds). This study adopted a longitudinal repeated measures design, whereby the participants served as their own controls, with the intervention active for eight months. Participants completed three 45-min sessions per week with an online cognitive coach who demonstrated the tasks and provided feedback on the performance and task-specific structured strategies (including cognitive flexibility and executive functioning). They offered a 10-dollar incentive for each session completed. In Mariano et al.'s (2018) study, their original research was extended to see if positive impacts on cognitive performance were sustained over a longer period in the same participants, 6 months post-intervention.

Two studies (Glaser et al., 2018; Shashi et al., 2015) looked at improving social skills within their respective studies. Shashi et al. (2015) aimed to see if social cognition could be improved through a small-group social cognitive

Table 1 Quality assessment of included studies

	Buijs et al. (2021)	Busch et al. (2022)	Dowdy and Tincani (2020)	Fjermestad et al. (2015)	Glaser et al. (2018)	Harrell et al. (2013)	Mariano et al. (2015)	Mariano et al. (2018)	Shashi et al. (2015)
Participant inclusion criteria	✓	✓	✓	✓	✓	✓	✓	✓	✓
Reliable and standard condition measurement for all participants	✓	✓	✓	✓	✓	✓	✓	✓	✓
Valid participant condition identification methods	✓	✓	✓	✓	✓	✓	✓	✓	✓
Consecutive inclusion of participants (case series only)	N/A	N/A	✓	✓	X	N/A	x	x	N/A
Report of participant demographics	✓	✓	✓	✓	✓	✓	✓	✓	✓
Report of participant demographics	✓	✓	✓	✓	✓	✓	✓	✓	✓
Report of case outcomes and follow-ups	✓	✓	✓	x	✓	✓	✓	✓	✓
Reporting of site/clinic demographics	✓	✓	✓	✓	✓	✓	✓	✓	✓
Appropriate statistical analysis	✓	✓	✓	✓	✓	✓	✓	✓	✓
Description of diagnostic tests and assessments	✓	✓	✓	✓	✓	✓	✓	✓	✓
Description of interventions and treatment procedures	✓	✓	✓	✓	✓	✓	✓	✓	✓
Description of post-intervention clinical condition	✓	✓	✓	x	✓	✓	✓	✓	✓
Identification and description of adverse or unanticipated events	✓	✓	✓	x	✓	✓	✓	✓	✓
Takeaway lessons provided	✓	✓	✓	✓	✓	✓	✓	✓	✓
Takeaway lessons provided	N/A	N/A	N/A	N/A	N/A	✓	✓	✓	✓
Comparable groups (presence/absence of disease in cases/controls (case control studies only)	N/A	N/A	N/A	N/A	N/A	✓	✓	✓	✓
Proper matching of cases and controls (case control studies only)	N/A	N/A	N/A	N/A	N/A	✓	✓	✓	✓
Valid, reliable, and standard measurement and length of exposure (case control studies only)	N/A	N/A	N/A	N/A	N/A	✓	✓	✓	✓
Identification and proposed management of confounding factors (case control studies only)	N/A	N/A	N/A	N/A	N/A	✓	✓	✓	✓
Valid, reliable, and standard measurement of outcomes	✓	✓	✓	x	✓	✓	✓	✓	✓

Table 2 Summary of Included Studies

Study reference	Study design; follow-up	Population	Research aims	Intervention	Outcome measures	Outcomes
Buijs et al. (2020)	Case study	Intervention group: 2 22q11.2DS (aged 19 and 21 years), Control group: None	Aimed to explore the feasibility and efficacy of CBT to inspire a larger-scale intervention study of people with 22q11.2DS and a comorbid anxiety disorder	13 weeks, 1 × 45–60 min sessions per week, individual CBT	Clinical interviews and observations, State Trait Anxiety Inventory for Children (STAIC-c), World Health Organisation Quality of Life Scale (WHOQOL-BREF), Outcome Rating Scale (ORS), Session Rating Scale (SRS)	Client A—poor-reasonable satisfaction on SRS, no improvement observed in clinical interviews, no significant difference in STAIC-c scores, minimal differences observed on WHOQOL-BREF, improvements on ORS Client B—decrease in anxiety on STAIC, improvement in well-being on ORS, decreased scores on clinical interviews and observations, WHOQOL-BREF indicating lower quality of life, poor satisfaction on SRS
Busch et al. (2022)	Controlled single-case experimental design FU: 6 months and 12 months post-intervention	Intervention group: 2 22q11.2DS (aged 26 and 63 years), Control group: None	Aimed to evaluate behavioural interventions for severe behaviour problems in people with 22q11.2DS	17–21 × 5 min sessions across 1–2 days, DRA therapy	Functional analysis	Patient A—elimination of inappropriate touching significant in the intervention and 6- and 12-month follow-up Patient B—zero levels of aggressive/disruptive behaviour, and high levels of cooperation achieved and maintained at 3- and 12-month follow-up
Dowdy and Tincani (2020)	Case study	Intervention group: 1 17-year-old diagnosed with ASD, ADHD, intellectual disability, Marfan's syndrome and DiGeorge syndrome, and 1 10-year-old diagnosed with ASD, ADHD, intellectual disability, intermittent explosive disorder and pica Control group: None	Aimed to evaluate the effectiveness of differential reinforcement without extinction using the interview informed synthesised contingency analysis (IISCA) method to reduce problem behaviour in a pool setting	10 min sessions conducted within 30 min pool access sessions per day, IISCA procedures based on differential reinforcement excluding extinction	IISCA, functional assessments, modified version of Treatment Acceptability Rating Form—Revised	No transition refusal behaviours exhibited for both participants in last phase of treatment, transition refusal behaviours remained low at 1- and 2-month follow-up, lifeguards scored social validity of the assessment and treatment very highly
Fjermestad et al. (2015)	Longitudinal design	Intervention group: 12 22q11.2DS (aged 12–17 years) Control group: None	Aimed to assess psychosocial functioning in adolescents with 22q11.2DS using CBT	5 days, 7 × 45 min sessions, group CBT	Child Behaviour Checklist (CBCL) and the K-SADS (Kiddie Schedule for Affective Disorders and Schizophrenia) screening interview	Social, school, and total competence scores on CBCL very low, K-SADS indicated that ADHD, anxiety problems, depression, and potential PTSD were most prevalent in participants

Table 2 (continued)

Study reference	Study design; follow-up	Population	Research aims	Intervention	Outcome measures	Outcomes
Glaser et al. (2018)	Longitudinal design	Intervention group: 22 22q11.2DS (aged 11–26 years) Control group: None	Aimed to initiate improvement in social responsiveness, social withdrawal, and anxiety in young adults with 22q11.2DS	12 weeks, 1 × session per week, SOSTA-22 Digital Version; computerised software programme	Raven Progressive Matrices, Peabody Picture Vocabulary Test, satisfaction rating scale (bespoke) for parents	Receptive vocabulary abilities in the low-average range on the Peabody Picture Vocabulary Test, low scores on Raven's Progressive Matrices, high satisfaction with programme and minimal need to assist child in sessions
Harrell et al. (2013)	Longitudinal design	Intervention group: 13 22q11.2DS (aged 12–17 years) Control group: 10 22q11.2DS (aged 12–17 years), randomly assigned)	Aimed to determine whether cognitive skills in those with 22q11.2DS could be improved using a digital cognitive remediation programme	12 weeks, 4 × sessions per week, BrainWorks™; an online computerised software programme Incentive: 10 dollars per week of completed sessions	CBCL, Continuous Performance Task (IP version), California Verbal Learning Test (Children's version), Digit-Span subtest of WISC-IV/WAIS-IV, Spatial Span subtest on WISC-IV, Stroop Colour-Word Test, Porteus Mazes (Vineland Edition)	Cognitive composite score (combination of all measures) indicated overall positive effect in treatment group
Mariano et al. (2015)	Longitudinal design FU: 8 months post-intervention	Intervention group: 22 22q11.2DS (aged 12–16 years) Control group: None	Aimed to improve cognitive skills over time in adolescents with 22q11.2DS using cognitive remediation	8 months, 3 × 45 min sessions per week; digital cognitive remediation programme Incentive: 10 dollars per CR session	CNS Vital Signs, Behaviour Assessment System for Children Second Edition Parent Rating Scale	Significant change on five of the ten composite scores on CNS Vital Signs, for cognitive flexibility, executive function, reaction time, working memory, and complex attention
Mariano et al. (2018)	Longitudinal design FU: 6 months post-intervention	Intervention group: 21 22q11.2DS (aged 12–18 years) Control group: None	Aimed to determine if a computerised cognitive remediation programme had lasting positive impacts on people with 22q11.2DS	8 months, 3 × sessions per week; cognitive coach, Challenging Our Minds; cognitive remediation programme Incentive: 10 dollars per CR session	CNS Vital Signs	Found that the effects in previous study (Mariano et al., 2015) remained steady at 6-month follow-up

Table 2 (continued)

Study reference	Study design; follow-up	Population	Research aims	Intervention	Outcome measures	Outcomes
Shashi et al. (2015)	Longitudinal design	Intervention group: 13 22q11.2DS (aged 12–17 years) Control group: 9 22q11.2DS (aged 12–17 years)	Aimed to determine whether social cognition in people with 22q11.2DS could be improved using a social cognitive training programme	6 months, 1 × 60 min session per week, group social cognitive training Incentive: 10 dollars per session attended	Verbal and performance scales on WISC-IV/WAIS-IV, Mayer-Salovey-Caruso Emotional Intelligence Test-Youth Version, The Diagnostic Analysis of Nonverbal Accuracy, Global Functioning-Social, Social Skills Rating Scale, Adaptive Behaviour Assessment Systems (2nd edition), Computerised Diagnostic Interview Schedule for Children, Side Effects Rating Scale	Significant improvement on the composite index of social cognition (all scores combined), significant difference between the groups on MSCEIT, no significant group differences on social competence, global functioning, social and general adaptive functioning

training (SCT) coaching programme that involved one session per week across 6 months. The groups included 3–5 participants and were completed face-to-face. The programme included a structured curriculum based on Cognitive Enhancement Therapy (CET) but was modified to specifically target known social-cognitive difficulties associated with 22q11.2DS including perspective taking, social appraisals, and affect recognition. The activities included case scenarios, video clips, and pictures. Parents were provided with weekly updates on content and homework exercises. A 10-dollar incentive was also offered for each session that was attended. Glaser et al. (2018) investigated techniques to enhance social responsiveness and reduce social withdrawal and associated anxieties. This study used a modified version of the SOSTA-FRA (originally designed for autistic young people) and named the SOSTA-22 digital programme once per week across 12 weeks. The group programme was adapted to meet the social needs of the participants and delivered online using Skype to increase accessibility. Each group included 4–6 participants who were of similar age. Each group had a group leader (a psychologist) who modelled positive social behaviour and each session focused on building different skills. The three skill areas (communication, emotions, and social reciprocity and interaction) progressively became more complex across the duration of the programme and were practised within the sessions as role-play and as homework assignments. Parents were also invited to monthly meetings to discuss skills their children had practised.

Two studies (Buijs et al., 2021; Fjermestad et al., 2015) utilised CBT intending to improve well-being. Fjermestad et al. (2015) aimed to assess the psychosocial functioning of adolescents with 22q11.2DS through seven 45-min-long CBT sessions administered across five days in a residential stay. The therapy sessions were presented in a group setting (6 participants) and included basic CBT tasks including emotional awareness, cognitive restructuring, and problem-solving aimed to prevent anxiety and depression. One session focused on the lived experience of having 22q11.2DS. Parents attended lectures about 22q11.2DS in parallel as well as being provided information about the adolescent group content. Each group was led by a mental health professional (psychiatrist/clinical psychologist). Buijs et al. (2021) aimed to explore the feasibility and efficacy of a CBT intervention, to inform a larger-scale investigation on people with 22q11.2DS and a comorbid anxiety disorder. The case study included two young adults who participated in individual 45–60 min long CBT sessions once a week over 13 weeks. The CBT interventions were based on standard CBT protocols and delivered by an experienced CBT practitioner. Participants were expected to do homework activities.

The last two studies (Busch et al., 2022; Dowdy & Tincani, 2020) explored the use of behaviour analytic

procedures and principles to reduce problematic behaviours in participants with complex needs. Dowdy and Tincani (2020) reported on a case study that included one young man (17 years old) with a complex presentation including DiGeorge syndrome, autism, ADHD, Marfan syndrome, and a profound intellectual disability. The young man was non-speaking and communicated using a speech-generating device. Functional assessments including interview, observation, and functional analysis were completed based on an interview-informed synthesised contingency (IISCA) analysis before the implementation of a differential reinforcement without extinction behavioural intervention including demand and contingency-specifying rules (3-step prompting procedure and reward). This was designed to reduce problematic behaviours and teach more appropriate and safe behaviours when exiting an indoor pool. Busch et al. (2022) investigated behavioural challenges that had become problematic and dangerous for two males with 22q11.2DS. Both participants had complex presentations including intellectual disabilities and schizophrenia (current/remission). Both received support from a forensic mental health care team. Problematic behaviours included inappropriate touching of other people; acts of aggression towards others or objects such as hitting, kicking, scratching, pushing, or throwing; and verbal threats towards others. An assessment was completed including direct observations and interviews as well as a functional analysis of the behaviour. Following this, intensive Differential Reinforcement of Alternative Behaviour (DRA) therapy was implemented to reduce problematic behaviours. The intervention included training staff in the treatment procedure, and multiple follow-up sessions were carried out up to 12 months post-intervention.

Feasibility and Satisfaction

Six studies (Buijs et al., 2021; Glaser et al., 2018; Harrell et al., 2013; Mariano et al., 2015, 2018; Shashi et al., 2015) assessed the feasibility of the interventions. In the study by Harrell et al. (2013), nine of the thirteen participants completed the programme indicating a reasonable compliance. The engagement by the four participants who discontinued was varied due to inconsistent/unreliable internet access and/or a lack of motivation of children or parents. The acceptability and satisfaction were generally good with most parents indicating that they were very or somewhat satisfied with the projects. Additionally, only 12% of the children reported that they were upset when it was time to do the tasks again, although 56% of the children reported that they were happy the programme was over. The studies by Mariano and colleagues demonstrated good adherence with few cancellations, and the accessibility of the programme was also acceptable with few technical issues (Mariano et al., 2015, 2018). The fidelity across coaches was satisfactory

with moderate to high correlations. Shashi et al. (2015) reported that the feasibility of the programme was high with all participants completing the programme with attendance ranging from 82 to 92%. All reasons for absence were reasonable and included illnesses and family commitments. The satisfaction levels across parents and children were high across all domains with a majority wanting to attend future small-group sessions. Parents noted that the topics covered were relevant, the group was deemed a safe place and that communication with leaders was important. However, they did agree that finding suitable times was difficult and that setting time aside for homework was challenging. In the study by Glaser et al. (2018), 18 of the original 22 participants completed the follow-up. Of the four participants who did not complete the whole study, one participant could not make the time set for the intervention, two participants (and their families) were under acute stress and had to drop out, and one participant attended less than 75% of the sessions. Most participants attended all sessions (67%). All reasons for absence were reasonable and related to medical problems. Parents reported a high degree of satisfaction with the programme, and that only minimal effort was required to assist their children during the sessions. While most parents rated the length of the programme as adequate, only 33% were satisfied with the duration of the programme with others deeming it too short. Most parents deemed the content somewhat or very useful.

Buijs et al. (2021) reported that six individuals met the inclusion criteria and expressed interest in participating in the study. Of these, two chose not to participate due to the geographic location, the frequency of the sessions, or dislike of the therapeutic setting. Only two provided written informed consent. Both participants attended most of the sessions, but timeliness was an issue for one participant, highlighting that family support was important for attendance. Homework was challenging for both participants, but practical exercises were more achievable for one participant. Both participants benefited from supportive therapeutic structures and understood basic CBT principles, but one participant benefited from simplified and concrete language. Contradictory to clinical observations, only poor-to-reasonable therapeutic alliance was reported.

Outcomes

There were five computerised or hybrid interventions included in this systematic review (Glaser et al., 2018; Harrell et al., 2013; Mariano et al., 2015, 2018; Shashi et al., 2015). In the Harrell et al. (2013) study, preliminary effectiveness was measured using seven neuropsychological or behavioural assessments. Cognitive improvements were measured in the composite cognitive score and simple processing speed on the Stroop task. The intervention group

had improved performance compared to the control group on most tasks including the composite cognitive measure. Mariano et al. (2015) tracked outcomes using three neuropsychological assessments and reported that the hybrid approach showed preliminary success in improving cognitive skills across domains including working memory, shifting attention, and cognitive flexibility. Their later study in 2018 found that the improvement in the composite cognitive measure remained steady after the intervention was completed. Similarly, Shashi et al. (2015) used a mixture of qualitative and quantitative information to explore the effectiveness of the programme. Most parents reported that they had noticed improvements in social interactions outside of the group although some parents had hoped for more significant changes. Moderate improvements were reported for social cognition including the perception of emotions compared to the control group. However, no significant differences were found for social competence, global functioning (social) or general adaptive functioning. Glaser et al. (2018) used parent-rated questionnaires to assess the outcomes of their study. It was found that social awareness and motivation as per the Social Responsiveness Scale (SRS) improved over the course of the programme. No other pre-post differences were identified on the SRS or the Child Behaviour Checklist/Adult Behaviour Checklist. Overall, the parents reported that the programme was useful to improve emotional awareness, general well-being/mood, reciprocal conversations, and recognising/naming one's emotions.

There were four case studies/series exploring the implementation of psychotherapeutic and/or applied behavioural interventions (Buijs et al., 2021; Busch et al., 2022; Dowdy & Tincani, 2020; Fjermestad et al., 2015). Fjermestad et al. (2015) did not use any post-intervention tests to explore the efficacy of the intervention due to having a low sample size and argued that it would have been difficult to accurately determine if outcomes were a direct cause of the intervention due to the study's short duration. However, they provided a clear outline of modifications, including frequent breaks to improve focus, engagement with participants during break times to facilitate social interaction, introducing turn-taking to facilitate engagement and provide safety, and using clear structures with frequent reminders. Frequent use of repetition and the provision of adequate processing time was important to ensure that participants understood and retained the content. It was advised to avoid too many extra materials to reduce distractions. Content was also adjusted to allow for differences in experiences including cognitive restructuring, identifying alternative thoughts, and problem-solving. Buijs et al. (2021) used two self-report psychological questionnaires of anxiety and quality of life plus a visual analogue self-report scale, the Outcome Rating Scale (ORS) at the start of each session to measure the outcomes in their CBT-based study. Client A reported positive outcomes with regard

to developing a better understanding of their thoughts and feelings, improved emotion regulation, and improved quality of life. Client B reported a decrease in anxiety and improvements in well-being. Observations of client B included an improvement in the awareness of feelings and emotions; however, self-report of quality of life decreased over time. Through this, they were able to provide suggestions for how CBT could and should be specifically adapted to be more beneficial for those with 22q11.2DS. Some of these suggestions included being proactive and factoring in more time in the therapy sessions. The authors concluded that the participants required external support to attend, session flexibility was important and content and materials should be personalised to increase concreteness and appeal. In addition, adaptations concerning specific phenotypic characteristics are required and may include a multidisciplinary approach. Buijs et al. (2021) and Fjermestad et al. (2015) concluded that while CBT can be successfully implemented in this population, the content and delivery should be modified due to the specific needs of individuals with 22q11.2DS.

Dowdy and Tincani (2020) used IISCA procedures to collect data and facilitate a functional analysis to investigate if the DRA intervention was successful in reducing problematic and dangerous behaviour when exiting an indoor pool in a residential treatment facility. These behaviours included delays in transitioning out of the pool, hitting, pulling, pushing, or grabbing the therapist when asked to exit the pool and re-entering the pool without supervision. The functions of the behaviour were identified, and the intervention achieved expected outcomes. Effects were maintained over 1-month and 2-month follow-ups. In addition, the social validity of the functional assessment and intervention procedures was scored as high by therapists. Busch et al. (2022) used observations to collect data to facilitate functional analyses to investigate if a DRA intervention resulted in a reduction in challenging behaviours. Using a controlled single-case experimental design and implementation of a function-based behavioural intervention, a reduction of the targeted challenging behaviour for both clients was achieved. The effects were maintained over 3-month and 12-month follow-ups. The reduction of problematic behaviours led to positive changes in weekly activities, less incidents, and restrictive practises. To conclude, these studies provide emerging evidence that applied behavioural interventions may be an effective approach to those with 22q11.2DS and co-occurring significant intellectual developmental disorder and behavioural problems; however, further investigation is required.

Quality Assessment

Most articles met each of the applicable criteria according to Joanne Briggs' critical appraisal tool checklists,

indicating appropriate study quality. A minor issue in two case series studies (Mariano et al., 2015, 2018) was that they did not address consecutive inclusion of participants. However, Fjermestad et al.'s (2015) study was of lower quality compared to all other studies, as it did not acknowledge any adverse events, failed to report any post-intervention outcomes or clinical conditions of participants, and did not conduct any follow-up assessments. While this study was included in the review, the findings should be interpreted with caution.

Discussion

This systematic review identified nine studies investigating the effectiveness of different types of psychological interventions in addressing cognition, behaviour, and/or mental health of individuals with 22q11.1DS. All included studies were research articles, and the interventions presented were based on social and cognitive remediation, cognitive behavioural therapy, and applied behavioural interventions.

Successful Intervention Components Identified Within Included Studies

There were several important findings about the most successful and suitable aspects of interventions for individuals in this population. It was found that having maintained family support, extended therapy timeslots (Glaser et al., 2018), frequent breaks, allowing time for processing, few distractions (Fjermestad et al., 2015), and more appealing written homework tasks (Buijs et al., 2021) throughout interventions were preferred by participants. However, it is important to consider the difficulty in implementing these factors successfully in such a heterogeneous population, presenting with diverse needs and preferences. Specifically, many participants required parental assistance to complete the homework—a factor that is often observed in this population due to developmental delays, which highlights the potential challenge of incorporating a homework component in future, larger scale studies (Harrell et al., 2013). Additionally, participants and parents in the study by Glaser et al. (2018) appreciated the online mode of the social skills training intervention, as it was more convenient and required less travel in between many other appointments. Although, Harrell et al. (2013) also highlighted that technical issues with online programmes can lead to frustration. While online interventions are very cost and time effective, Shashi et al. (2015) argued that their participants benefitted greatly from the face-to-face interaction with cognitive coaches and other individuals with 22q11.2DS. Harrell et al. (2013) emphasised the importance of considering other demands such as homework and extracurricular activities when designing

interventions, with parents suggesting shorter usage periods to enhance engagement. Mariano et al. (2015) found that older participants navigated the programme more easily, underscoring the need to factor in participants' developmental stages when designing interventions. Overall, one of the key messages across all the studies was that interventions should be tailored to address participants' specific needs, both in terms of their abilities and challenges. Moreover, it was clear that ensuring accessibility and reducing barriers to participation were an important part of the intervention planning process.

Methodological Limitations of Included Studies

While the findings of this systematic review have been highly valuable, there were some consistent methodological limitations identified within the included studies. All the studies had non-randomised and small sample sizes, limiting the generalisability of findings to this population and lowering the statistical power to detect small effects (Buijs et al., 2021; Busch et al., 2022; Fjermestad et al., 2015; Glaser et al., 2018; Harrell et al., 2013; Mariano et al., 2015, 2018). Participants were also either self-referred or individually targeted to become involved in each study, which calls into question the participants' motivation and willingness to engage in the research (Buijs et al., 2021). Consequently, motivation was a moderator in these studies, as some study participants were highly motivated, and other study participants had low motivation, serving as a barrier to accurately measuring the effectiveness of the interventions. Furthermore, Buijs et al.'s (2021) study was conducted while participants were also receiving pharmacological treatment. While participants in this study were only included if they had not undergone any recent modifications to their pharmacological treatment, it remains difficult to clearly determine the isolated treatment effects of the psychological and behavioural intervention. One of the articles did not report on outcome measures of the CBT intervention (Fjermestad et al., 2015) due to the low sample size and time constraints of the study, highlighting the need for more time-intensive studies assessing the effectiveness of interventions being developed for this population. There were also only two studies that incorporated a control group into their intervention (Harrell et al., 2013; Shashi et al., 2015), and two in which participants served as their own controls (Mariano et al., 2015, 2018). Additionally, randomisation was lacking in the studies which increased the risk of selection bias. While this is a disadvantage, it must be considered that controlled and randomised designs within this population are more difficult, time-consuming, and expensive due to the heterogeneity of the participant groups and the limited availability of eligible participants making these studies an important starting point for future research.

Inconsistent Outcomes Between Included Studies

There were also some inconsistencies in findings between the studies, highlighting the need for more extensive research in this field with thorough, high-quality methodological designs. A few studies reported high participant and parent satisfaction rates with the interventions, or feedback indicating that they would return to the programme or participate again if the option was made available (Buijs et al., 2021; Glaser et al., 2018; Harrell et al., 2013; Shashi et al., 2015). However, many of the included studies did not include an assessment of the participants' acceptability or satisfaction with the interventions. It was also difficult to accurately assess the overall success of some interventions. Specifically, in Buijs et al.'s (2021) study, participants' follow-up self-reports did not align with therapists' clinical assessment of the therapy sessions, client progress, or client ratings of the therapeutic alliance interventions. Furthermore, Glaser et al.'s (2018) study only measured participant changes in social responsiveness, withdrawal, and anxiety via parent-reported scales, which often differ significantly from teacher or therapist outcome reports (Wray et al., 2013). Overall, there seemed to be mostly positive outcomes of the interventions. For instance, Shashi et al. (2015) and Harrell et al. (2013) reported preliminary, but significant, improvements in performance on cognitive tasks for the intervention participants in comparison to the control groups, and Mariano et al. (2018) observed improvements in cognitive functioning upon follow-up. Similarly, the case studies involving behavioural interventions for individuals with challenging behaviours demonstrated positive outcomes that were maintained over time (Busch et al., 2022; Dowdy & Tincani, 2020).

Future Research

Considering these findings, future research should aim to develop randomised controlled trials of psychological interventions that could include cognitive remediation, CBT, and social skills training interventions. The efficacy of such interventions must be systematically evaluated to determine the appropriateness of specific intervention approaches in supporting the psychological well-being of individuals with 22q11.2DS and to adequately control for influencing factors. Furthermore, it may be of interest to develop more appropriate tests and assessments for this population to measure outcomes more comprehensively, due to the inconsistencies between participant self-reports and clinician assessments.

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Availability of Data and Materials Data generated for this article are available from the corresponding author upon reasonable request.

Declarations

Competing Interests The authors declare no competing interests.

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