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Early intervention in autism spectrum disorder (ASD)

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OPINION
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From Social Distancing to Social Connections: Insights From the Delivery of a Clinician-Caregiver Co-mediated Telehealth-Based Intervention in Young Children With Autism Spectrum Disorder

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INTRODUCTION

The COVID-19 pandemic and efforts directed toward containing virus spread have led to significant disruptions to children's lives worldwide due to school closures, lockdowns, quarantines, reduced access to healthcare services, limited socialization, and significant reduction in opportunities to engage in physical activity (1, 2). The effects of the pandemic are more severe in children with intellectual and developmental disabilities including Autism Spectrum Disorder (ASD) (3–5). For families of children with ASD, the pandemic presents a host of challenges including, (1) reduced/modified virtual access to educational and healthcare services (Applied Behavioral Analysis (ABA), occupational therapy (OT), social skills training, speech language therapy (SLT), etc.) required to manage children's complex symptoms/comorbidities, (2) disruptions in structured routines, stay-at-home orders, and the unpredictability of the pandemic coupled with a lack of understanding of the world-wide crisis, leading to an aggravation of children's behavioral symptoms and increase in anxiety/distress, (3) difficulties complying with pandemic mitigation efforts of social distancing, limited outdoor activities, hand washing, mask wearing, etc. due to ASD-related cognitive, social, and sensory impairments, and (4) increased parental stress due to concerns for family's health, juggling multiple home-, work-, and caregiving/homeschooling-related responsibilities, as well as due to the economic, social, and psychological effects of the pandemic (6–9). Overall, the confluence of multiple pandemic-related stressors places significant strain on the family unit of children with ASD and deserves special consideration to address these impacts.

Over the past year, several countries have shifted to telehealth approaches to address the urgent educational and healthcare needs of citizens (10–13). Telehealth involves the use of electronic information and telecommunication technologies to support long-distance clinical health care delivery, patient health-related education, and public health (14). This includes synchronous, real-time video conferencing between families and clinicians as well as asynchronous transmission of content (instructional modules, videos/images, and websites) via the internet for caregiver coaching (15). The advantages of telehealth over traditional face-to-face (F2F) service delivery include cost-effectiveness, expanded geographic access, reduction in family and clinician travel costs, freedom to learn content at own pace (for asynchronous content), and reduced chances of infection due to in-person contact during the pandemic (16, 17). There is growing evidence for the use of telehealth-based service delivery in children for ABA-based services, OT, and SLT (18–22). A systematic review of 28 studies that provided telehealth-based ABA training to interventionists suggested that all studies found improvements in at least one outcome measure including challenging behaviors, social communication, and imitation skills in children with ASD as well as increases in procedural fidelity/skills of interventionists; however, included studies were methodologically weak necessitating more rigorous research before telehealth can be accepted as evidence-based practice in ASD (23). Another review of 14 studies in ASD suggested that telehealth-based services were comparable in efficacy to F2F interventions and significantly superior to control groups who received either no intervention or only self-directed training (24). Overall, telehealth seems to be a promising modality that can complement in-person practice, and in certain situations (i.e., the ongoing pandemic), even serve as an alternative to regular therapeutic practice (25).

Evidence on telehealth in ASD has mostly focused on training parents to facilitate their child's development (12, 23, 26). Involvement of parents in their child's therapy has clear advantages: (1) parents are their child's first teachers, (2) they are highly invested in their child's progress and can provide unique insights regarding their child's strengths and weaknesses, (3) their involvement makes the intervention ecologically valid, (4) parent coaching can train them to identify and harness teachable opportunities outside therapy sessions to promote target skills, and finally, (5) this approach facilitates generalization and maintenance of learned skills and also reduces parental stress (16, 27). However, self-directed parent training in addition to therapist coaching leads to greater improvements in children's skills, parent self-efficacy, as well as parental satisfaction and acceptance of telehealth programs compared to self-directed training alone, suggesting the importance of expert involvement (13, 16, 28). Next, we report preliminary insights from our ongoing randomized controlled trial (RCT) that assesses the effects of a telehealth-based, caregiver and clinician co-mediated, creative play intervention in school-age children with ASD. Our experiences also have implications for similar interventions in younger children with ASD. With the onset of the pandemic, our research team had to rapidly modify our in-person intervention protocol to be delivered virtually through videoconferencing platforms. The transition to telehealth-based research presented its set of challenges. Nevertheless, like any cloud has a silver lining, our experiences indicate that the transition to a clinician-caregiver collaborative virtual treatment approach makes our research more pragmatic and family-centric (29).

TELEHEALTH-BASED CREATIVE PLAY INTERVENTION

Our multi-site RCT compares the effects of a whole-body creative movement and play-based intervention with a seated play intervention on social communication, executive functioning, imitation, motor coordination, and social synchrony skills of children with ASD between 5 and 15 years. The broader goal of this project is to assess the utility of whole body, socially-embedded movement interventions in addressing both primary impairments and secondary co-morbidities in children with ASD. Our past work has suggested that music and movement-based "rhythm" interventions lead to an increase in socially-directed verbalization, imitation, and interpersonal synchrony skills, and also afford high levels of social attention and positive affect/smiling during training sessions (30–33). In the current study, we aim to replicate and further expand on our previous work by assessing the effects of a creative movement intervention combining elements of music, dance, and yoga in a larger sample of children with ASD across 2 different study sites. Children are matched on age, gender, and functional level and then randomly assigned to receive either the experimental "play" intervention or the control "seated play" intervention. The creative play group engages in music- and imitation-based, movement and social games including, (1) singing and ice-breaker activities, (2) action songs that focus on hand movements, (3) music making with instruments, (4) locomotor games, and (5) solo/partner yoga poses and breathing. The seated play group engages in standard-of-care, OT and special education-based activities including, (1) greetings and farewells, (2) reading story books, (3) fine motor games, (4) building activities using Play-doh® and Legos™, and (5) art-craft activities. The program has built-in opportunities for imitation, turn taking, call and response, and creative improvisation. Prior to the pandemic, training was conducted in a small group setting involving the child, clinician, and an adult confederate. As a facilitator, the clinician provided task instructions, activity demos, corrective feedback, prompting, and reinforcement, as well as used behavioral strategies to ensure task compliance. The adult confederate was the child's "buddy model" and supplemented the clinician's efforts by partnering with the child during games, providing motivational support, and hand-on-hand assistance as needed. With the transition to telehealth-based research, we have expanded our small group to also include the child's caregivers (parent &/or siblings). While the clinician and adult confederate serve as the child's "virtual buddies," caregivers serve as their "in-person" buddies during online training sessions.

In our experience so far of working with 9 families of children with ASD through telehealth, we find that a collaborative caregiver and clinician co-mediated effort works really well. Our insights are also supported by other research that suggests that the telehealth-model of intervention delivery requires greater active participation from parents to ensure intervention success compared to F2F delivery (16). Parents in fact report greater beneficial effects of having ongoing, synchronous clinician input and assistance compared to a purely self-directed or asynchronous model of telehealth (16, 17, 20). Below we provide further explanation of why a clinician-caregiver co-mediated approach has salient benefits compared to other modes of intervention delivery.

From the clinician's perspective, a collaborative approach is beneficial as they can observe the child during real-world interactions and provide valuable feedback/suggestions to parents. For children with ASD requiring moderate-to-high

TABLE 1 | Challenges and potential solutions during telehealth sessions.

Challenges	Potential Solutions
Technical issues	
Lack of equipment	- A kit is mailed to caregivers which includes a microphone and a webcam that is already mounted on a tripod ready-to-use by families. - If a family does not have access to a laptop, we provide a laptop with pre-loaded videoconferencing software.
Setup and troubleshooting of hardware and software	- A step-by-step installation guide for hardware equipment (webcam, tripod, and microphone) and video-conferencing software setup including written instructions, snapshots, and instructional videos are provided via email. - Caregivers are guided through the actual hardware and software setup process during the tech-support session conducted via a phone call. - Following successful setup of the hardware and software, the family is sent an email with a password-protected Zoom link for a live session. - All audio and video settings are tested and optimally configured during this live session in preparation of the next virtual session with the child.
Connectivity issues	- If the family is facing streaming issues during the test video-call using video-conferencing software, we try to identify the area of their house where they may have the best internet access and test the quality of the connection from that location. - If needed, caregivers may be asked to limit the number of devices using the internet at the time of the scheduled call with the research team to ensure better streaming speeds and audio/video quality during the call.
Type of view on videoconferencing software	- Caregivers are provided information on different view types (e.g., gallery and speaker views) during the test video-call and the research team recommends the ideal view to be used during the intervention sessions. - Specifically, caregivers are asked to try out different viewing options during the virtual tech-support session so that they are familiar and comfortable changing these settings. - Caregivers are recommended to use the gallery/grid view during group training sessions (so that child can see all participants in the session) and speaker/focus view during fine motor activities using small objects.
Participant issues	
Setup of environment	- The caregiver in collaboration with the research team identify a quiet, distraction-free area during the tech-support session that can be reserved for training sessions. - Caregivers are requested to adjust furniture and remove any items that block views to ensure that both the child and caregivers are visible throughout the training sessions. - As mentioned above, caregivers are guided to figure out optimal camera position and room lighting in the reserved space for testing/training.
Child/or caregiver not in view	- Adjustments to camera position are made by the caregiver in an ongoing manner during the session to ensure that the child is always in full view of the camera.
Child/caregiver not heard	- Caregivers are reminded to turn on the microphone at the start of every session and we request them to place it as close to the child as possible to ensure optimal sound quality. - If it is hard to hear the child's responses, we always ask the caregivers for clarification on what the child is trying to communicate. Caregivers are also encouraged to intimate the clinician/confederate if they observe any non-verbal communicative behaviors (pointing, signs for "more," "all done," etc.) that the clinician/confederate may have missed.
Clinician not seen/heard	- To ensure that the clinician/confederate are appropriately visible and heard, they also use a tripod mounted webcam and a microphone at their end.
Intervention-related issues	
Clinician-played music not heard	- To allow music played on the clinician's laptop to be transmitted through video-conferencing software and be audible to the child/caregiver, we enable settings in the video-conferencing software that allow the clinician to "share sound." - The clinician uses a speaker to ensure adequate amplification of played sound so that it can be heard loud enough at the child's end. - In addition, the music files are also sent to caregivers ahead of time of the session. In case caregivers are having trouble hearing the music, they are asked to play these music files at their end during the sessions.
Unclear expectations regarding sessions	- We use picture boards to clearly indicate the activities for the day and transitions between activities to the children. - We make a behavioral agreement with the child at the start of each session using a rules sheet that uses words and pictures to list do's and don'ts for the session. The child is provided an intermittent reminder of the rules as needed during the rest of the training session to ensure the child's compliance.
Clinician movements/training activities not clear	- The clinician and the adult confederate ensure that their movements are large and exaggerated in amplitude to be clearly visible to the child and their caregiver. - The clinician, confederate, and the child/caregiver have identical kits of training supplies. This allows children to better follow the instructional bids of the clinician/confederate using supplies/props. - Instructions are provided in a multimodal format, i.e., we show children pictures of movements to be practiced, the virtual and in-person partners provide a visual demonstration of movements, we use short verbal descriptors of movements such as "tap and clap," "hands up and down" to cue key movement components during our demonstration and during the child's practice, and the caregiver may also provide manual assistance or physical prompting as required by the child during movements/activities.

(Continued)

TABLE 1 | Continued

Challenges	Potential Solutions
Child running away during sessions	- We set clear expectations with the child about session structure at the outset of the session by using a visual schedule and by going through a rules sheet for the session. - During sessions, the child is encouraged by the clinician to clearly communicate gesturally/verbally/using pictures if they need a break. - We solicit parental input on strategies to engage the child, for e.g., call-response ideas such as "macaroni & cheese… everybody freeze" (to get the child to stay on their spot), or use of phrases such as "eyes on John" (to get the child to focus on their virtual partner), or showing pictures of cartoon characters doing exercises (to motivate the child to exercise with their favorite character), etc. - The session is structured to include short 3–5 min activity bursts followed by opportunities for scheduled 30 sec to 1 min breaks if required by the child. - We work with the family to identify the child's familiar/preferred reinforcement system and adopt it during our sessions, for example, token economy, stickers, quick iPAD break, etc.
Child inattention toward laptop screen	- Caregiver is asked to provide a visual model of ideal interactions with virtual partners. - The clinician and confederate use loud voices and clear, brief instructions to solicit and sustain child's attention. - During whole-body activities, there are built-in times between activities when caregivers and the child are asked to sit down in front of screen to observe the movement demo provided by the clinician/confederate, or to engage in conversations/social exchanges, or to see pictures of activities that will be practiced next, or power point slides of their favorite cartoon characters encouraging them to practice training activities. - The clinician/confederate regularly (typically after every activity) initiate gestural reinforcement bids such as virtual high-fives, fist bumps, etc. where children are typically asked to come to the screen and give high-fives to their virtual partners. - We also use call-response strategies to solicit child's attention: e.g., "Hocus-focus… time to focus," etc. - We use playful games with clear functional goals (improve accuracy, timing, speed, etc. of movement performance) to challenge the child.
Inadequate practice of training activities	- Caregivers are provided a list of online resources (short YouTube videos) and parent training activities every week that are tailored to their child's interests to facilitate practice of similar activities beyond the training sessions. - Caregivers are also sent email or text reminders to practice activities with their child each week. These activities are also documented in a weekly training diary that is filled out by researchers in collaboration with caregivers at the end of the training sessions.

levels of support or for younger children, telehealth automatically heavily engages the caregiver to build and facilitate the clinician-child relationship. Although the clinician and adult confederate continue their instructional and motivational roles, the caregiver primarily assumes the following responsibilities: serving as the child's in-person, social, behavioral, and motor role- model and providing reinforcement, prompting, and manual assistance as needed during activities. Based on caregiver insights of their child's strengths and difficulties, clinicians and caregivers can collectively develop meaningful intervention goals for the child, design activities that provide the optimal, "just-right" challenge, tailor activities to suit child preferences, and plan treatment progression based on ongoing child response monitoring. A clinician-caregiver co-treatment approach allows a truly family-centric training program (a continuation of the early intervention model) with ongoing feedback from caregivers and also empowers caregivers for an easier translation of training principles and strategies into the child's daily routines.

From the caregiver perspective, anecdotal data from our study collected through structured exit interviews with caregivers at the end of the study suggest that they appreciate the opportunity to engage in enjoyable, collaborative movement games with their child within a small social group context. Such activities naturally afford abundant opportunities to promote joint attention, sharing of supplies, spontaneous and responsive social bids, turn taking, imitation, and social-motor attunement/synchrony in their child. The mutual clinician-caregiver relationship allows collective planning of training goals, activities, and strategies and also allows caregivers to learn effective strategies from clinicians and observe their child's progress over time. Moreover, involvement of siblings during training promotes family bonding and generalization of learned skills to broader family interactions. With pandemic-induced heightened stress levels, caregivers frequently confide in clinicians during and even beyond the training period regarding challenges faced in caring for their child. They report this to be a beneficial social connection as they cope with their ongoing struggles during these stressful times.

From a child's perspective, interacting remotely may be less intimidating than in-person interactions for some children (8). For others, particularly younger children, virtual interactions might in fact be difficult to engage in, especially given the requirements of focusing on the small laptop screen, the physical and social disconnect compounded by internet connectivity issues, and the need to follow remotely-delivered instructions. However, over the past year, many children have become used to online schooling and virtual interactions with remote instructors. In our experience, for a subgroup of children with more severe impairments and inattention, telehealth may not be an ideal model to promote target skills and may increase parental stress levels. For younger children, we find that use of principles from naturalistic developmental behavioral interventions (34) including tying training activities to children's interests (e.g., cartoon characters, favorite movies, etc.), incorporating multiple, competitive goal-oriented games, and caregiver modeling helps to engage children during training. Overall, virtual therapies are ideally suited for children requiring low-to-moderate support who are able to attend at least briefly to virtual partners during training sessions.

DISCUSSION: CHALLENGES, RECOMMENDATIONS, AND FUTURE DIRECTIONS

Although our initial results pertaining to implementation feasibility, fidelity, and familial acceptance of a telehealth-based intervention are promising, there are several challenges with this approach (see **Table 1**). For instance, the virtual mode has specific hardware, software, and connectivity requirements that some families and healthcare providers find challenging. There are also some inherent limitations with videoconferencing software: audio interruptions when multiple people speak/sing simultaneously, difficulties with transmission of audio clips/sounds across platforms, and drowning out of non-human audio sounds (e.g., musical instrument sounds). The training also requires significant parental buy-in in terms of patience and additional setup time for problem-solving the technology and the software settings as well as time and effort dedicated toward being part of the intervention. Moreover, for younger children, the success of the intervention hinges on parental involvement to provide demonstrations and prompting/assistance during training and further use learned interaction strategies/training activities with their child during and outside the training context. For children of any age requiring more support, the tele-therapy model may in fact lead to growing child frustration and parental stress (12, 13).

Presently, a glimmer of light exists at the end of the COVID tunnel. Widespread vaccinations over the next several months may help us slowly transition back to a socially-close world resembling the pre-pandemic state. As we return to conventional F2F research, our learnings over the past year clearly suggest that telehealth-based research can serve as a valuable complement to F2F research even beyond the pandemic. Telehealth-based settings afford greater involvement of the child's family during training, provide opportunities to use household training supplies, and allow practice of activities within naturalistic settings, making the training truly ecologically valid. These factors, coupled with the economic and geographic access-related advantages of virtual interventions, may lead to some families preferring to engage in virtual research exclusively (25, 35). Therefore, it would be prudent for researchers to provide families with the flexibility to choose between F2F interventions with adequate precautions and virtual training sessions (15, 17, 36). Although this adds variability to collected data, meticulous documentation of intervention format-related variables (F2F vs. virtual, clinicians alone or clinicians + caregivers) can allow researchers to systematically assess the effects of these variables on treatment effects (35). Moreover, researchers should consider tailoring the level of parental involvement based on the child's abilities; for instance, verbal children with ASD may be able to independently participate in virtual sessions, whereas low-verbal and younger children may require greater parental support (12). Although there is preliminary evidence in support of the equivalence of F2F and telehealth-based training approaches in ASD (24, 37), more rigorous research is needed on this topic. Overall, our experiences suggest that a collaborative clinician-caregiver co-mediated, telehealth-based intervention is a feasible, ecologically valid, and acceptable modality to promote social communication, behavioral, and motor skills in children with ASD.

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SS was involved in the conception and writing of the first draft of the manuscript. All authors were involved in proof-reading and editing of the manuscript.

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Cognitive, Language, and Behavioral Outcomes in Children With Autism Spectrum Disorders Exposed to Early Comprehensive Treatment Models: A Meta-Analysis and Meta-Regression

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Background: Early comprehensive treatment models (CTMs) have been developed as effective treatments for children with autism spectrum disorder (ASD). Numerous studies have suggested that CTMs can improve short-term outcomes, but little is known about precise outcome information in childhood. The current meta-analysis reviewed studies reporting broader outcomes in children with ASD who had ever participated in a CTM and examined the predictors of developmental gains.

Methods: We searched eight databases up to June 13, 2019, for relevant trials and natural experiments. Longitudinal studies were selected if they investigated the outcomes of CTMs. Two meta-analyses were undertaken to provide a summary estimate of change in treatment outcomes and to evaluate the effect of CTMs; one used the standardized mean change between the pretest and posttest, and the other was a classical meta-analysis. Stratified and random-effects meta-regression analyses were performed to search for outcome differences among studies.

Results: Eighteen intervention studies (involving 495 children with ASD) met all the inclusion criteria: 12 used early intensive behavioral intervention (EIBI), and two used the Early Start Denver Model (ESDM). Outcomes were categorized into three parts: cognitive, language and behavioral (e.g., adaptive functioning and symptomatology). Overall, most children with ASD who had ever participated in an early CTM made gains in many areas of functioning, especially in terms of symptom- and language-related outcomes. Stratified analyses indicated that the ESDM displayed the largest effect on IQ improvement (ES = 1.37, 95% CI: 0.95 to 1.80), while EIBI was more effective for symptom reduction (ES = −1.27, 95% CI: −1.96 to −0.58). Further, meta-regression suggested that interventions with parent involvement, higher intensity, and longer treatment hours yielded greater improvements in IQ and social adaptive functioning, respectively.

Conclusion: The results demonstrate a positive association between CTMs and better prognosis in childhood, especially regarding symptoms, and language. However, most extant research involves small, non-randomized studies, preventing definitive conclusions from being drawn. Clearly, the outcomes of children with ASD are still far from normal, especially with respect to adaptive functioning, and the four mediating variables pertaining to treatment elements can affect their gains, including approach, implementer, intensity, and total treatment hours.

Systematic Review Registration: [www.crd.york.ac.uk/PROSPERO], identifier [CRD42019146859].

Keywords: autism spectrum disorders, comprehensive treatment models, EIBI, ESDM, outcomes, childhood, meta-analysis

BACKGROUND

Autism spectrum disorder (ASD) is a common neurodevelopmental disorder characterized by persistent impairment in social communication and repetitive, restricted patterns of behaviors and interests (1–3); it affects 1–2% of children (4, 5) and usually has a serious influence on development and lifetime costs (6). Behavioral treatments are considered as the recommended therapies to treat symptoms of ASD (7). As therapy progresses, it has moved from isolated teaching episodes toward teaching in the natural environment. Besides, a growing number of interventions are informed by child development theories (8).

Many behavioral interventions, particularly for young children with ASD, have shown positive effects on cognition, language functioning, and core symptoms (9, 10); in most cases, only immediate outcomes at the end of the intervention or during the first 5 years of life were reported (11, 12). However, even significant improvements in short-term outcomes do not fully establish treatment effectiveness because developmental gains could diminish after intensive services end (13). Two narrative reviews that sought to clarify the long-term effects were limited due to the small number and poor quality of eligible follow-up studies (14, 15). Robust studies on novel comprehensive treatment models (CTMs), such as Learning Experiences - An Alternative Program for Preschoolers and Parents (LEAP), are regarded as the key to long-term efficacy (7). Thus, more subsequent trials in this field should be replicated and validated in different countries in the future.

It is likely that the increase in functional skills (i.e., intelligence) that allows children to gain more from later experiences is a long-term mediating mechanism allowing them to maintain gains (16), highlighting the importance of outcomes in each postintervention period. Most existing systematic reviews focused on the effect of early autism interventions and involved mainly the outcomes in preschool children (17, 18). However, there is limited understanding of outcomes post-middle childhood (i.e., 5 years and later) (19). Moreover, the existing findings regarding mid-childhood cognitive ability and adaptive functioning outcomes in children with ASD have shown considerable variability. For example, Magiati et al. (20) reported negative outcomes on children aged 10 years, but Este et al. (13) reported the opposite results in children aged 6 years. In addition, a comprehensive collaboration among the families, the intervention team, and the receiving teachers as well schools is frequently lacking during the young children's transition to school. A recent meta-analysis indicated that almost half of individuals with ASD had poor outcomes in later adolescence and adulthood (21). However, we still lack any secondary research evidence focused explicitly on the outcomes in 5–18-year-old children. Increasing our understanding of outcomes in childhood is helpful to enact effective school curriculum and targeted support.

In addition to understanding the outcomes, it is also important to identify the factors influencing developmental gains, which can help to explain the heterogeneity across the studies and inform the establishment of intervention strategies. A small amount of evidence indicates that children's pretreatment levels and treatment elements may affect the efficacy of treatment (22, 23), raising questions about the predictors of developmental gains for children. Both of the more well-established CTMs for ASD, referred to as early intensive behavioral intervention (EIBI) and the Early Start Denver Model (ESDM), are rooted in principles of applied behavior analysis (ABA). However, ESDM is also a parent-involvement, relationship-based intervention that fuses approaches validated by the science of child development, and there are few comparative evaluations of different programs (11). If intervention approaches play a role, this role should not be underestimated. Thus, given that the transition to school and community is often difficult and stressful for individuals with

Abbreviations: ABA, Applied Behavior Analysis; ASD, Autism Spectrum Disorder; CI, Confidence Interval; CTM, Comprehensive Treatment Model; DLS, Daily Living Skills; DSM, The Diagnostic and Statistical Manual of Mental Disorders; EIBI, Early Intensive Behavioral Intervention; ES, Effect Sizes; ESDM, Early Start Denver Model; FIP, Focused Intervention Practices; GRADE, Working Group Grades of Evidence; IQ, Intelligence Quotient; JASPER, Joint Attention, Symbolic Play and Engagement Regulation; LEAP, Learning Experiences - An Alternative Program for Preschoolers and Parents; MeSH, Medical Subject Headings; NICE, National Institute for Health and Care Excellence; PACT, Pre-school Autism Communication Trial; RCT, Randomized Controlled Trial; SMD, Standardized Mean Difference; UCLA, University of California, Los Angeles; VABS, Vineland Adaptive Behavioral Scales.

ASD and their families, there is a pressing need for systematic knowledge of the outcomes in childhood and their predictive factors in children with ASD who have been exposed to a CTM to provide timely support (24).

Above all, the present study aims to extend previous reviews by conducting a meta-analysis and meta-regression of longitudinal studies from early childhood to adolescence. The study aimed to (1) report outcomes for specific domains of functioning and behavior (including cognition, language, adaptive functioning and symptomatology); (2) discover whether there are significant improvements in those outcomes for children with ASD and the effect of the CTMs; and (3) examine the influence of childhood pretreatment characteristics, study characteristics, and intervention elements on gains.

METHODS

The protocol for this meta-analysis was registered in the PROSPERO database of prospectively registered systematic reviews (www.crd.york.ac.uk/PROSPERO; CRD42019146859), and the completed study conforms to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (25).

Search Strategy and Selection Criteria

A systematic literature search was performed in eight electronic databases: PubMed, EMBASE, PsycINFO, Scopus, the Cochrane Library, OVID, ERIC, and Web of Science. Each database was initially searched for relevant literature in English from its inception through June 13, 2019. We developed a search strategy for PubMed based on MeSH (Medical Subject Headings) terms and text words from key research that we identified a priori (see **Supplementary Table 1** for the full search strings). We reviewed the reference lists of key publications and relevant narrative reviews to identify studies that might have been missed in the database searches. To check for possible publication bias, we also undertook a gray literature search in clinical trial registries (http://www.ClinicalTrials.gov) using identical inclusion criteria to identify unpublished trials.

After the removal of duplicates, two independent investigators performed title scans and abstract reviews, and they screened the full-text articles to assess their eligibility for inclusion. Concordance among the investigators was satisfactory, with a positive agreement of 0.83; any disagreements between the authors were resolved by consultation with the third investigator. A number of prespecified inclusion and exclusion criteria were used to select key studies. The inclusion criteria were as follows: (a) randomized controlled trials (RCTs), quasi-experimental studies (i.e., non-equivalent control group design, one-group pretest/posttest design), and natural experiments (a form of observational study in which the researcher cannot control or withhold the allocation of an intervention to particular areas or communities; thus, natural or predetermined variation in allocation occurs); (b) longitudinal studies with at least one assessment in early childhood and one in mid-childhood or adolescence; (c) mean age of participants at first assessment ("early childhood") <5 years; (d) mean age of participants at last assessment ("mid-childhood or adolescence") between 5 and 18 years; (e) professional/clinical diagnosis of ASD, autism, PDD-NOS, or Asperger syndrome based on DSM criteria; (f) English-language articles published in a peer-reviewed journal (dissertations were excluded); and (g) articles assessing the effectiveness of a CTM and reporting primary outcome variables focused on child functioning.

The following exclusion criteria were applied: (a) studies including children with medical complications or who were receiving drug treatment; (b) pharmacological or dietary interventions, focused intervention practices [FIP, e.g., Pre-school Autism Communication Trial (PACT), Joint Attention, Symbolic Play and Engagement Regulation (JASPER)], and other interventions with unclear evidence according to National Institute for Health and Care Excellence (NICE) guidance, such as secretin, chelation, or hyperbaric oxygen therapy; (c) studies reporting on a CTM that was not present in at least two other studies, that is, "isolated intervention approaches"; and (d) studies for which pre- and posttest means and standard deviations were not available after attempts to contact the authors and could not be calculated from the descriptive data or statistical tests in the study manuscript. For multiple studies on the same cohort, we selected the publication with the longest follow-up, provided it included results with detailed demographic and intervention information.

Data Extraction and Quality Assessment of the Included Studies

Pairs of investigators independently performed data extraction with a predesigned standardized form, and discrepancies were resolved by repeated discussion until consensus was reached. To ensure the accuracy and completeness of the extracted information, the third investigator repeatedly verified the extracted data abstraction for all the included studies. The following information from each included study was extracted: first author; region, study design, and year of publication; population characteristics at intake, including subtype of sample, age, and sex (% male); intervention characteristics, including intervention approaches (e.g., EIBI, ESDM), setting (clinical/home), implementer (therapists/therapists and parents), intensity and duration in weeks and months; type of comparison (e.g., treatment as usual, implementer, intensity, and no comparison group); assessment times (i.e., pre, post, follow-up); the measures employed in each study; and the outcomes reported in childhood (e.g., autism symptomatology, IQ, adaptive behavior, language).

Two independent investigators applied the Evaluative Method for Determining Evidence-Based Practices in Autism to assess the quality of the included studies (26), which is available for many study designs. A previous study suggested that this tool can be applied to evaluate intervention studies and produce valid assessments of the empirical evidence on practices in children with ASD (27). Six primary and eight secondary quality indicators were applied and are annotated in **Supplementary Table 3**, including the characteristics of the participants, independent variables, dependent variables, comparison conditions, random assignment, blinding of raters, and fidelity. Divergence between the two investigators who evaluated the quality of the studies was resolved by discussion. The quality of a study was assessed as "strong" when all the primary indicators received high quality ratings and there were four or more secondary indicators; "adequate" when more than four primary indicators received high ratings, with no unacceptable ratings and evidence of at least two secondary indicators; and "weak" otherwise.

Calculation of Effect Sizes

Because the instruments for evaluating a given outcome differed across studies (e.g., Wechsler Intelligence Scale for Children vs. Merrill-Palmer Scales of Mental Tests), we used standardized ESs to obtain standardized measurements of the effect of the intervention on the outcome variables. According to the methodology of Reichow and Wolery (28), two types of ES were computed: the standardized mean change ES (g_c) and the standardized mean difference (SMD) ES (g_d). We took two steps to ensure the most conservative ES. First, ESs were calculated only when the data necessary for the calculation were available. If an outcome variable was missing the necessary data for the calculation of an ES, no ES was calculated for that outcome of the study. Hence, no data were extrapolated or interpolated for the calculation of ESs. Second, ESs based on small samples are known to be biased (29), so we multiplied them by the small sample correction factor (30).

The first ES analyses were calculated for the intervention groups in all the included studies and examined the differences between the average gains made by distinct samples. This comparison revealed the absolute difference within a sample from preintervention to childhood without regard to the comparison group in between-group studies. We calculated the g_c by dividing each adjusted mean change by the pooled standard deviation.

For the between-group studies, the g_d was used to show the magnitude of the difference between the group receiving a CTM and the comparison group. The ES (g_d) was calculated by dividing each adjusted mean difference by the pooled standard deviation.

Meta-Analytic Procedures

We combined findings from all the included studies using prespecified meta-analytic methods to determine the effect of CTMs in children with ASD. Data synthesis involved two steps: (1) Meta-analysis I was performed to estimate longitudinal changes in broader outcomes in children with ASD who were exposed to a CTM. (2) Meta-analysis II was performed to assess the effect of CTMs on those outcomes in the test group compared to the control group. The standardized mean change/difference and 95% confidence interval (CI) for each intervention effect were the primary outcome measures in the meta-analysis. Due to the diversity in population characteristics and intervention approaches, we expected a conservative estimation of the ESs. Consequently, a meta-analysis was performed on studies judged sufficiently similar and appropriate to pool using random effects models. Cohen's criteria (31) were applied to determine the magnitude of the effect. The magnitude of the effect was assessed as "trivial" when the ES was <0.2, "small" when the ES was between 0.2 and 0.49, "medium" when the ES was between 0.5 and 0.79, and "large" when the ES was ≥ 0.8.

Prespecified and exploratory stratified analyses were conducted to assess differences in ESs based on the use of (1) EIBI, (2) ESDM, and (3) other interventions to examine the consistency of the intervention approaches. Outcomes reported in fewer than six studies and parental outcomes were discarded from the meta-analysis, and studies were rank-ordered by quality rating in the forest plots.

The I^2 statistic was used to assess the potential heterogeneity of ESs across interventions. An $I^2 > 50\%$ was considered evidence of heterogeneity. Potential publication bias was assessed in two ways: a funnel plot and Egger's linear regression test. When publication bias was identified, a non-parametric trim-and-fill method was used to adjust for the publication bias. Sensitivity analysis was performed by reanalyzing the data using a fixed effects model and by omitting one study at a time to assess the impact of each individual study on the overall pooled estimate. Moreover, we re-ran all the Meta-analysis I models restricting the study design to the between-group controlled studies.

Meta-Regression

Although, there are certainly variations across the included studies (i.e., varying amounts of time between posttreatment and the collection of follow-up data, total treatment hours), we applied random-effects meta-regression analyses to examine the effect of moderators and mediators on primary outcomes and to explore the potential heterogeneity. A moderator (baseline variable) suggests for whom or under what conditions a treatment might affect the outcome of interest. A mediator (intervention variable) suggests how or why the treatment might work. Three categories were defined a priori in the protocol: (1) internal validity (risk of bias, sample size), (2) population characteristics (preintervention age, preintervention IQ, time interval between postintervention and follow-up, age at the last assessment), and (3) intervention characteristics (intervention approaches, total intervention hours [duration multiplied by intensity], intensity (hours/week), duration (months), implementer [therapist, therapist and parent]). To reduce the risk of type II errors, we abstained from performing regression with predictors that were available for <6 of the included trials, and univariate meta-regression was used for predictors available in 6–10 of the included trials. Only for IQ, which was reported in >10 trials, were all variables that predicted variance ($p < 0.05$) included in a multivariate regression model, and forward elimination was performed. Given the type I errors of the multivariate meta-regressions, we also applied the Monte Carlo permutation test. Besides, we performed some binary meta-regression plots to evaluate the linear relationship between intervention characteristics and the primary outcome measures.

All meta-analytic procedures were performed with STATA 12.0 (Stata Corp., College Station, TX, USA).

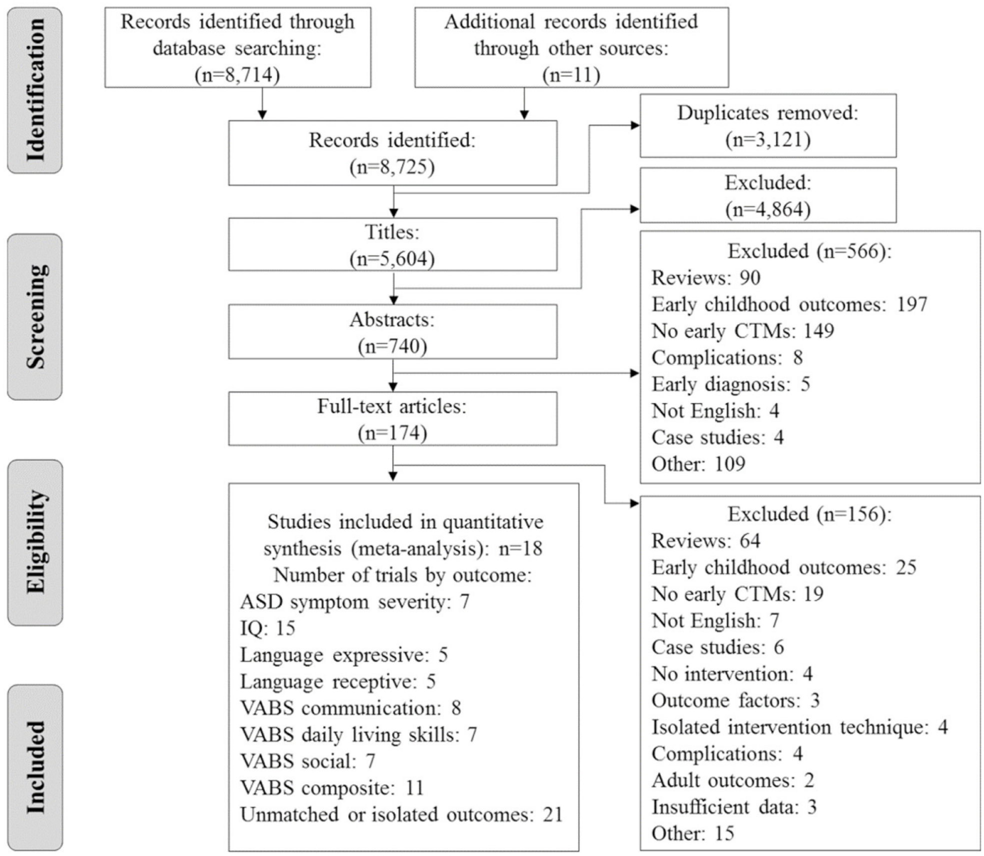

FIGURE 1 | Flowchart of the retrieval and selection of references. ASD, autism spectrum disorder; CTM, comprehensive treatment models; IQ, intelligence quotient; VABS, Vineland Adaptive Behavioral Scales.

RESULTS

Literature Search and Study Characteristics

A flow diagram detailing the selection process is presented in **Figure 1**. We identified 8,725 potentially relevant citations, and 174 full citations were retrieved. Two reports, Lovaas (32) and McEachin et al. (33), used the same participants. The latter was selected because it has the longest follow-up. Overall, 18 unique citations were deemed eligible for the systematic review and meta-analysis (13, 20, 33–48).

A systematic description of eight between-group studies and 10 prepost studies (including 495 non-overlapping participants with ASD) is provided in **Table 1**. Three of the 10 prepost studies with within-subject designs were natural experiments, and the intervention characteristics were reported by parents. Half of the included studies were postintervention follow-ups and thus had a period of time during which the intervention was not being implemented; the outcomes from these studies were defined as "long-term." These studies used a wide range of measures to assess autism symptom severity, cognitive and language abilities, and adaptive behavior (**Supplementary Table 2**). Most employed standardized measures and researcher-developed interviews, and all the repeatedly measured outcomes were standard scores. Moreover, six studies (33%) received the highest rating (strong), two (11%) received the middle rating (adequate), and 10 studies (56%) received the lowest rating (weak; **Supplementary Table 3**) based on the assessment of research report rigor.

Population and Intervention Characteristics

The mean pre-IQ, reported in 15 studies, was 50–64; the mean pretest age was 24–49 months, and the mean age at the last assessment was 66–192 months. Of the 18 studies included, 12 conducted EIBI [seven applied the UCLA model (32)], two used the ESDM, and four used other interventions. Other interventions (e.g., community intervention) include the combination of standard interventions. With regard to the intervention characteristics, eight studies were implemented by therapists and parents. The intervention duration and intensity ranged from 6 to 60 months and from 15 to 40 weekly hours, respectively. Six studies reported that participants were receiving supplemental treatments. Moreover, the comparison conditions in the eight between-group studies, which included 6 EIBI programs and 2 ESDM programs, were treatment as usual (k = 5), different implementers (k = 2), and active comparison (k = 1).

TABLE 1 | Characteristics of the studies included in the meta-analysis reporting multiple outcomes in children with ASD.

Study	Region	Design	Participants				Intervention characteristics[c]					Control group	Rigor rating[d]
			Sample[a] (*n*, male%)	Diagnosis (criteria)	Pre-test CA[b] (months)	Pre-IQ	Methods (model)	Intensity (h/week)	Duration (months)	agent	Post-test/ follow-up CA (months)		
Akshoomoff et al. (34)[#]	USA	Pre-post experimental	20 (90.00%)	AD PDD-NOS (DSM-IV)	28.90 (2.70)	—	others[e]	31.00	7.70 (2.20)	T + P	85.30 (27.80)	NO	Weak
Bibby et al. (35)	UK	Pre-post observational	22 (83.33%[‡]) 21[f]	ASD PDD	45.00 (11.20)	50.80 (20.60)	EIBI (UCLA)	30.30 (5.50)	31.60 (11.90) 33.20[f]	T	77.40 (15.00) 78.70[f]	NO	Weak
Clark et al. (36)	AUS	Pre-post observational	48 (75%)	AD ASD (DSM-IV)	25.45 (2.12)	65.68 (11.87)	others	NR	NR	T	96.50 (6.60)	NO	Weak
Cohen et al. (37)[g]	USA	Between-group NRT	21 (85.71%)	AD PDD-NOS	30.20 (5.80)	61.60 (16.40)	EIBI (UCLA)	35–40	36.00	T + P	66.24 (5.76)	YES N-R	Strong
Estes et al. (13)#	USA	Between-group RCT	21	AD PDD-NOS (DSM-IVTR)	23.90 (4.00)	61.00[h] (9.20)	ESDM	31.50	24.00	T + P	72.90 (2.60)	YES Random	Strong
Gabriels et al. (38)	USA	Pre-post[i] observational	17 (70.59%)	Autism PDD-NOS	30.60 (7.27)	57.81 (25.88)	others	22.63	36.00	T	68.70 (10.11)	NO	Weak
Harris et al. (39)	USA	Pre-post experimental	27 (85.19%)	AD (DSM-III-R)	49.00 (31-65)	59.33 (23.75)	EIBI	35–45	36.00	T + P	85.00	NO	Weak
Howard et al. (40)	USA	Between-group NRSI observational	29 (86.00%)	AD PDD-NOS (DSM-IV)	30.86 (5.16)	60.57 (17.48)	EIBI (IBT)	35–40	37.90 (2.98)	T + P	69.24 (5.01)	Yes N-R	Strong
Kovshoff et al. (47)[#]	UK	Between-group NRT	23	Autism	35.70 (4.00)	61.43 (16.43)	EIBI	25.60 (4.80)	24.00	T + P	83.70	Yes N-R	Adequate
Landa and Kalb (41)[#]	USA	Pre-post experimental	48 (81.25%)	ASD	27.20 (2.80)	60.10 (11.90)	others	10.00	6.00	T + P	72.60 (17.50)	No	Weak
McEachin et al. (33)[j#]	USA	Between-group NRT	19 (84.21%)	Autism (DSM-III)	34.60	53.00 (30–82)	EIBI (UCLA)	40.00	60.00	T + P	156.00 (108-228)	YES N-R	Strong
Magiati et al. (20)[#]	UK	Pre-post experimental	36	Autism ASD	38.90 (7.10)	64.40 (30.00)	EIBI (UCLA)	30.00	57.90 (21.20)	T	123.60 (9.60)	No	Weak
Perry et al. (48)[#]	CA	Pre-post experimental	21 (90.48%)	AD PDD-NOS (DSM-IV)	40.92 (12.60)	—	EIBI	20–40	26.76 (9.84)	T	192.20 (21.48)	No	Weak
Sallows et al. (42)	USA	Between-group RCT	13 (84.61%)	Autism (DSM-IV)	33.23 (3.89)	50.85 (10.57)	EIBI (UCLA)	38.60 (2.91)	48.00	T	83.23 (8.92)	Yes Random	Strong
Smith et al. (43)[#]	USA	Between-group RCT	15 (80.00%)	Autism PDD/NOS	36.07 (6.00)	50.53 (11.18)	EIBI (UCLA)	24.52 (3.69)	33.44 (11.00)	T	94.07 (13.17)	Yes Random	Adequate

(Continued)

TABLE 1 | Continued

Study	Region	Design	Participants				Intervention characteristics[c]					Control group	Rigor rating[d]
			Sample[a] (*n*, male%)	**Diagnosis (criteria)**	**Pre-test CA[b] (months)**	**Pre-IQ**	**Methods (model)**	**Intensity (h/week)**	**Duration (months)**	**agent**	**Post-test/ follow-up CA (months)**		
Smith et al. (44)[#]	USA	Pre-post experimental	64 (84.51%)[‡]	ASD	39.12 (7.92)	58.80 (13.39)	EIBI (UCLA)	16.66	12.00	T	67.80 (9.72)	No	Weak
Vinen et al. (45)	AUS	Between-group NRSI	31 (87.10%)	ASD (DSM-IV, DSM-V)	39.16 (9.91)	55.42[h] (8.74)	ESDM	≥15	22.44	T + P	79.97 (7.99)	Yes N-R	Strong
Weiss and Delmolino (46)	USA	Pre-post experimental	20 (95.00%)	Autism PDD/NOS (DSM-IV)	41.50 (20–65)	—	EIBI (IBT)	40.00	48.00	T	89.5	No	Weak

[a]*Total number of subjects at the last measurement for pre-post studies and subjects in the experimental group for between-group studies.*
[b]*Chronological age at which the participants entered the study or started the intervention.*
[c]*Intervention characteristics for pre-post studies and the experimental group's features for between-group studies.*
[d]*The quality assessment was examined by the Evaluative Method for Determining Evidence-Based Practices in Autism (51).*
[e]*Others (other interventions) refers to the combination of standard interventions, including discrete trial training, incidental teaching, pivotal response training, structured teaching, and the picture exchange communication system (e.g., community, inclusive intervention).*
[f]*The samples are inconsistent between the two outcomes reported by Bibby et al. (35).*
[g]*Sufficient data were acquired from the figures in Cohen et al. (37).*
[h]*The early learning composite (ELC) from MSEL was used to report cognition function.*
[i]*Gabriels et al. (38) was a retrospective case-control study conducted on one sample receiving the same treatment and examined the influencing factors of the best outcomes.*
[j]*Two reports, Lovaas (32) and McEachin et al. (33), used the same participants. The McEachin et al. (33) report was used because it has the longest follow-up.*
[‡]*Male% was not reported in follow-up subjects. We used male% at intake to replace it.*
[#]*Those included studies were postintervention follow-ups and thus had a period of time during which the intervention was not being implemented.*
ABA, applied behavior analysis; AD, autism disorder; ASD, autism spectrum disorder; AUS, Australia; CA, chronological age; CA, Canada; DSM, The Diagnostic and Statistical Manual of Mental Disorders; EIBI, early intensive behavioral intervention; ESDM, the Early Start Denver Model; IBT, intensive behavioral treatment; IQ, intelligence quotient; PDD/NOS, pervasive developmental disorder not otherwise specified; T, therapist; T + P, therapist and parents; N-R, non-random; NR, not reported; NRT, non-randomized trial; NRSI, non-randomized study for intervention; RCT, randomized controlled trial; UCLA, University of California, Los Angeles.

TABLE 2 | Summary of cognitive, language, symptomatic, and adaptive functioning outcomes in childhood.

Study	IQ[d]		Expressive language[e]		ASD Symptom Severity[f]		Adaptation composite[g]	
	Preintervention	Middle childhood	Preintervention	Middle childhood	Preintervention	Middle childhood	Preintervention	Middle childhood
Bibby	50.80 ± 20.60	55.00 ± 22.30					54.50 ± 13.00	63.40 ± 21.90
Clark[a]	65.68 ± 11.87	102.71 ± 19.55			6.45 ± 2.08	6.20 ± 2.68		
Cohen[b]	61.60 ± 16.40	87.00 ± 25.26	52.90 ± 14.50	78.00 ± 29.91			69.80 ± 8.10	79.00 ± 19.77
Estes[c]	61.00 ± 9.20	90.52 ± 26.36					69.50 ± 5.70	81.41 ± 17.27
Gabriels	57.81 ± 25.88	62.94 ± 30.79						
Harris	59.33 ± 23.75	77.59 ± 28.10						
Howard	60.57 ± 17.48	89.43 ± 23.99	49.73 ± 16.34	83.25 ± 29.88			72.00 ± 7.73	76.00 ± 15.94
Kovshoff	61.43 ± 16.43	64.65 ± 33.04					60.22 ± 5.82	55.13 ± 19.40
Landa	60.10 ± 11.90	81.50 ± 24.40			7.30 ± 2.20	7.40 ± 2.00		
McEachin[c]	53.00 ± 13.00	84.50 ± 32.40						
Magiati	64.40 ± 30.00	52.60 ± 21.80	2.60 ± 7.30	34.50 ± 37.90	36.70 ± 7.20	32.40 ± 10.00	58.70 ± 5.90	37.20 ± 17.90
Perry					34.16 ± 5.49	26.63 ± 6.40	63.45 ± 8.95	66.85 ± 17.18
Sallows	50.85 ± 10.57	73.08 ± 33.08	47.92 ± 6.17	53.38 ± 31.91			59.54 ± 5.31	69.00 ± 28.04
Smith 2000	50.53 ± 11.18	66.49 ± 24.08	15.13 ± 0.52	44.53 ± 23.48			63.44 ± 9.35	61.19 ± 29.72
Smith 2015	58.80 ± 13.39	64.93 ± 18.01			8.51 ± 1.76	6.45 ± 2.15	62.68 ± 9.02	59.89 ± 14.65
Vinen	55.42 ± 8.74	76.06 ± 20.82			7.39 ± 2.09	7.97 ± 2.60		
Weiss					45.68 ± 5.30	26.58 ± 8.60	49.85 ± 7.84	76.05 ± 36.01

[a] *Data were acquired from the merging of subgroups in Clark et al. (36).*
[b] *Data were acquired from the figures in Cohen et al. (37).*
[c] *The standard deviation is calculated from the range of the outcomes in Estes et al. (13) and McEachin et al. (33).*
[d] *IQ was measured by a series of instruments, including WISC, BSID, WPPSI, and so on.*
[e] *Language was measured by Reynell, SICD-R, EOWPVT, and BPVS-2.*
[f] *ASD symptom severity was measured by ADOS, ADI-R, and CARS.*
[g] *Adaptation composite was measured by VABS.*
*Akshoomoff et al. (34) reported the subdomains of adaptive functioning and non-verbal/verbal IQ, which are not represented in **Table 2**. ASD, autism spectrum disorder; IQ, intelligence quotient.*

Outcomes and Meta-Analysis I: Longitudinal Change in Childhood

Although, a number of studies evaluated outcomes across multiple domains, others focused on specific areas, such as intellectual abilities, adaptive functioning, language outcomes, or autism severity. A summary of reported outcomes is presented in **Table 2**; generally, positive ESs (g_c) suggest that children's performance improved on average after the preintervention stage in multiple dimensions of functioning (see **Figures 2**, **3**).

The pooled standardized mean change ES for IQ, covering 420 participants, was 0.85 (95% CI: 0.47 to 1.22). Only one study (20) had a negative ES for IQ, while 10 of the other samples yielded an ES for IQ equal to or >0.50. Five EIBI studies reported data on language skills, four of which reported favorable effects on both expressive and receptive language. The pooled ESs for expressive language and receptive language were 1.12 (95% CI: 0.70 to 1.53) and 1.11 (95% CI: 0.83 to 1.40), respectively. Regarding the longitudinal changes in ASD symptom severity, seven studies reported relevant data, and three of them showed a favorable effect. The pooled ES was −0.68 (95% CI: −1.24 to −0.12). For adaptive functioning, the subdomains showed heterogeneity (**Figure 3**). A medium ES was found for both communication (ES = 0.75, 95% CI: 0.47 to 1.02) and social (ES = 0.55; 95% CI: 0.17 to 0.92), whereas, a trivial ES was found for daily living skills (DLS) (ES = −0.05, 95% CI: −0.49 to 0.39) and composite score (ES = 0.15, 95% CI: −0.28 to 0.57).

Meta-Analysis II: Effects of EIBI on Outcomes in Childhood Compared to Those in the Control Group

As presented in **Figure 4**, the majority of the SMD ESs (g_d) were positive, which indicates that the functioning of children with ASD in the EIBI group was generally better than that in the comparison group in multiple dimensions. In line with the longitudinal change results, EIBI had small to medium effects in terms of improving IQ (ES = 0.53, 95% CI: 0.16 to 0.90), communication (ES = 0.38, 95% CI: 0.03 to 0.73), and social (ES = 0.38, 95% CI: 0.03 to 0.73). The ES for DLS was also non-significant in four studies (ES = 0.18; 95% CI: −0.16 to 0.53). However, we failed to find a favorable improvement in expressive and receptive language when the analysis was applied solely to controlled studies (ES = 0.46, 0.42; 95% CI: −0.08 to 1.0, −0.06 to 0.91, respectively). Additionally, adaptation composite scores were reported in five studies, resulting in a significant effect size of 0.47 (95% CI 0.11 to 0.83).

The controlled ESDM studies and the outcome for ASD symptom severity were discarded from meta-analysis II because of inadequate or isolated data.

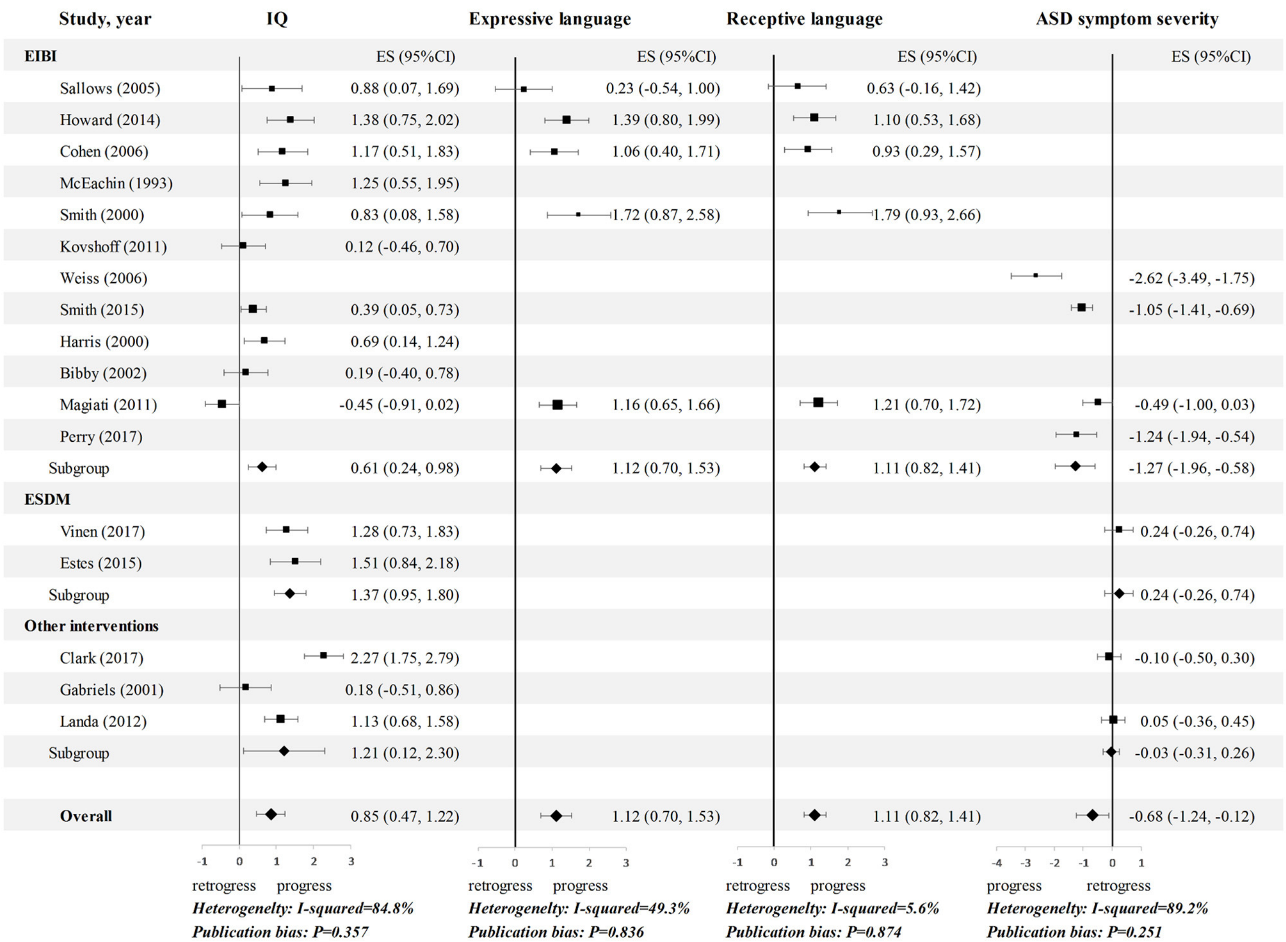

FIGURE 2 | Meta-analysis 1: Effect sizes (gc) for IQ, language and symptom outcomes in children with ASD. Hedges' g effect sizes represented in black and confidence intervals are reported. Random effects models were used on all outcomes, and the studies were rank-ordered by quality rating. ASD, autism spectrum disorder; CI, confidence interval; EIBI, early intensive behavioral intervention; ES, effect sizes; ESDM, Early Start Denver Model; IQ, intelligence quotient.

Stratified Analyses

The results for the comparison of the three intervention approaches in the stratified analyses of meta-analysis I revealed disparate effects. Notably, the ESDM group had a significantly higher ES for IQ than the EIBI and other interventions groups (g_c = 1.37, 0.61, and 1.21, respectively; **Figure 2**). Regarding other outcomes, the number of ESDM studies is insufficient for comparison. Nevertheless, the opposite occurred for symptom outcomes (ASD symptom severity and social adaptive functioning), as the EIBI group had clearly greater symptom improvement than the other interventions group ($g_c = -1.27$, 0.65 vs. $g_c = -0.03$, 0.19). Additionally, stratified analyses could not be conducted in meta-analysis II because of the limitations of the controlled studies.

Sensitivity Analysis

Sensitivity analyses suggested that the estimates were not substantially modified by any single study. There was an exception for the adaptive composite score, as a small effect with a g_c of 0.31 (95% CI 0.002 to 0.62) was shown when Magiati et al. (20) was removed in meta-analysis I. The sensitivity analyses did not yield different findings after the data were reanalyzed either using a fixed effects model or restricting to the between-group studies (see **Supplementary Figures 1, 2** for the latter).

Publication Bias

No sign of publication bias was found in the funnel plots and Egger's test for any outcome.

Meta-Regression

Across 11 predictors in univariate meta-regressions (**Table 3**), five mediators of longitudinal change in childhood outcomes emerged: (1) EIBI was more effective in reducing symptom severity than non-EIBI programs, and this explained 64% of the heterogeneity (Coefficient = −1.31, P = 0.045). (2) Higher total and social adaptive functioning were associated with longer total hours of the intervention explained 78 and 100% of the heterogeneity (Coefficient = 0.0001, P = 0.021; Coefficient = 0.0002, P = 0.032, respectively). Consistent

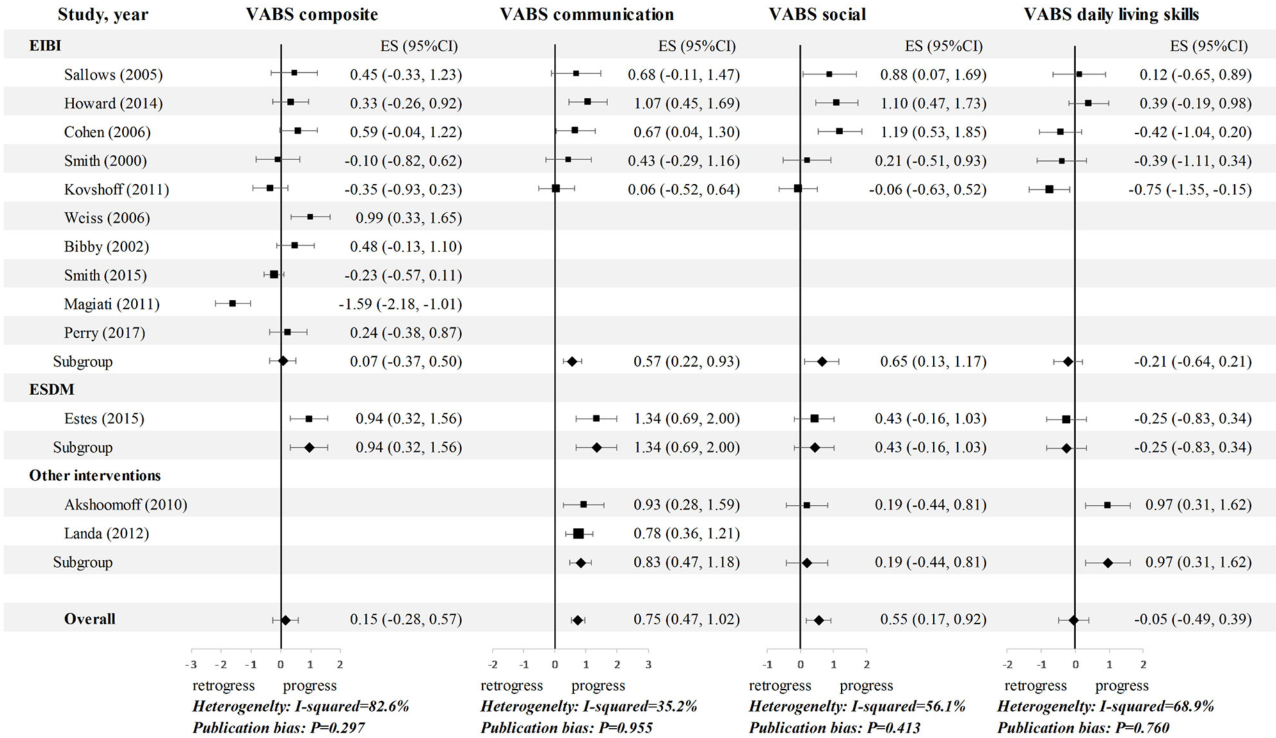

FIGURE 3 | Meta-analysis 1: Effect sizes (gc) for adaptive functioning in children with ASD. Hedges' g effect sizes represented in black and confidence intervals are reported. Random effects models were used on all outcomes, and the studies were rank-ordered by quality rating. CI, confidence interval; EIBI, early intensive behavioral intervention; ES, effect sizes; ESDM, Early Start Denver Model; VABS, Vineland Adaptive Behavioral Scales.

results were found in the intensity of intervention, which both explained 100% of the heterogeneity (Coefficient = 0.047, $P = 0.004$; Coefficient = 0.087, $P = 0.026$, respectively). (3) Higher social adaptive functioning was also associated with a higher risk of bias (Adj $R^2 = 100.00\%$, Coefficient = 0.78, $P = 0.026$), and a shorter time interval between postintervention and follow-up (Adj $R^2 = 95.50\%$, Coefficient = −0.022, $P = 0.033$). In addition, the above results were verified by the regression plots, which displayed many significant linear correlations (see **Figures 5**, **6**). No other confounding factors affected the change in the four outcome measures, and its regression plots were shown in **Supplementary Figures 3–6** in the supplementary file.

The multivariate meta-regressions demonstrated a clear effect of implementer (therapist or therapist and parents) on IQ after the *p*-value was adjusted ($P = 0.028$, **Table 4**). Specifically, the involvement of parents in implementing intervention strategies had a more beneficial effect on IQ enhancement than the involvement of a therapist alone.

DISCUSSION

To the best of our knowledge, this is the first comprehensive study to systematically and quantitatively assess a series of developmental and symptom outcomes for children with ASD. Overall, we found positive effects of early CTMs on longitudinal changes in intelligence, language development, communication and social adaptation, and core symptom severity in children with ASD but negligible effects on DLS and total adaptive behavior. In addition, there is preliminary evidence to suggest that children in the EIBI group have made greater gains than children in the control group with respect to intelligence, communication, and social adaptation. It is noteworthy that the outcomes and the risk of bias in most of the included studies are not optimistic. Nevertheless, we demonstrated that the treatment characteristics played a major role in the later outcomes for children younger than 5 years of age, which may also apply to some novel interventions.

The findings from this study are similar to those of a narrative review that examined the long-term effects of early intervention (EI) in primary school (15). The review included eight eligible studies, five of which were also included in our study. Both this review and the narrative review indicate that most children with ASD who have ever participated in a CTM make gains in many areas of functioning. However, only nine long-term follow-up studies were found based on our inclusion and exclusion criteria. In other words, the number of well-designed longitudinal studies is still insufficient to determine the long-term effects; therefore,

Study, year	Weight (%)	SMD (95%CI)
IQ		
Sallows (2005)*	13.53	-0.22 (-1.05,0.61)
Howard (2014)	16.12	1.00 (0.28,1.72)
Cohen (2006)	19.14	0.59 (-0.03,1.21)
McEachin (1993)[I]	17.17	0.94 (0.26,1.62)
Smith (2000)*	14.82	0.74 (-0.04,1.51)
Kovshoff (2011)	19.22	0.08 (-0.53,0.70)
Overall	100.00	0.53 (0.16,0.90)
Heterogeneity: *I*-squared=41.3%, Publication bias: *P*=0.901		
Expressive language		
Sallows (2005)*	21.87	-0.19 (-1.02,0.63)
Howard (2014)	25.85	1.19 (0.50,1.89)
Cohen (2006)	28.22	0.39 (-0.23,1.01)
Smith (2000)*	24.06	0.36 (-0.39,1.11)
Overall	100.00	0.46 (-0.08,1.00)
Heterogeneity: *I*-squared=56.1%, Publication bias: *P*=0.543		
Receptive language		
Sallows (2005)*	20.95	-0.30 (-1.13,0.53)
Howard (2014)	26.35	0.98 (0.30,1.66)
Cohen (2006)	29.24	0.40 (-0.22,1.01)
Smith (2000)*	23.46	0.48 (-0.28,1.23)
Overall	100.00	0.42 (-0.06,0.91)
Heterogeneity: *I*-squared=45.5%, Publication bias: *P*=0.451		
VABS composite		
Sallows (2005)*	15.50	0.10 (-0.73,0.92)
Howard (2014)	18.51	1.10 (0.36,1.84)
Cohen (2006)	23.75	0.68 (0.06,1.31)
Smith (2000)*	18.29	0.11 (-0.64,0.85)
Kovshoff (2011)	23.95	0.30 (-0.32,0.92)
Overall	100.00	0.47 (0.11,0.83)
Heterogeneity: *I*-squared=24.2%, Publication bias: *P*=0.739		
VABS communication		
Sallows (2005)*	15.22	-0.25 (-1.08,0.57)
Howard (2014)	19.21	0.78 (0.06,1.50)
Cohen (2006)	23.28	0.74 (0.10,1.37)
Smith (2000)*	18.06	0.28 (-0.47,1.02)
Kovshoff (2011)	24.23	0.19 (-0.42,0.81)
Overall	100.00	0.38 (0.03,0.73)
Heterogeneity: *I*-squared=21.0%, Publication bias: *P*=0.412		
VABS social		
Sallows (2005)*	15.14	0.26 (-0.57,1.08)
Howard (2014)	18.46	0.98 (0.24,1.71)
Cohen (2006)	24.15	0.57 (-0.05,1.19)
Smith (2000)*	18.11	-0.12 (-0.86,0.63)
Kovshoff (2011)	24.14	0.19 (-0.42,0.81)
Overall	100.00	0.38 (0.03,0.73)
Heterogeneity: *I*-squared=20.8%, Publication bias: *P*=0.891		
VABS daily living skills		
Sallows (2005)*	17.29	0.09 (-0.73,0.92)
Cohen (2006)	31.30	0.13 (-0.49,0.74)
Smith (2000)*	21.32	-0.03 (-0.77,0.71)
Kovshoff (2011)	30.09	0.45 (-0.18,1.07)
Overall	100.00	0.18 (-0.16,0.53)
Heterogeneity: *I*-squared=0.0%, Publication bias: *P*=0.446		

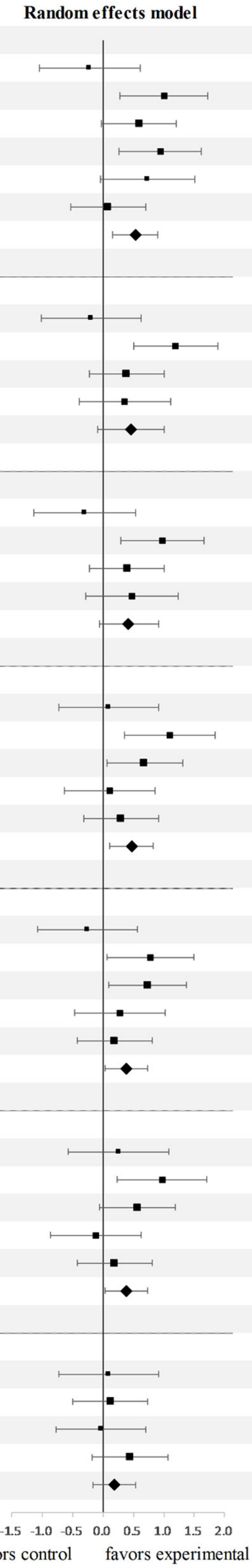

FIGURE 4 | Meta-analysis 2: SMD (gd) for multiple outcomes of EIBI in children with ASD. comparison type * EIBI therapist vs. EIBI parents; I EIBI vs. EIBI minimal intensity. CI, confidence interval; ES, effect sizes; IQ, intelligence quotient; SMD, standardized mean difference.

TABLE 3 | Results of the univariate meta-regression analyses by adaptation and symptomatic variables.

	ASD SS		Composite[e]		DLS		Social	
	Coeff	***P***	**Coeff**	***P***	**Coeff**	***P***	**Coeff**	***P***
Internal Validity								
Risk of bias[a]	1.100	0.33	0.450	0.16	0.019	0.97	**0.780**	**0.03***
Sample size	0.020	0.41	−0.014	0.15	−0.037	0.63	−0.033	0.62
Population Characteristics								
Pre age	−0.080	0.17	−0.018	0.48	−0.046	0.46	−0.027	0.61
Pre IQ	−0.029	0.75	0.001	0.98	−0.014	0.74	0.011	0.83
Time interval[b]	−0.002	0.85	−0.002	0.65	0.009	0.53	**−0.022**	**0.03***
Post age[c]	−0.005	0.64	−0.001	0.89	0.0006	0.98	−0.039	0.05
Intervention Characteristics								
Approaches[d]	**−1.310**	**<0.05***	−0.704	0.18	−0.550	0.30	0.330	0.47
Total treatment hours	−0.0002	0.19	**0.0001**	**0.02***	−0.0001	0.82	**0.0002**	**0.03***
Intensity	−0.071	0.06	**0.047**	**<0.01***	0.048	0.35	**0.087**	**0.03***
Duration	−0.021	0.40	0.025	0.05	−0.014	0.50	0.026	0.10
Delivery agents	1.180	0.15	0.097	0.77	0.120	0.84	0.033	0.95

[a] *Categorical variable, strong = 1, non-strong (adequate and weak) = 0.*
[b] *Time interval between postintervention and follow-up.*
[c] *Mean age of participants at last assessment.*
[d] *Categorical variable, EIBI = 1, non-EIBI (ESDM and other interventions) = 0.*
[e] *Based on the result of sensitivity analysis, Magiati et al. (20) was removed from the meta-regression analyses.*
ASD SS, ASD symptom severity; Coeff, unstandardized meta-regression coefficient; Composite, Vineland adaptive composite score; DLS, Daily living skills; Pre, preintervention.
ASD SS: Weiss and Delmolino (46); Smith et al. (43); Magiati et al. (20); Perry et al. (48); Vinen et al. (45); Clark et al. (36); Landa and Kalb (41).
Composite: Sallow and Graupner (42); Howard et al. (40); Cohen et al. (37); Smith et al. (43); Kovshoff et al. (47); Weiss and Delmolino (46); Bibby et al. (35); Smith et al. (43); Perry et al. (48); Estes et al. (13).
DLS and Social: Sallow and Graupner (42); Howard et al. (40); Cohen et al. (37); Smith et al. (44); Kovshoff et al. (47); Estes et al. (13); Akshoomoff et al. (34).
**$p < 0.05$.*
ASD symptom severity - Approaches: Adj $R^2 = 64.19\%$. Vineland adaptive composite score - Total treatment hours: Adj $R^2 = 78.06\%$. Vineland social adaptive score - Total treatment hours: Adj $R^2 = 100.00\%$. Vineland social adaptive score - risk of bias: Adj $R^2 = 100.00\%$. The bold values represents the p value < 0.05.

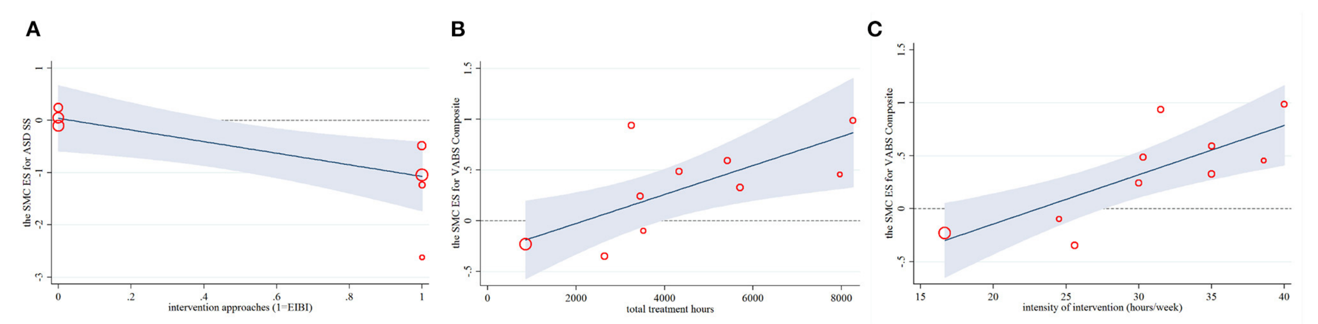

FIGURE 5 | Regression plots for the primary intervention characteristics versus the ES for ASD symptom severity **(A)** and VABS composite **(B,C)**. ASD SS, ASD symptom severity; ES, effect size; SMC, standardized mean change; VABS, Vineland Adaptive Behavioral Scales.

more emphasis should be placed on empirical studies in this field in the future.

Although, favorable effects were apparent across most outcomes, language-related outcomes (IQ, receptive language, expressive language, and communication adaptation) were distinctly superior to social adaptation and ASD symptom severity, with ESs approaching 1.2 for receptive and expressive language. This finding is highly consistent with previous findings from a meta-analysis on the effects of ABA intervention in early childhood that included studies with a minimum intervention duration of 1 year (49) and has been attributed to the amount of time devoted by most behavioral interventions to language and communication skills (50).

In addition, there is some evidence that EIBI leads to a small to moderate effect in youth with ASD compared to the effect of treatment as usual, EIBI parent-mediated or EIBI minimal treatment controls in terms of IQ and Vineland social, communication, and adaptive composite scores. This is particularly noteworthy because these ESs were smaller than

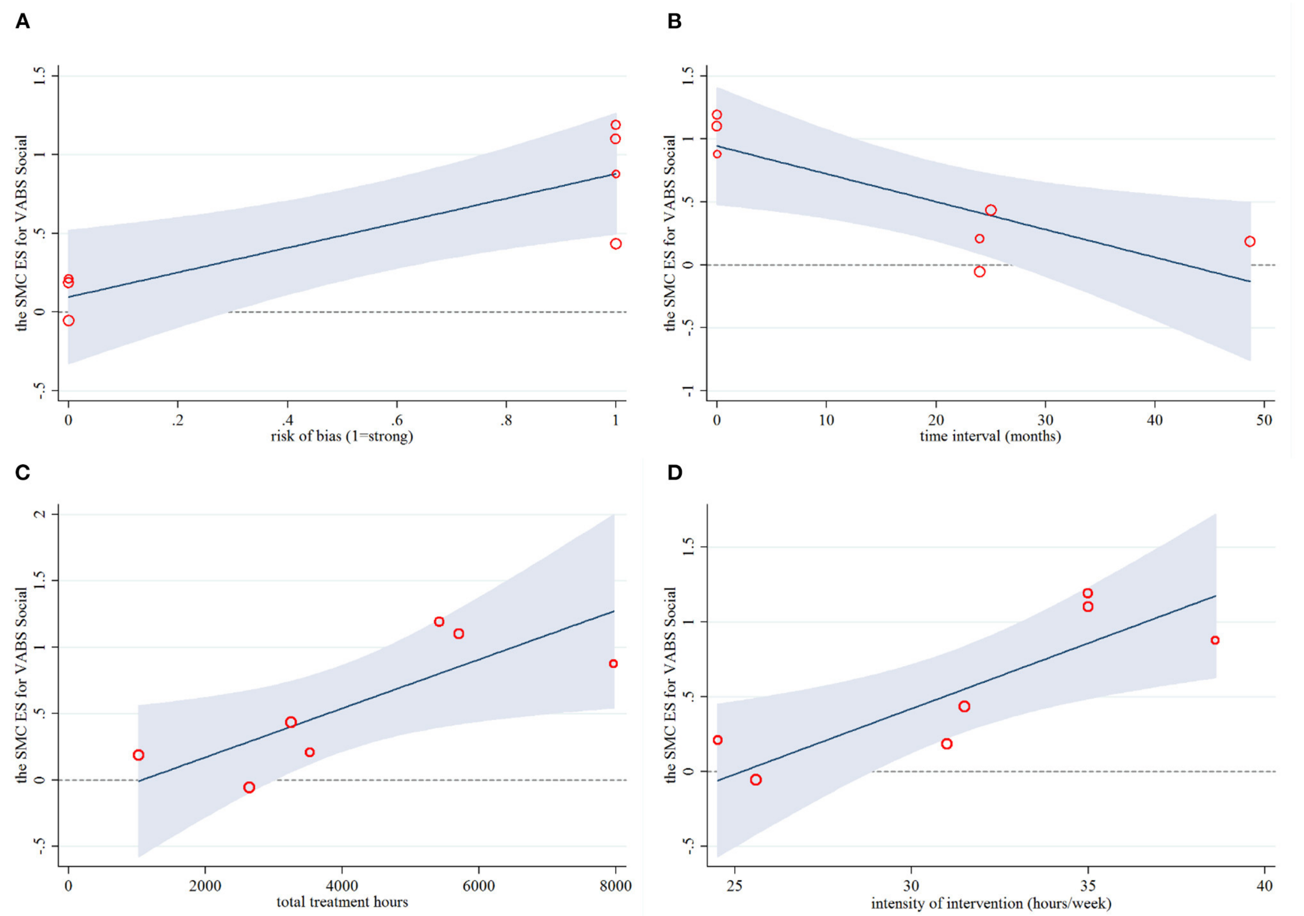

FIGURE 6 | Regression plots for the primary intervention characteristics versus the ES for VABS social. ES, effect size; SMC, standardized mean change; VABS, Vineland Adaptive Behavioral Scales.

TABLE 4 | Results of the multivariate meta-regression analyses by cognitive function.

	Coefficient	SE	95% CI	*P*	tau^2	k	Adj R^2 (%)	Model *P*	Type I errors[a]
IQ									
Delivery agents[b]	0.6756	0.2637	[0.0881, 1.2632]	**0.028***					
Pre age	−0.0289	0.0204	[−0.0742, 0.0165]	0.187	0.1294	14	52.15	**0.048***	not
Total treatment hours	0.00000184	0.000046	[−0.0001, 0.0001]	0.969					

[a]Monte Carlo permutation test was applied to correct type I errors for multiple covariate meta-regressions.
[b]Categorical variable: therapist = 1, therapist + parents = 2.
CI, confidence interval; Coefficient, unstandardized meta-regression coefficient; CTM, comprehensive treatment model; IQ, intelligence quotient; k, number of studies or "clusters"; Pre, preintervention; SE, standard error.
IQ: Sallow and Graupner (42); Howard et al. (40); Cohen et al. (37); McEachin et al. (33); Smith et al. (43); Kovshoff et al. (47); Smith et al. (44); Harris and Handleman (39); Bibby et al. (35); Magiati et al. (20); Estes et al. (13); Vinen et al. (45); Clark et al. (36); Gabriels et al. (38); Landa and Kalb (41).
**p < 0.05. The bold values represents the p value < 0.05.*

those from a Cochrane Collaboration systematic review and meta-analysis of studies comparing EIBI to treatment as usual in the community (51), which found medium to large significant positive effects. The comparison types of the controlled studies varied across the included studies, with nearly half of them involving implementer comparison (therapist vs. therapist and parents); stratification by comparison type was impossible due to the very small number of studies. Actually, the available evidence has proven the effectiveness of parent-mediated EI, showing improvement comparable with that achieved with therapist-mediated EI (52). Needless to say, the existence of this comparison type would weaken the ES.

It is generally believed that children participating in early CTMs will have a reduced need for support and programs as they go through school (47), but our study highlighted that despite some improvements, the outcomes of children with ASD are still far from normal. Thus, ongoing intervention is necessary, especially for adaptive functioning in real life. Even so, almost 30% of US children with ASD did not receive behavioral or medication treatment (53), and multiple gaps were identified across all the stages of intervention development and testing from conceptualization to community implementation (54). These may be crucial issues to fill to improve outcomes for individuals with ASD in the future.

Furthermore, a systematic review (19) of outcomes in late adolescence and adulthood was selected for comparison with our results to draw more reliable conclusions, and improvements in language and symptom outcomes were found in both children and adult populations. Our results, however, showed a significant gain in IQ and negative findings for adaptive functioning and DLS. Analyses of the distinctiveness of developmental trajectories with respect to these outcomes provided evidence of steady and remarkable improvements in verbal and non-verbal IQ from childhood to adolescence when the pre-IQ range in the included studies was 50–60 (55). Similarly, individuals with moderate adaptive functioning at baseline (standard score of ∼75) had a stable trajectory (56). These findings suggest that longitudinal change could be influenced somewhat by the baseline level of participants, and our result explains the prognosis of ASD children with moderate functioning in terms of IQ and adaptation at baseline. Viewed from another angle, we did not find enough studies reporting the prognosis of lower- and higher-functioning ASD. Regarding the negative findings for DLS, Di Rezze et al. (57) indicated that an improvement in trajectory was associated only with lower and improving ASD symptom severity, whereas, none of the seven studies reported symptom-related data. We did not find any statistically significant population characteristics in the meta-regression, probably because the mean values of preintervention population variables were relatively concentrated among our included studies. Therefore, we propose that developmental and symptom outcomes could affect each other over time, and the effectiveness of CTMs should be examined by controlled studies designed for multiple subpopulations. Furthermore, the environmental factors that may be associated with continued changes in those outcomes from childhood to adulthood remain largely unknown (58) and may be responsible for the difference in the results.

Due to the variation in changes in childhood, we sought to explore the sources. Although, the ESDM was the most effective in improving IQ and EIBI showed greater efficacy in ASD symptom severity reduction in affected children, we are still far from establishing an evidence basis for the superiority or inferiority of the ESDM program because of the limited number of appropriately designed relevant studies. However, meta-regression provided a clear account of the impact of the implementer and intervention approach and verified the results of the stratified analyses: (1) IQ tended to benefit more from intervention programs mediated by parents and therapists, while the ESDM is an intervention strategy with parental involvement; (2) symptoms tended to benefit more from EIBI programs than non-EIBI programs. We did explore whether the quality and sample size of the studies, initial IQ or age of participants were related to deterioration/improvement in all outcomes over time. Only five significant associations were identified: intervention approach, implementer, total treatment hours, intervention intensity, and risk of bias; these derive almost entirely from intervention elements. Makrygianni et al. (23) have also suggested that the program intensity and duration are important predictors of the effectiveness of treatment on adaptive functioning. Thus, insufficient treatment time may account for the negligible effects on adaptive behavior.

Limitations

The conclusions of this review should be interpreted with caution in light of its limitations. First, very few high-quality studies have specifically examined outcomes in childhood, and the numerous methodological weaknesses of the studies reviewed here limit the conclusions that can be drawn. Given that the studies varied widely in terms of cohort selection, treatment features, and assessment reliability, we could not establish an unbiased way of taking into account all these factors in judging research quality. We strongly endorse the conclusions of some reviews that rated the overall quality of evidence as "low" or "very low" using the GRADE system (7). Nevertheless, according to the current quality assessment, the quality level necessary to perform meta-regression was met, and most of the changes in the outcomes have nothing to do with the quality. Unfortunately, the LEAP program (59), which has a rigorous research-based design, was excluded from this review because of insufficient initial data.

Second, to achieve a certain statistical power, this study combined single-group prepost studies with between-group controlled studies to analyze the ES, although, this approach is somewhat controversial. However, similar results were obtained when we performed the meta-analysis II among the between-group studies only, indicating the reliability of our results.

Third, we used the group average age data as one of inclusion criteria due to a lack of individual raw data; therefore, it is inevitable that some children were preschoolers at follow-up and some were in their late teens. However, our results showed that the age at the last assessment did not affect the gains. We are looking forward to a time when investigators are willing to share their unpublished data, allowing meta-analyses on this topic to be more complete.

Finally, fidelity measures and standards cannot currently be assumed for studies in this field, and most did not provide information about additional treatment received after the intervention services ended.

Recommendations for Future Research

In sum, recommendations for clinicians and researchers planning to conduct empirical studies in this area include the following: (1) employ study designs that use randomized controlled trials whenever possible and match treatment intensity and duration across groups; (2) record the specific intervention approaches and components in detail and monitor the fidelity of the intervention process; (3) collect detailed information on education and intervention strategies applied during mid-childhood and adolescence; (4) due to the current need, explore ESDM programs and lower- and higher-functioning ASD; and (5) focus on follow-up measurement and record the initial measurement as comprehensively as possible.

CONCLUSION

Overall, there is some evidence that most children with ASD who participate in an early CTM make gains in many areas of functioning, especially with respect to symptom- and language-related outcomes. However, most of the existing research relies on small studies that are non-randomized, forestalling definitive conclusions. What is certain is that the childhood outcomes of children with ASD are still far from normal, especially with respect to adaptive functioning, and the mediating variables of developmental gains were primarily intervention elements, including approach, implementer, intensity, and total treatment hours. Furthermore, the ESDM displayed the largest effect in terms of improving intelligence development, and EIBI showed greater efficacy in reducing ASD symptom severity.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

BS, LC, and JJ were involved in the conception and design of the review. BS, WW, and MD contributed to the data collection. JZ and JL contributed to the quality assessment. BS and JZ conducted the meta-analyses. BS and MD contributed to interpretation of data. The review was conducted by BS and WW, who completed initial drafts of the paper. LC, BW, and JJ gave critical comments and advice that helped shape the review. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

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Inclusive Early Childhood Education for Children With and Without Autism: Progress, Barriers, and Future Directions

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University-affiliated lab and model schools play an important role in creating educational innovations in inclusive early childhood education (ECE) for young children with Autism Spectrum Disorder (ASD). In the United States, access to inclusive high-quality ECE programs for young children with disabilities has been required by law for over 40 years, has been recommended by leading professional organizations, and has been emphasized in federal public policy initiatives. Yet, improvement in the rates of young children with disabilities experiencing inclusion has been limited. This review article consists of three parts. First, we identify and describe four barriers to wide-scale implementation of inclusive ECE programs for children with ASD in the US. These barriers include (1) the fragmented nature of the ECE system in the United States, (2) the age at which ASD is typically first diagnosed in the community, (3) the diverse presentation/support needs of children with ASD, and (4) the thoughts and feelings of parents of children without disability about inclusion. Second, we used a snowball sampling approach to identify nine leading university-affiliated, inclusive lab and model schools for young children with ASD. By describing these programs, we highlight similarities and differences between programs, and capture the unique ways in which these programs adapt to local conditions, resources, and barriers (e.g., federal and state regulations, funding sources, community resources, institutional structures and priorities, professional orientation and training, access to families and staff). Finally, we propose a roadmap for researchers focused on the development, evaluation, and implementation of community-viable inclusive ECE programs in ASD. This roadmap leverages synergies between inclusive university-affiliated lab and model preschools in ASD, and proposes the formation of a research network that creates an infrastructure for cross-program collaboration.

Keywords: autism, inclusion, preschool, early childhood education, early intervention

INTRODUCTION

Adopted in 2006, the United Nations Convention on the Rights of Persons with Disabilities requires that "States Parties ... shall ensure that ... persons with disabilities can access an inclusive, quality and free primary education on an equal basis with others in the communities in which they live" [(1), Article 24]. Further, the United Nations Educational, Scientific and Cultural Organization (2) defines inclusion as a "process of addressing and responding to the diversity of needs of all learners through increasing participation in learning, cultures and communities, and reducing exclusion within and from education" (p. 13). Guided by the conviction that it is the responsibility of the regular system to educate all children, individual differences among students are viewed "not as problems to be fixed, but as opportunities for enriching learning" for all children (p. 9). Moreover, while the UN Convention on the Rights of Persons with Disabilities focuses on primary education, international organizations such as the Enabling Education Network (https://www.eenet.org.uk) have highlighted opportunities for inclusion within Early Childhood Education (ECE) settings. Due to its focus on foundational learning skills (e.g., cooperating, personal skills like managing emotions, physical skills like manipulating small objects) and play-based learning, early childhood settings are ideally suited for promoting inclusive learning opportunities from early on (3).

Despite world-wide efforts to promote inclusive education, the origin and application of these efforts differs substantially by country and geographic region. For example, in northern countries (including the US), inclusion emerged as a response to segregation of students with disabilities in special education and mainstreamed settings, while developing countries tend to be more broadly concerned with school access for a wider range of children (4). While there is not a single model for promoting inclusion of children with disabilities that is applicable across the globe, important lessons can be learned from the journeys of individual countries. Guided by this approach, the current article focuses on the unique conditions, barriers, and opportunities for inclusive ECE in the United States. Further, because the current manuscript aims to develop a roadmap for researchers focused on the development, evaluation, and implementation of community-viable inclusive ECE options for children with ASD, our review explores the conditions of ECE inclusion in the US with a focus on this population of children.

Access to Inclusive Early Childhood Education for Students With Disabilities in the US

In 2015 and 2017, the US Departments of Education (US DOE) and Health and Human Services (US DHHS) published a joint policy statement, stressing that "all young children with disabilities should have access to inclusive high-quality early childhood programs" (5). Access to inclusive learning environments has been required by US law for over 40 years [Individuals with Disabilities Education Act (IDEA), (6)], and strongly recommended by two prominent ECE organizations in the US [Division for Early Childhood (DEC) and National Association for the Education for Young Children (NAEYC), (7)]. Yet, improvement in the rates of children experiencing inclusion has been insubstantial (8, 9). Barton and Smith (10) used annual reports to congress prepared by the USDOE to estimate the percentage of children with disabilities, aged 3-5 years, who receive special education and related services in regular ECE classrooms. Although the classification terminology has changed somewhat across the decades, the authors estimate that this percentage increased from 36.8% in 1984/1985 (11) to 42.5% in 2011/2012 (12). Data from the most recent report to congress (12) indicate that this percentage continued to increase to 45.5% in 2017/2018. Thus, between 1985 and 2018 (33 years!), the practice of providing special education to children with disabilities, 3-5 years, in regular ECE settings appears to have increased by <10%.

Contextually-Based Interventions for Young Children With ASD

Just like world-wide educational policy leaders are embracing the value and practice of inclusion, the emerging consensus among intervention researchers in ASD has coalesced around the notion that, to the extent possible, learning opportunities for children with ASD should be embedded within children's natural environment, particularly within familiar daily life routines that are predictable, meaningful, motivating, and developmentally-appropriate [Naturalistic Developmental Behavioral Interventions, NDBI, (13)]. Relevant routines and interactions occur at home (e.g., caregiving activities, play, and common household tasks/chores), in the community (e.g., going to a store, visiting a park), and in settings where interactions occur with typically developing children (e.g., ECE classrooms).

The current focus on contextually-based interventions in ASD has several roots, both in science and society. First, research on behavioral learning techniques has shown that contingency-based skill building is most effective when it is embedded in social interactions and activities that are motivating, meaningful, and allow children to experience the natural contingencies of their own behavior (14). By teaching skills within children's natural environments with multiple materials and interactive partners, learning and generalization of skills is optimized (13). Second, clinical practice guidelines for young children with ASD emphasize the intensity of children's learning opportunities. It is commonly recommended that children with ASD spend at least 25 h per week actively engaged in planned learning activities (15). Embedding planned learning activities within and across natural environments provides a feasible strategy for maximizing the intensity of children's learning opportunities. Third, during the last decade, intervention researchers in ASD have begun to leverage implementation science methods to plan, adapt, and implement evidence-based practices in community settings (16, 17). Implementation science methods provide researchers with a new set of tools for (a) adapting intervention strategies to fit the settings in which they need to be implemented, and (b) partnering with community practitioners and systems that interact with young children with ASD (18). Finally, during the last decades, societal views on disabilities have undergone a paradigm shift, away from medical models that emphasize charity, treatment, and social protection, and toward social models that emphasize respect for difference, acceptance, participation, and inclusion (1). In addition to references to human rights and equity, advocates for inclusive education also emphasize its utility-related benefits, arguing that inclusion is potentially the most cost- and time-efficient way of improving access to education for all children (4).

BARRIERS TO INCLUSIVE EARLY CHILDHOOD EDUCATION FOR CHILDREN WITH AUTISM SPECTRUM DISORDER

Creating and sustaining inclusive ECE options for young children with ASD in US community settings is challenged by multiple factors, including (1) the fragmented nature of the broader ECE system in the United States, (2) the age at which ASD is typically first diagnosed in the community, (3) the diverse presentation/support needs of children with ASD, and (4) the thoughts and feelings of parents of children without disability about inclusion.

The Fragmented Nature of the Broader ECE System in the United States

The historical roots of the ECE system in the United States can be traced back to two distinct streams, both emerging in the 1830s—day nurseries and nursery schools (19). Day nurseries emerged in response to pressures created by rapid industrialization and immigration and emphasized basic care and supervision. Nursery schools, on the other hand, emerged in the context of the educational reform movement, and envisioned ECE as a means of escaping the intergenerational transmission of poverty. Throughout the last 200 years, these two major functions (i.e., care and education) have remained separate, both in their own ways being shaped by large-scale, historical developments including: (1) the rise of workforce participation of women during the second half of the 20th century (20), (2) growing interest in school readiness (21), and (3) the "welfare reform" legislation of 1996, which included work requirements for poor women with young children. Given these conflicting values and historical forces, the broader ECE system in the US today varies greatly in terms of geography, public/private mix, and access/coverage.

Empirical data on the utilization of early childcare and education programs in the US must be gleaned from multiple data systems that are not fully integrated. Laughlin (22) evaluated data collected by the US Census Bureau during spring 2011, providing valuable information about childcare arrangements prior to children's 3rd birthday. Data indicate that childcare arrangements differed vastly, both by child age and maternal employment (for children $<$ 1 years and 1-2 years, 52 and 54% of mothers were employed, respectively). For employed mothers, 16% of children $<$ 1 year, and 30% of children 1-2 years attended an organized childcare facility (including day care centers, nurseries/preschools, and Early Head Start programs). For unemployed mothers, 3% of children $<$ 1 year, and 4% of children 1-2 years attended an organized childcare facility.

Annual data on the utilization of ECE programs of 3- and 4-year-old children in 2019 are reported by The National Institute for Early Education Research (23). In this report, the percentage of the population enrolled in ECE is reported separately, based on child age (3 and 4 years) and program type (i.e., Public Pre-K, Private ECE, Head Start). The presented data show that 35% of 3-year-olds, and 20% of 4-year-olds were enrolled in private ECE programs. In addition, 6% of 3-year-olds, and 37% of 4-year-olds were enrolled in public Pre-K (either state or locally funded). In 2019, 45 states (incl. D.C.) offered a state-funded preschool program, and programs differed vastly with regard to eligibility requirements (e.g., 33 state programs had an income requirement), access for 3-year-olds (offered by 32 states, including D.C.), the state agencies charged with primary oversight (81% of state preschool programs were administered at least partially by the State Education Agency), and state preschool policies related to program quality. Finally, in 2019, 7% of 3-year-olds, and 8% of 4-year-olds attended Head Start, a federally-funded, comprehensive early education program for low-income families. Because of the federal requirement that at least 10% of enrollment consists of children with disability, Head Start is a major provider of inclusive ECE services in the US.

The reports by Laughlin (22) and Friedman-Krauss et al. (23) paint a complex picture of the participation of US children in ECE programs. Access and coverage differ by age, the availability of public options, and the families' socio-economic circumstances. For public school systems, the provision of inclusive learning options for 3- and 4-year-olds typically requires accessing funding through the state-funded Pre-K or the federally-funded Head Start system. While Early Head Start provides center-based program options for children younger than three years, the number of funded slots is relatively low. According to the National (Early) Head Start Services Snapshots for 2018-2019, about 100,000 center-based slots were funded in Early Head Start (children $<$ 3 years), compared to about 650,000 slots in Head Start [children $\geq$ 3 years; (24, 25)]. Thus, creating inclusive learning options for children younger than 3 years requires the involvement of private ECE programs (e.g., day care centers, nurseries/preschools).

The Age at Which ASD Is Typically First Diagnosed in the Community

During the last two decades, research has made tremendous progress with regard to early identification and diagnosis of ASD. As a result, in many cases, ASD can now be reliably diagnosed between 18 and 24 months of age (26). Advances in best practices related to early identification are reflected in a 2006 policy statement published by the American Academy of Pediatrics (27), asserting that Primary Care Providers (e.g., family physicians, pediatricians) administer formal screening tests during every well-child visit scheduled at 18 and 24 months, independent of known risk factors or reported concerns. Moreover, Primary Care Providers are urged to promptly refer children for Early

Intervention services as soon as ASD is seriously considered as a possibility for diagnosis.

While the age of first diagnosis has gradually decreased during the last two decades, population-based studies reveal that most children with ASD in the US continue to be diagnosed after their 4th birthday (28). According to the most recent report by the Autism and Developmental Disabilities Monitoring (ADDM) Network, an active surveillance program that estimates the prevalence of ASD among children aged 8 years residing in 11 ADDM Network sites in the US, 18.5 out of 1,000 children meet surveillance criteria for ASD (1 out of 54 children), and 13.2 out of 1,000 children have a documented clinical ASD diagnosis (28). Among the children with a documented clinical ASD diagnosis, children's median age at first diagnosis was 51 months. The median age of children's first comprehensive developmental evaluation was 40 months, with 44% being first evaluated at or prior to 36 months, and 37% being first evaluated later than 48 months.

The intersection between (1) the complex ECE system in the US, and (2) characteristic delays in ASD diagnoses has important implications for children's access to inclusive ECE environments. On one hand, many children who are eventually diagnosed with ASD are enrolled in ECE programs prior to receiving a formal diagnosis. Thus, ECE teachers serve as an important source of social and professional support during a time when parents begin to recognize concerns about their child's social-communication development, navigate the diagnostic process, and begin to access ASD-specific resources. In many instances, ECE teachers begin to implement individualized instruction and classroom adaptations prior to children's ASD diagnoses. On the other hand, because most children with ASD do not receive their formal ASD diagnosis until they are 4 years of age or older, the Pre-K and kindergarten years are often the first realistic opportunity for implementing formal special education services in inclusive classroom settings.

The Diverse Presentation/Support Needs of Children With ASD

While access to inclusive ECE placements is important, learning occurs when children are active, independent participants within their classroom communities. Thus, successful inclusion of children with ASD requires that educators provide adequate individualized interventions (by embedding instruction within/across routines, activities, environments) and classroom adaptations (by embedding organizational, communication, sensory, or behavioral supports to make content accessible) to ensure that children are actively engaged in learning throughout the preschool day (29). Consistent with current principles of developmentally-appropriate practice for all young children (30), a comprehensive understanding of active engagement goes beyond simple "task attendance" and emphasizes children's social emotional engagement, which is critical for learning in ASD (31–33). To date, only three rigorous intervention studies in ASD have used mediation analyses to investigate the intervention mechanisms underlying children's learning outcomes (33–35). While only one of these three studies was completed in the classroom context (33), all three studies reveal that treatment-related outcomes were mediated by children's social engagement with a supportive adult (e.g., child initiations, parent synchronous responsiveness and mirrored pacing, joint engagement).

The nature and intensity of individualized interventions and classroom adaptations necessary to maximize classroom active engagement in ASD varies greatly across children (29). Inclusive model and lab preschools for ASD implement one of two broad strategies to accommodate this variability in children's clinical presentation and support needs. Most programs are designed to maximize flexibility in accessing resources and supports. This includes (1) hybrid programs that integrate clinical/behavioral intervention services (e.g., funded through health insurance providers) and inclusive ECE programming, (2) ECE programs that are operated by local school systems and are able to access system-wide supports for children with disabilities (i.e., Individualized Education Programs), or (3) programs that are affiliated with academic training programs for teachers and related professionals, providing flexibility in classroom staffing due to the availability of student interns. Alternatively, inclusive model programs have elected to limit variability in clinical presentation and support needs as part of the enrollment process. That is, programs set and implement specific enrollment criteria to ensure that all children who attend the program are likely to be successful, given the program's existing teacher-student ratios and teacher qualifications. While procedures to limit eligibility seem inconsistent with philosophical aspirations of inclusive education, a certain level of screening seems necessary to ensure the community-viability of inclusive ECE options in the US. In fact, students with ASD enrolled in most inclusion programs are not representative of the population of children with ASD, either because children's educational needs are specified in their Individualized Education Programs, because parents select programs that are likely to meet their children's needs, or because programs/parents dismiss/withdraw children if their educational needs are not met (36).

The Thoughts and Feelings of Parents of Children Without Disability About Inclusion

Wide-scale access to inclusive learning environments for children with disabilities can only become a reality when parents of typically developing children value the benefit of such experiences for their own children and for society, and eventually select inclusive over non-inclusive alternatives when making decisions about preschool enrollment. Because the early childhood period is critical for children's language and social development, parents tend to carefully weigh their options before making these important decisions. Research using surveys and qualitative interviews reveals that most parents of young typically developing children express general positive attitudes about the value and benefits of inclusive classrooms (37). When asked about possible benefits for their own children, parents of typically developing children emphasize social emotional outcomes (e.g., promoting acceptance and empathy), while benefits for their child's academic outcomes are expressed to a lesser extent (38, 39).

Research investigating attitudes about inclusion has also shown that parental attitudes differ based on the specific diagnosis of children to be included (40, 41). That is, more positive attitudes are expressed toward inclusion of children with hearing impairment, while inclusion of children with complex behavioral disorders including ASD are viewed more cautiously. Specific parental concerns include the potential for behavioral disruptions, teachers' ability to divide attention among all children (38, 39, 42), and whether professional preparation of the ECE workforce is adequate for meeting the needs of children with disabilities (43).

Most available research used survey- or interview-based research methods to investigate parental attitudes about inclusion. The interpretation of this body of literature is complicated by (1) concerns about the social acceptability bias inherent in survey-based research (44), (2) evidence suggesting that parents have limited knowledge of what childhood inclusion entails in practice (45), and (3) questions about the extent to which generalized attitudes about inclusion have direct implications for parents' enrollment choices for their children (42). Moreover, the exact mechanisms that explain individual variation in parental attitudes about inclusion are poorly understood. A better understanding of variables that give rise to or impact parental attitudes could guide future efforts to raise awareness about the benefits of preschool inclusion. The mechanisms that underlie parental attitudes about inclusion are likely complex and may include cultural [e.g., collectivistic vs. individualistic values, (45)], philosophical [e.g., whether social justice orientation may serve as a motivating factor, (46)], curricular [e.g., whether parents value socialization-related or academic outcomes for young children, (38)], or personal factors [e.g., personality traits such as parental conscientiousness, (40)]. Further, parental attitudes about inclusion have been linked to the amount and quality of the parents' prior experiences with individuals with disabilities and/or inclusive education (37, 39).

INCLUSIVE LABORATORY AND MODEL PRESCHOOLS IN ASD

For several decades, university-affiliated lab and model programs have played an important role in creating educational innovations in the area of ECE inclusion for ASD. Most programs originate at a specific time and place, and find unique ways of adapting to their local environment: (1) federal legislation and funding sources, (2) state-specific regulations, support structures, and funding mechanisms, (3) operating procedures and resources at the academic host institutions, (4) professional background and experiences of the program developers, (5) diagnostic and intervention resources in the community, and (6) access to teaching/intervention staff and student populations. While these unique adaptations are an important source of innovation, the uniqueness of each program also poses challenges for rigorous program evaluations (e.g., generalizability of results) and complicates efforts of program replication (e.g., community-viability). In the following, we will identify and compare existing university-affiliated lab and model programs in ASD with the goal of creating a roadmap for researchers focused on the development, evaluation, and implementation of community-viable inclusive ECE programs in ASD. By identifying and describing existing programs, we aim to identifying synergy and opportunities for research collaborations between these programs.

To identify programs eligible to be included in this review, we used a "snowball sampling" approach. That is, we identified an initial set of programs based on a review of the literature, and then contacted program directors with the request to nominate additional programs. Criteria to be included in this review were (1) the program is affiliated with an academic institution, (2) the program provides inclusive ECE experiences for children younger than 5 years, and (3) the program is specifically designed to address the learning needs of children with ASD. We opted for this "snowball sampling" approach over a systematic review of the published literature since our focus was not on integrating findings about student outcomes, but rather on identifying active, university-affiliated lab/model programs. Based on this sampling approach, we identified nine leading programs, all except one located within the US. The nine programs vary widely in how long they have been operating, how far they have advanced on their path toward creating a community-viable inclusion model, and the extent to which student outcomes have been evaluated empirically.

Project DATA (Developmentally Appropriate Treatment for Autism) [University of Washington]

Project DATA is one of five programs within the Experimental Education Unit at the University of Washington Haring Center of Inclusive Education. The Haring Center first opened in 1964 as a pilot school for children with neurological injuries, and has since evolved and expanded to educate children with diverse backgrounds and needs. Since its inception in 1997, Project DATA has been the site of critical intervention/education research in ASD. With funding from a Model Demonstration Grant (U.S. Department of Education, Office of Special Education Programs), Dr. Ilene Schwartz and her colleagues set out to develop a program that is data-based, effective, developmentally-appropriate, and acceptable to consumers (47). Core components of Project DATA include (1) an inclusive early childhood experience (about 12 h per week), (2) extended intensive instruction (10-12 h per week), (3) technical and social support for families (e.g., assistance with transportation, etc.), (4) collaboration and coordination across systems of childhood service, and (5) a quality-of-life influenced curriculum. During the inclusive early childhood experience, six children with ASD and 10 typically developing children are supported by 3-4 staff members. Extended intensive instruction is implemented in three sessions of eight children with ASD each. Students in each session are supported by 4-6 staff members, led by a Board Certified Behavior Analyst (BCBA) and assisted by masters students in applied behavior analysis (ABA). Currently, Project DATA is funded through grants from local school systems. Preliminary data from quasi-experimental research suggest that children who complete the program show significant developmental gains in adaptive (+22%), cognitive (+11%), social communication (21%), social (+24%), and fine motor (+30%) domains over the span of 16 months (47).

Early Emory Center for Childhood Development and Enrichment [Emory University]

Early Emory was founded as the Walden Learning Center at the University of Massachusetts at Amherst in 1985 and moved to Emory University in 1991. Currently, Early Emory operates four age-grouped classrooms (64 children total, including 21 children with ASD), starting from Toddler (1-year-olds) to Pre-K (4-year-olds). Early Emory is guided by principles of incidental teaching and ABA, implements at least 30 h of instruction per week, and emphasizes peer engagement, social interaction, and parent involvement (48). The Early Emory curriculum employs the use of "teacher zones" in the classroom; teachers are trained to rotate across different "teacher zones" such that they develop the skills to engage children across different classroom activities and routines. Classroom-based ABA treatment and family engagement are integral components of the program. Parents are extensively coached for the first 6 months of their child's enrollment, biweekly for the next 6 months, and monthly for the remaining sessions. As a part of the childhood enrichment program, families are also encouraged to participate in monthly family activities and bi-annual parent teacher conferences.

Outcome data from Walden/Early Emory suggests three primary areas of improvement for children graduating from the program: verbalizations, peer interactions, and future placements. In a sample of 34 graduates, 30 children acquired meaningful verbal language (as defined by more than 10 verbalizations in functional, unprompted speech) with a 10% increase in verbalizations on average (49). In terms of peer interactions, 17 of the 34 children who graduated from the program were receiving increased peer social bids relative to program entry ($M = 11\%$, *Range*: 1–27%). Last, 26 out of the 34 Early Emory graduates enrolled in regular kindergarten programs with varying degrees of individualized supports.

Alexa's PLAYC [Rady Children's Hospital-San Diego]

Alexa's PLAYC, formerly known as the Children's Toddler School (CTS), is lab-based ECE program at Rady Children's Hospital in San Diego. The program opened in 1998, serving eight children with ASD and eight typically developing children from 18 months to 3 years. Four children with ASD attend a morning session, and four children with ASD attend an afternoon session. CTS began as a partial replication of the Walden Program, including core program features such as comprehensive teacher training, ABA, incidental teaching, and parent training, with a classroom staffed by three teachers (50). However, CTS differs from the Walden program in the provision of 1:1 programming outside of the classroom (as opposed to classroom-based ABA), a broader range of behavioral treatment strategies (e.g., pivotal response training, discrete trial training), and use of augmentative and alternative communication modalities. Further, to facilitate replication of the preschool model, CTS elected not to use Walden's characteristic "teacher zones" and rotation. CTS was re-named Alexa's PLAYC in 2010 when it expanded to include preschool in addition to toddler programs.

Using a quasi-experimental design, Stahmer and Ingersoll (50) reported on outcomes of 20 children with ASD served by CTS for a minimum of 6 months. Standardized assessments and measures of functional outcome were compared at program entry and exit. Results revealed significant increases in standard scores on measures of cognitive development and adaptive behavior as well as significant improvements in functional measures (e.g., response to others' initiations and engagement in reciprocal interaction). Compared to 11% at entry, 37% of the children were functioning in the typical range on measures of cognitive development at exit. A 10-year report of 102 children with ASD participating in the CTS yielded similar findings with significant improvements observed in developmental level, adaptive behavior and communication after an average of 8 months of program participation (51).

Achievements [Kennedy Krieger Institute]

The Achievements program is a lab-based ECE program operated at the Center for Autism and Related Disorders (CARD) at the Kennedy Krieger Institute in Baltimore, Maryland. Founded by Dr. Rebecca Landa in the early 1990s, Achievements offers a variety of clinical models for children, from 22 months to 6 years of age. The program has eleven classrooms across two locations with a total capacity of 46 children. Each classroom serves 3–5 children; children are supported by one speech-language pathologist and 1–2 therapeutic assistants per class. Students also receive occupational therapy once per week and psychology and social work consults as needed. Attendance is billed through insurance as group therapy. Typically developing children from the Model Inclusion Childcare Classroom at CARD participate in the classroom as peer models. Instructional strategies used in the classroom include a continuum of approaches ranging from highly structured to routines-based intervention approaches. Visually-based organizational systems are provided and augmentative and alternative communication systems are used as needed. Achievements specifically targets socially engaged imitation, joint attention, and affect sharing.

Outcome data have been reported for the Early Achievements (for 2-year-olds) program in two published randomized trials (RCTs). Landa et al. (52) evaluated the impact of supplementing a comprehensive intervention (i.e., the early childhood program at Kennedy Krieger) with a curriculum targeting socially synchronous behavior [later referred to as Early Achievements; (53)]. For this study, 50 toddlers with ASD (aged 21–33 months) were randomized to either the comprehensive classroom intervention alone or the classroom intervention plus the Interpersonal Synchrony curriculum. Socially engaged imitation more than doubled with a significant treatment effect in favor of the Interpersonal Synchrony group. Imitation skills generalized to unfamiliar contexts and were maintained through follow-up. Similar gains were observed for initiation of joint attention and shared positive affect, but between-group differences did not reach statistical significance.

More recently, Early Achievements has been translated and tested in public childcare settings (53). Forty-eight childcare providers from 27 centers and 46 toddlers with social and/or communication delays (mean age = 28.5 months) participated in a cluster-randomized controlled trial. Early Achievements was adapted to community settings (Early Achievements for Childcare Providers; EA-CP) and compared to instruction-as-usual. EA-CP is delivered within shared book reading activities and includes a coaching framework that is implemented over 5-months and targets the use of various NDBI strategies (13). At the end of the study, providers in the EA-CP condition were implementing the intervention at an average of 80% fidelity. Although students in the EA-CP condition did not demonstrate significantly greater scores on developmental assessments than those in the instruction-as-usual condition, they did demonstrate significantly greater change in raw scores ($M = 4.4$, SD = 4.6) on the Social-communication Assessment in Book Sharing [SABS, (54)] compared to toddlers in control classrooms with a large effect size in favor of the EA-CP group.

Preschool Education Lab [Marcus Autism Center/Emory University]

The Preschool Education Lab (PEL) at Marcus Autism Center/Emory University opened in 2018 and was developed by Dr. Michael Siller and Dr. Lindee Morgan. PEL functions as model inclusion preschool and a as a laboratory preschool to advance the science of inclusive ECE in ASD. Community viability is central to the program's design. That is, the program is designed to operate under the same financial and operational constraints as comparable high-quality preschool programs in the community. PEL is a full-day preschool program that is licensed as a Child Care Learning Center by the state, participates in state-wide quality improvement processes (Quality Rated Child Care), and implements state-wide early learning standards. The program includes two tuition-funded classrooms for 2- and 3-year-olds, and a state-funded Pre-K classroom for 4-year-olds. The three classrooms include 12, 16, and 18 children, respectively. Each classroom includes six children with ASD and is supported by a team of three teachers. All teachers have degrees/experiences in early childhood education (at the BA or AA level), but no specialized training in ASD interventions (with the exception of the Pre-K classroom which includes one teacher with a special education background). The teaching staff is supported by a classroom coach (30% effort) who supports the teachers in developing individualized learning outcomes and classroom supports. PEL uses the SCERTS framework (55) to develop individualized student outcomes and tailor classroom supports for students with ASD. Direct 1:1 intervention sessions are not implemented as part of PEL, although some children may be supported by community-based speech-language or ABA therapists during part of the day.

Because the general program structure (e.g., teacher-student ratio) of PEL is relatively fixed and the ability to allocate additional individualized resources is limited, the program has developed an eligibility process to ensure that all enrolled students with ASD are ready for the provided classroom-based learning experiences. The eligibility process includes a combination of parent surveys, a structured eligibility observation with a clinician/researcher, and a classroom visit [a detailed description of eligibility and enrollment procedures is reported in (36)]. Program outcome data have not been published to date.

Early Learning Institute [Michigan State University]

The Early Learning Institute (ELI) at Michigan State University was developed by Dr. Joshua Plavnick (BCBA-D) and Laurie Linscott (M.A.) in 2015. The program is housed within the Child Development Laboratories and was created with the goal of providing early intervention services to children with ASD and creating a context for training service providers to learn about evidence-based practices. ELI utilizes a combination of ABA and parent coaching to address the needs of families. To be eligible, children must be diagnosed with ASD, be between the ages of 2 and 4 years by the beginning of the program, and be eligible for high level of ABA services. Once enrolled, children attend the program from 8:30 AM to 4:00 PM Monday through Thursday, year-round. Although an ASD diagnosis is a prerequisite for enrollment, there are opportunities to foster inclusive settings within the broader Child Development Laboratories classrooms. To date, the program has served a total of 29 families and trained 19 researchers and service providers. As a relatively newer program, outcome data on children completing ELI have not been published.

Susan Gray School [Vanderbilt University]

The Susan Gray School (SGS) is operated by Peabody College at Vanderbilt University, a world-class college of education and human development. Originally named the Peabody Experimental School, SGS opened in 1968 as an on-campus research-oriented school devoted to educational research involving young children with developmental disabilities and children whose future development was at risk because of conditions such as poverty. Currently, SGS offers eight classrooms from infancy through Pre-k, serving about 92 students in total (30% with disabilities; 10% from economically disadvantaged backgrounds). The school has 16 full-time teachers. Moreover, SGS functions as a training site for students from various disciplines including Special Education, Teaching and Learning, Psychology, Human Development, and Speech and Hearing. Aside from the eight inclusion classrooms, SGS also includes a community outreach program, which currently serves children with developmental delays/disabilities from birth to 36 months (about 20 case visits per week). While faculty affiliated with SGS have produced a range of publications on inclusive ECE, program outcome data have not been published to date.

Learning Experiences and Alternative Program for Preschoolers and Their Parents

Learning Experiences and Alternative Program for Preschoolers and Their Parents (LEAP) is a manualized intervention approach that aims to enhance the social interactions of young children with special needs. LEAP can be implemented within high-quality, general education settings for preschool-aged children. Key features of LEAP include: (1) targeting of individualized objectives within classroom activities with an emphasis on peer-mediated methods, (2) systematic focus on generalization, and (3) achievement of intervention intensity by maximizing instructional opportunities (56).

Strain and Bovey (57) completed an RCT of LEAP in 56 inclusive classrooms serving 294 children with ASD. The program implementation included structured parent-training component and detailed treatment fidelity procedures. After a 2-year period of training and mentoring, children in LEAP classrooms showed significantly greater improvement than controls on measures of global development, language, social skills, behavior, and ASD symptoms (moderate to large effect sizes). Further, results from a long-term follow up study showed intervention-related gains in social and cognitive skills were maintained over a 4-year post intervention period (58). A recent cluster RCT comparing LEAP to TEACCH-based and non-model specific classrooms showed that all children, independent of treatment condition, showed comparable improvements after 1 year of intervention implementation (59).

Group—Early Start Denver Model

Another example of a manualized intervention model for inclusive ECE classrooms is a group-based adaptation of the Early Start Denver Model [ESDM (60)]. ESDM was originally designed to be delivered by a trained therapist on a 1:1 basis with implementation targeted for 15-20 h per week. This approach has demonstrated positive effects on improving cognitive, adaptive, and language outcomes for young children with autism (61, 62). Group—Early Start Denver Model (G-ESDM) was developed to provide children with ASD intervention within the context of a high-quality ECE classrooms. The primary goals of the G-ESDM are to support active engagement in group activities and routines throughout the school day with an emphasis on promoting the use of communication with peers and adults, successfully negotiate transitions, and develop skills necessary for participation in classroom environments (63, 64). Individualized goals are addressed using a variety of intervention strategies consistent with NDBI (13), including antecedent-behavior-consequence contingencies, peer-mediated teaching, and strategies for emotional and motivational regulation.

To evaluate the feasibility and initial efficacy of implementing G-ESDM in inclusive settings, Vivanti et al. (65) randomized 44 preschoolers with autism to either inclusive or special education classrooms, all implementing G-ESDM. After 12 months, children in both classroom types showed equivalent and significant gains on proximal measures of spontaneous communication and social interaction as well as distal measures of verbal cognition, adaptive behavior, and autism symptoms.

LEVERAGING LABORATORY AND MODEL PRESCHOOLS TO CREATE A PROGRAM OF RESEARCH TO ADVANCE THE SCIENCE OF INCLUSIVE EARLY CHILDHOOD EDUCATION IN ASD

Successful lab or model preschools in ASD find unique ways of leveraging local resources, including (1) affiliations with academic training programs in education, ABA, and related disciplines to create training opportunities and improve teacher-student ratios (e.g., Susan Gray School, Project DATA, Early Learning Institute), (2) opportunities to create hybrid programs that combine intensive clinical/behavioral intervention services (e.g., ABA) with inclusive learning opportunities within ECE classrooms (e.g., Project DATA, Early Learning Institute, Early Emory, Alexa's PLAYC, Achievements), and (3) affiliations with local school systems (e.g., Project DATA, LEAP). As emphasized above, these unique adaptations are an important source of innovation. At the same time, the uniqueness of each program also poses challenges for rigorous program evaluations (e.g., generalizability of results), and complicates efforts of program replication (e.g., community-viability).

In the following, we will propose a roadmap for researchers focused on the development, evaluation, and implementation of community-viable inclusive ECE programs in ASD. This roadmap leverages synergies between inclusive university-affiliated lab and model preschools in ASD, and proposes the formation of a research network that creates an infrastructure for cross-program collaboration. During the last decades, similar research networks have led to significant advances in the science of early identification (i.e., Autism Baby Siblings Research Consortium; https://www.babysiblingsresearchconsortium.org/) and early intervention [i.e., Autism Speaks Toddler Treatment Network (66)] in ASD. The proposed research program includes nine interrelated research aims.

Research Aim #1: Create a Comprehensive, Systematic Review of Existing Inclusive Laboratory/Model Preschool Programs in ASD

The current chapter provides brief descriptions of nine programs, identified through a snowball sampling approach. This approach is limited in several regards. First, the list of included programs is likely incomplete, particularly with regard to programs that are more loosely affiliated with academic institutions and programs that operate outside of the US. Second, the information used to describe individual programs was largely based on online searches and published literature. Future research should use a standardized data collection process (e.g., program director surveys or interviews) to gather information about similarities and differences between programs more systematically.

Research Aim #2: Support Inclusive Laboratory/Model Preschool Programs in Publishing Outcome Data

Because of the nature of these programs, experimental research designs are often not feasible when evaluating learning outcomes of children enrolled in individual inclusive lab/model preschool programs (e.g., biased, self-selected samples, lack of adequate control groups, ethical/practical concerns about random assignment). However, given the current state of the field, carefully planned quasi-experimental designs and pre-post comparisons of enrolled students can provide useful information about (1) promising outcome measures, (2) measures that predict intervention response, and (3) process measures (e.g., classroom active engagement) that explain individual differences in learning outcomes. Most importantly, this research should focus equally on students with and without ASD. A better understanding of the benefits of inclusive learning environments for typically developing children could inform parents' enrollment decisions as well as the programs' curricula and educational approaches.

Research Aim #3: Facilitate Collaborations Between Inclusive Laboratory/Model Preschool Programs to Investigate Shared Process and Outcome Measures

To gain a mechanistic understanding of the processes that underlie learning in inclusive classroom environments, inclusive lab/model preschool programs should collaborate and collect shared process and outcome measures. The collection of process measures may involve a standard protocol for collecting classroom videos, and observational coding systems to capture elements of student active engagement (e.g., investment, independence, social initiations) and teacher measures of implementation fidelity (e.g., individualized interventions, classroom adaptations).

Research Aim #4: Create an Implementation Science Framework for Scaling Existing Inclusive Laboratory/Model Preschool Programs in Community Settings

Most inclusive lab/model preschool programs have intermediate- or long-term plans to create a generalizable inclusion model that can be replicated and implemented in community settings. However, given the complexity of the ECE system in the US, the field would benefit greatly from a consistent framework for adapting, manualizing, replicating, and scaling inclusion models. Community implementation may either focus on scaling entire program or classroom models (e.g., Alexa's PLAYC), or focus on program components central to the inclusion model (e.g., LEAP).

Research Aim #5: Use Causal/Experimental Methods to Evaluate the Learning Outcomes of Children With and Without ASD

Eventually, wide-scale implementation of inclusive preschool models for children with ASD will require rigorous research documenting program efficacy/effectiveness for both children with and without ASD. This research should involve collaborations between existing lab/model programs, focus equally on short-term and long-term child outcomes, resist temptations of "intervention branding," and investigate learning outcomes associated with intervention mechanisms shared across different programs. The NDBI moniker may serve as a fruitful framework for this work.

Research Aim #6: Investigate the Feasibility of Inclusive ECE Models Across Multiple ECE Systems

As described above, the ECE education system in the US is rather complex, and inclusion models will need to be adapted to meet the needs of different service systems, including public Pre-K, private childcare, Head Start, and Early Childhood Special Education. Moreover, because early identification and intervention are crucial components of effective intervention programs in ASD, the field requires inclusive ECE options for infants and toddlers, including children who have not yet received a formal ASD diagnosis. Such programs should find ways to leverage available early intervention (Part C) resources.

Research Aim #7: Investigate Whether Inclusive Options Should Be Specific to ASD or Incorporate Children Across Multiple Societal or Disability Categories

Efforts to create an inclusive society need to move beyond targeted inclusion programs for specific societal categories (e.g., children with ASD), and strive toward learning environments where all young children are accepted and supported in accordance with their unique learning style and needs. However, this philosophical orientation may be at odds with the practical constraints inherent in effective and efficient workforce development. The field would benefit from comparisons between inclusion programs targeting ASD, and inclusion programs targeting children with disabilities/developmental delays more broadly. Importantly, this work should focus equally on student (e.g., development, learning) and teacher (e.g., efficacy, burnout) outcomes.

Research Aim #8: Gain a Better Understanding of How Parents of Typically Developing Children Think and Feel About ECE Inclusion

Parents of typically developing children who seek enrollment in inclusive lab/model preschool programs constitute a highly self-selected group of families. To make inclusive ECE programs a reality on a larger scale, the field would greatly benefit from a better understanding of factors that influence parental thoughts, feelings, and buy-in. This information could inform individual programs' procedures for student recruitment as well as population-wide public awareness campaigns about the benefits of inclusive ECE.

Research Aim #9: Develop Adaptive Interventions That Guide Decisions About Combining/Transitioning Between Clinician-Delivered Interventions and Classroom-Based Inclusive Learning Opportunities

It is likely that not all children with ASD benefit equally for inclusive, classroom-based learning environments. Some children may require intensive clinician-delivered interventions prior to transitioning to inclusive ECE programs. Other children may benefit from a combined approach that integrates clinician-delivered and classroom-based learning opportunities. Recent advances in the evaluation of adaptive interventions (67) provide a framework for embedding evidence-based decision points within children's comprehensive intervention/education programs.

CONCLUSION

During the last decade, intervention researchers in ASD have converged on the notion that, to the extent possible, learning opportunities should be embedded within children's natural environment and involve (1) play or familiar daily life routines that are meaningful, rich in affect, and motivating, and (2) quality relationships with other people, including adults and peers (13). ECE programs provide a prime context for creating and embedding these kinds of learning opportunities for children with ASD. University-affiliated model and laboratory schools play an important role in creating the educational innovations necessary to flexibly integrate clinical/behavioral interventions and inclusive ECE programs to meet the learning needs of young children with ASD. Further, collaboration between these university-affiliated model and laboratory schools has the potential to impact community practice by establishing consensus about the essential elements of high-quality inclusion, developing a shared measurement framework for program fidelity and child outcomes, collaborating on large-scale effectiveness trials, and creating an implementation framework for moving educational innovations from university-affiliated to community programs.

AUTHOR CONTRIBUTIONS

MS wrote the first draft and outline of the manuscript. MS, LM, QW, and AR wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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SYSTEMATIC REVIEW
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Parent-Mediated Interventions for Children and Adolescents With Autism Spectrum Disorders: A Systematic Review and Meta-Analysis

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There has been increasing interest in parent-mediated interventions (PMIs) for children with autism spectrum disorders (ASDs). The objective of this systematic review and meta-analysis was to examine the effect of PMIs compared to no PMI for children with ASD aged 2–17 years. The primary outcome was adaptive functioning rated by a parent or clinician. The secondary outcomes were long-term adaptive functioning rated by the parents, adverse events, core symptoms of ASD, disruptive behavior, parental well-being, quality of life of the child rated by the parents and anxiety. The MEDLINE, PsycInfo, Embase, and CINAHL databases were searched in March 2020. The Cochrane Risk of Bias Tool was used to rate the individual studies, and the certainty in the evidence was evaluated using GRADE. We identified 30 relevant randomized controlled trials (RCTs), including 1,934 participants. A clinically relevant effect of PMIs on parent-rated adaptive functioning was found with a low certainty of evidence [Standard mean difference (SMD): 0.28 (95% CI: −0.01, 0.57)] on Vineland Adaptive Behavior Scales (VABS), whereas no clinically relevant effect was seen for clinician-rated functional level, with a very low certainty of evidence [SMD on Clinical Global Impressions (CGI)-severity scale: SMD −0.45 [95% CI: −0.87, −0.03)]. PMIs may slightly improve clinician-rated autism core symptoms [SMD: −0.35 (95% CI: −0.71, 0.02)]. Additionally, no effect of PMIs on parent-rated core symptoms of ASD, parental well-being or adverse effects was identified, all with a low certainty of evidence. There was a moderate certainty of evidence for a clinically relevant effect on disruptive behavior [SMD: 0.55 (95% CI: 0.36, 0.74)]. The certainty in the evidence was downgraded due to serious risk of bias, lack of blinding, and serious risk of imprecision due to few participants included in meta-analyses. The present findings suggest that clinicians may consider introducing PMIs to children with ASD, but more high-quality RCTs are needed because the effects are not well-established, and the results are likely to change with future studies. The protocol for the systematic review is registered at the Danish Health Authority website (www.sst.dk).

Keywords: autistic disorder, autism spectrum disorder, parent-mediated intervention, caregiver-mediated intervention, early intervention, treatment outcome

INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by early-onset difficulties in social interaction, communication and stereotyped repetitive behaviors and interests (1, 2), and it affects ∼1% of the population in high-income countries (3). The disorder is expected to be lifelong, and people on the spectrum are reported to have an elevated mortality risk, lower educational level, reduced quality of life and higher frequency of comorbid disorders, e.g., depression and anxiety (2, 4–6).

Various behavioral and structural interventions have been developed to improve adaptive functioning, behavioral problems and quality of life for people with ASD, and some interventions reduce ASD symptomatology (2, 7, 8). Several early behavioral interventions have also been developed (9). In recent decades, increasing interest in early parent-child interactions has been observed, the involvement of parents in therapy has increased, and various parent-mediated interventions (PMIs) have been developed.

PMIs are advantageous because they reduce the demands on children with ASD compared to behavioral approaches and bring treatment into a home and community setting, enabling the transfer of skills to real-life settings. PMIs engage parents in the role of a therapist to implement interventions in an individualized and sensitive way (10). Parents already spend much time with their children, which provides an obvious opportunity for a cost-effective intervention, with extensive implementation and generalization opportunities in everyday life and through different contexts (11).

The PMIs vary, including teaching comprehensive skills and others targeting specific impairments, e.g., joint attention, communication, or language (2). The various PMIs cover education, training and coaching from clinicians to parents, with the overarching aim of improving opportunities for children to learn through different contexts. This is essential to ensure generalization and maintain treatment gains (11, 12). Initially, PMIs targeted younger children with ASD; however, simultaneously with the broadening of treatment targets, the age group has broadened to include subjects from early childhood into young adulthood (11).

Several reviews with or without meta-analysis have been conducted in the research field (10, 13–16), but only a few have used Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) to assess the certainty of the evidence (10, 13), and none have addressed both beneficial and adverse aspects of PMIs. The outcome focus of the reviews varies considerably, differing from child outcomes, such as language, adaptive functioning and social communication, to parent outcomes, such as parental stress and quality of life; only a few reviews included a meta-analysis (10, 13, 15–17). Some reviews expanded the parent concept to parent-focused interventions and included all interventions that included parents (17).

A more recent systematic review and meta-analysis of outcomes of PMIs for younger children by Nevill et al. (13) found moderate positive outcomes of PMIs regarding language communication, autism symptom severity, and cognition, but the evidence of positive changes in socialization was very low. The review concluded that the overall quality of more recent randomized controlled trials (RCTs) is improving (13). Several RCTs have been published since the Nevill et al. (13) review and meta-analysis. Thus, to provide clinicians and guideline panels as well as caregivers with an updated overview of the current evidence from RCTs, the objective of this systematic review and meta-analysis was to synthesize the effect of PMIs for children and adolescents with autism aged 18 months−17 years on both beneficial and adverse outcomes.

In particular the following questions were addressed:

- What is the overall effect of the PMIs for children and adolescents with autism?
- What is the effect of the PMIs on parental stress, parental well-being and quality of life?
- Which adverse effects of the PMIs are seen in current research?
- What is the quality of the identified research in this field?
- Will current evidence of the PMIs be sufficient to recommend PMIs for children with autism?

METHODS

This systematic review and meta-analysis was conducted according to the recommendations of the Cochrane Handbook (18) and is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (19) (Prisma checklist is provided in **Supplementary Table 1**). The systematic review also follows the structure described by the population, intervention, comparison and outcome (PICO) characterization (20). The certainty in the evidence was rated by the GRADE approach (21). The study is part of the national Clinical Practice Guidelines on the treatment of ASD among children and adolescents published by the Danish Health Authority in 2021 (22). The content of the study protocol, including review question, search strategy, inclusion and exclusion criteria, and risk of bias assessment, was prespecified, registered and approved by the management at the Danish Health Authority in November 2019 (and the protocol is available at the Danish Health Authority website: www.sst.dk).

Search Strategy

The systematic search was conducted in March 2020 by a search specialist (B.H.P.). The databases searched were MEDLINE, PsycInfo, Embase, and CINAHL. The search was performed in two steps: (a) search for systematic reviews and meta-analyses with a filter and (b) search for primary literature, both with a combination of medical subject heading (MeSH)/index terms and free-text searches. The search was limited to articles in English and Scandinavian language referring to language skills of the review authors. The detailed search strategy is presented in the **Supplementary Table 2**.

A cross reference search and screening of reference lists of included articles and previous reviews was performed, and the guideline working group members (content experts) conferred whether any studies were missing from the search. Study authors were not contacted to identify additional studies.

Study Selection

Articles generated from the defined search strategy of individual RCTs were deduplicated and imported from RefWorks into Covidence software for literature screening and data management (www.covidence.org). According to prespecified PICO criteria, one reviewer (M.L.R.) evaluated the titles and abstracts of eligible articles (see below). The identified full-text articles were independently screened by two reviewers (review authors: M.L.R., C.C. and M.B.L.). Any disagreements were resolved through discussion. The eligible studies had to match the following criteria:

Population

Children and adolescents from 18 months to 17 years of age diagnosed with ASD according to diagnostic criteria with or without comorbidities.

Intervention

Parent-mediated interventions for children and adolescents with ASD with 8 or more sessions.

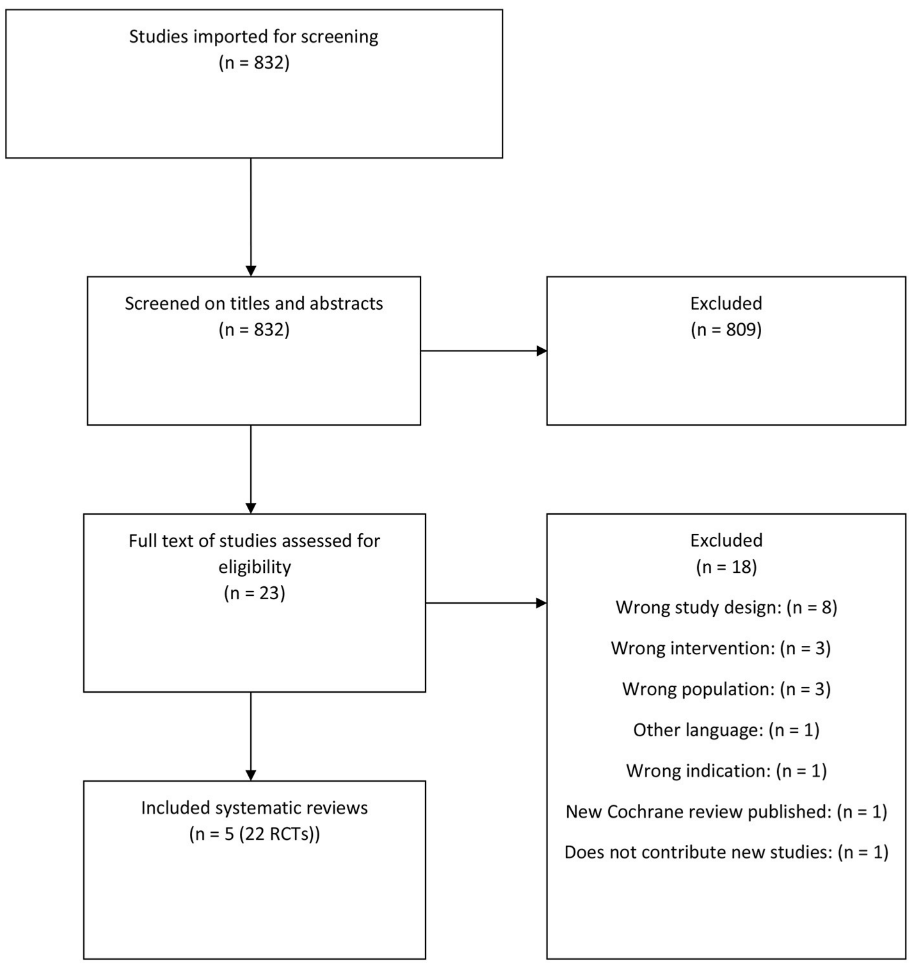


FIGURE 1 | Flowchart of the systematic reviews.

Comparator

No parent-mediated intervention.

Outcomes

Primary Outcome

Adaptive functioning was rated at a minimum of 8 weeks by the parent or clinician.

Secondary Outcomes

- Parent-rated adaptive functioning after at least 6 months of follow-up
- Adverse effects at minimum 8 weeks
- Core symptoms of ASD, parent- or clinician-rated at a minimum of 8 weeks
- Disruptive behavior, parent-rated at a minimum of 8 weeks
- Parental well-being at a minimum of 8 weeks
- Quality of life, parent-rated at a minimum of 8 weeks
- Anxiety at a minimum of 8 weeks

Study Design

Only RCTs were included in this review. The aim of random assignment used in RCTs is to prevent selection bias by distributing the characteristics of patients who may influence the outcome randomly between the groups; therefore, RCTs are considered to minimize the risk of confounding factors influencing the results, thus providing the most reliable evidence on the effectiveness of interventions.

Data Extraction of Individual Randomized Trials

A predefined template in Covidence software was used to conduct data extraction independently by two out of three reviewers (J.F.R., C.B.K., M.N.H.). Extraction of the following descriptive and quantitative characteristics was performed:

1. Characteristics of the study: authorship, year, country, setting, sample size, design, methods, duration of follow-up, source of funding, conflict of interest.
2. Characteristics of the population: age, race/ethnicity, socioeconomic status, cointerventions, information regarding respondent bias, or representativeness of the included population.
3. Description of the intervention.
4. Description of the comparator group.
5. Outcomes and timepoints for outcomes, as mentioned above.

Risk of Bias and Certainty of Evidence

We used GRADE to assess the certainty of evidence, which was categorized as very low, low, moderate, and high (21). Each RCT study started at a high certainty level and was assessed for possibly being rated down based on five domains: overall risk of bias, inconsistency, indirectness, imprecision, and publication bias. Following GRADE, whenever sample size in the analysis were <100 participants, the study was downgraded for imprecision.

The criterion provided by the Cochrane Collaboration's tool for assessing the risk of bias of RCTs (18) was used. The Cochrane

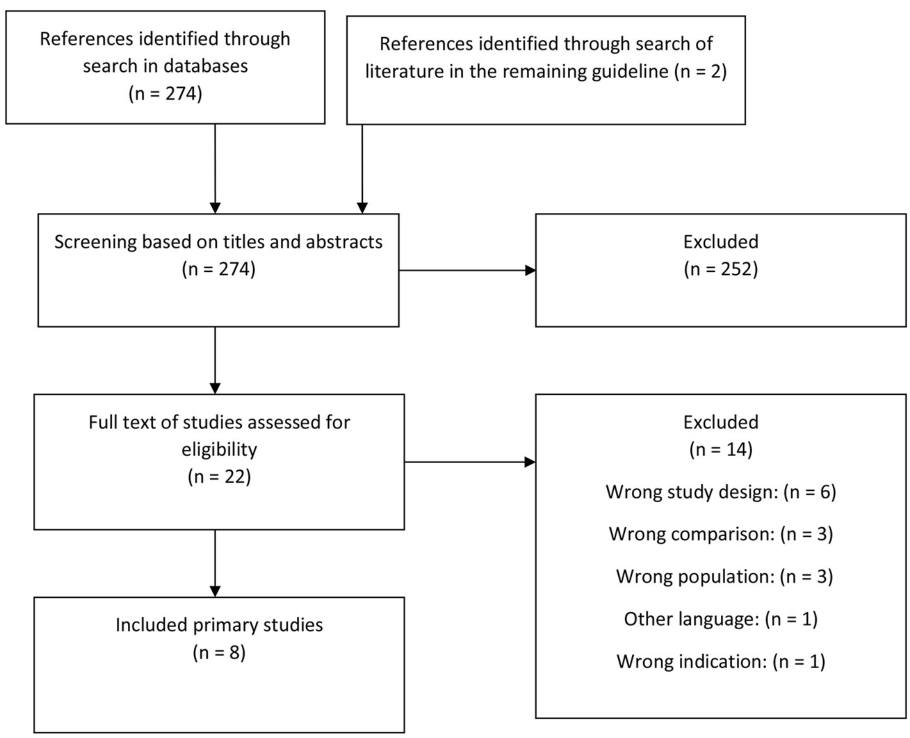


FIGURE 2 | Flowchart of primary studies.

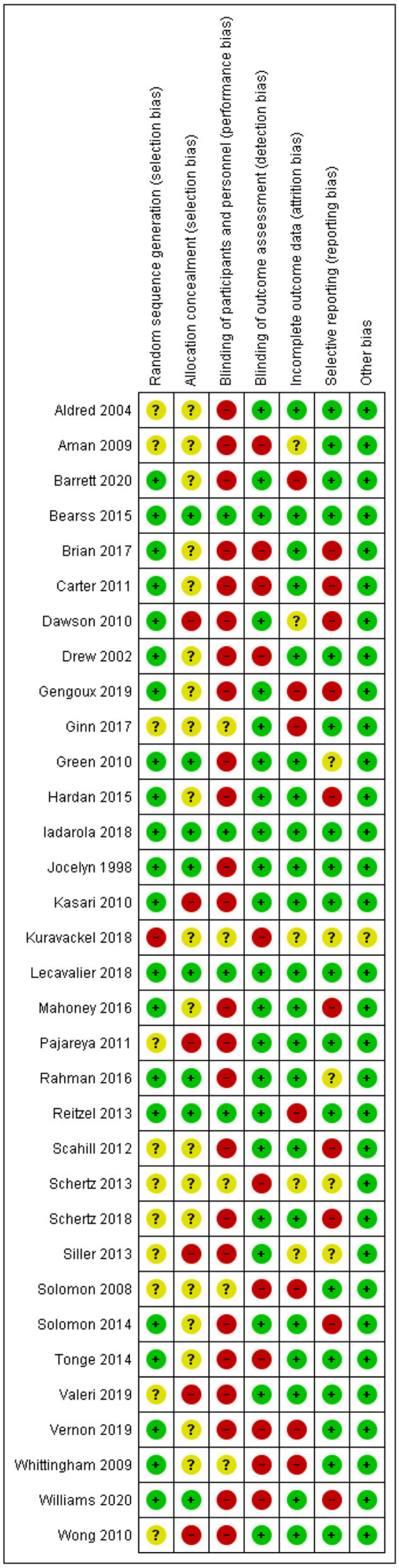


FIGURE 3 | Risk of bias.

Collaboration tool consists of seven quality domains, and each domain is classified into three levels of risk of bias (low, high, or unclear). The seven domains are: (a) sequence generation, (b) allocation concealment, (c) blinding of participants and personnel, (d) blinding of outcome assessment, (e) incomplete outcome data, (f) selective outcome reporting, and (g) other sources of bias. The quality of the included studies was assessed independently by two out of three reviewers (J.F.R., C.B.K., and M.N.H.).

Data Synthesis

The effect size was calculated using a standardized mean difference (SMD) [95% confidence interval (CI)] if data were reported as a continuous variable, and different between-study measurement methods were applied. The SMD was translated back to a mean difference for the primary outcome, parent- or clinician rated adaptive functioning using the SD from the control group from the median largest study with the lowest risk of bias.

Adverse effects were expressed as relative risk (RR) with 95% CI, and in the analysis, there were zero adverse effects in both the intervention and control groups, a risk difference meta-analysis (RD; 95% CI) was calculated.

The following subgroups of intervention targets and/or content were applied in the analysis: (a) language, (b) aggression management, (c) training in social skills, and (d) other interventions. For adverse events, the included studies had zero events in both the intervention and control groups; thus, a risk difference meta-analysis (RD; 95% CI) was calculated. A random-effect model was applied for all models. Statistical heterogeneity was quantified using I^2 statistics (23). Since only a few studies were included in each outcome, we did not perform funnel plots to address the potential risk of publication bias.

Review Manager Software (version 5.3) (The Nordic Cochrane Collaboration, Copenhagen, Denmark) (24) was used to perform the analysis and forest plots.

RESULTS

In the initial search, we identified five systematic reviews (10, 13–16) (**Figure 1**). From these, 22 RCTs were identified (25–46). Through a search for primary literature, an additional six RCTs were identified (47–52) (**Figure 2**). An additional two studies were included from reference lists in the included articles (53, 54). In total, 30 studies were included in this review and meta-analysis (25–52).

A list of the 14 excluded studies from full-text screening, including reasons for exclusion (55–68), is provided in the **Supplementary Table 3**.

Description of the Primary Studies

Characteristics of the included studies are presented in the **Supplementary Table 4**. The interventions of the included RCTs consisted of PMIs with various target groups and contents. The interventions' commonalities were the parents being direct

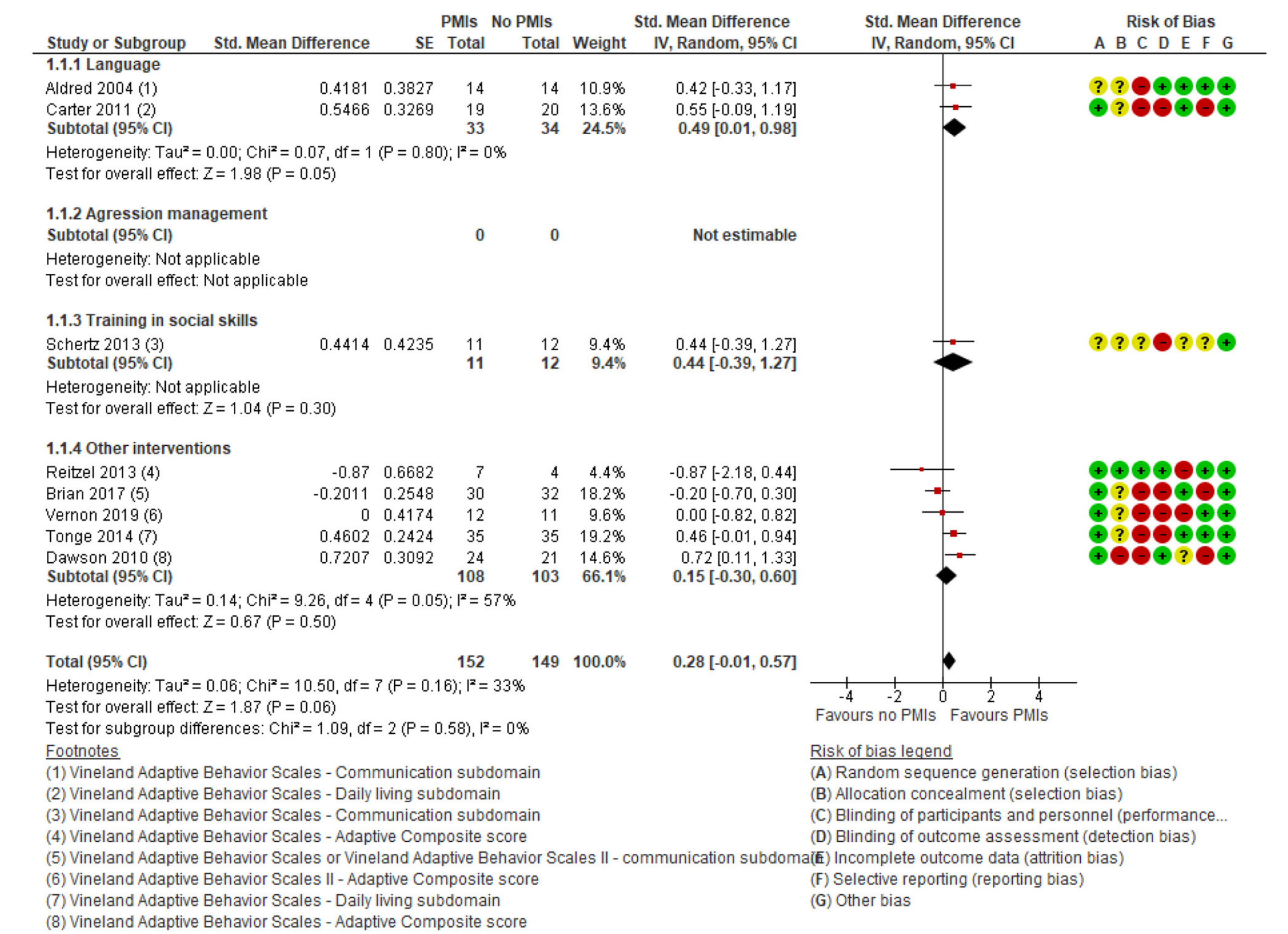


FIGURE 4 | Forest plot of comparison: PMI vs. no PMI, outcome: adaptive functioning, parent-rated, lower is better.

recipients of the intervention and the parents' intentions to implement and train applied skills with the child. In most studies, the intervention targeted specific areas of ASD (such as joint attention and social-communicative skills). However, in five studies (26, 27, 34, 42, 45), the intervention primarily focused on improving parent-child social interaction and reducing behavioral difficulties and demand-avoidant behavior. In total, parents of 1,934 children and adolescents participated in the studies, and the age range was 16 months to 17 years. Most of the trials were developed for younger children with ASD, with 23 of 30 studies including children 7 years of age and younger, and only seven studies focusing on children below 4 years of age (28–30, 36, 48, 53, 54). No studies investigated adolescents older than 14 years of age, and only four articles included children older than 11 (26, 37, 38, 42). These four interventions either targeted disruptive behavior or supported positive behavior. The intervention period in the included studies were 8 weeks-24 months.

The control groups consisted of waitlist or other passive control conditions in 11 of the studies (31, 36, 37, 42, 45–47, 49, 51, 52, 54); treatment/management as usual in 10 of the studies (25, 28, 30, 32, 39, 40, 43, 44, 48, 53); an active control with a less extensive educational program, psycho-education, placebo parent-intervention in eight of the studies; and anti-psychotic medicine (risperidone) alone in a single study (26, 27, 29, 33–35, 38, 41, 50). Four studies (36, 41, 47, 54) either did not report data predefined as primary or secondary outcomes in the present context or did not report data in a manner for them to be included in the meta-analysis. A conclusion as to whether the individual studies were rated with high, low or unclear risk of bias within each domain was reached (**Figure 3**).

Synthesis of the Results on Primary Outcome—Adaptive Functioning (Parent- and Clinician-Reported)

With respect to the primary outcome defined in this review and meta-analysis eight studies reported the effects of PMIs on parent-reported adaptive functioning (25, 28, 29, 40, 44, 48, 52, 53). There was a small but clinically relevant effect [SMD: 0.28 (95% CI:−0.01, 0.57)] (**Figure 4**), corresponding to an MD on

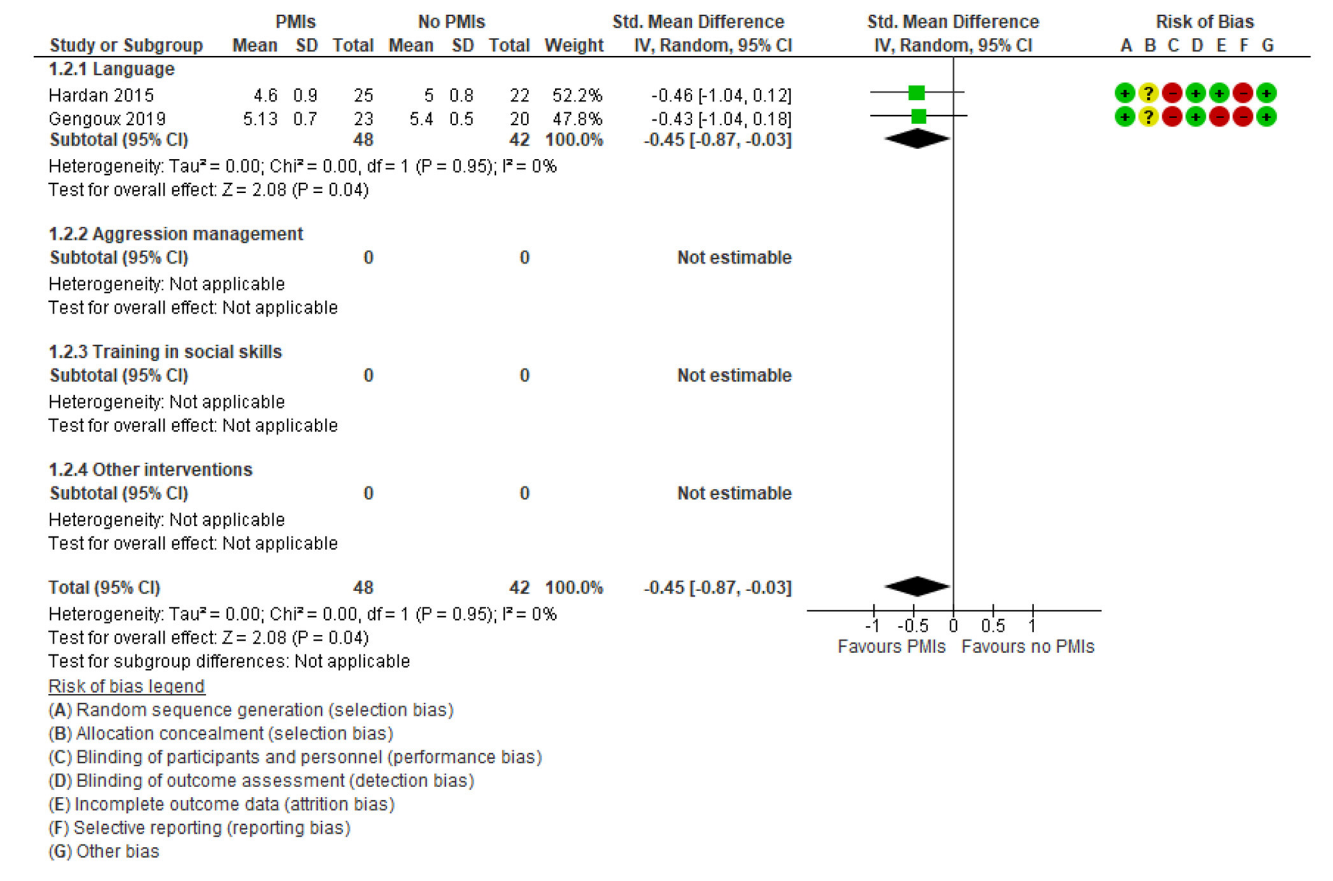


FIGURE 5 | Forest plot of comparison: PMI vs. no PMI, outcome: adaptive functioning, clinician-rated, (CGI severity), lower is better.

the Vineland scale of 3.5 [95% CI: 0.92, 6.02] calculated from the endpoint SD from the control group in Vernon (52). There was a low degree of heterogeneity ($I^2 = 10$). All studies included in the meta-analysis used the Vineland Adaptive Behavior Scales 1st or 2nd Edition to assess adaptive functioning; however, they did not all report scores on the same sub-domains. For the meta-analysis, the adaptive composite score was preferred; when not reported, the daily living subdomain was secondarily prioritized. However, three of the included studies (25, 48, 53) did not report any of these scores; for these, the Communications subdomain outcome was used for the meta-analysis. The outcomes were considered parent-rated when based on a parent-rated questionnaire or the clinicians rating a semi-structured interview with parents. One study Tonge et al. (44) combined the parent interview with a simultaneous observation of the child but was categorized as parent-rated since the main information for the scoring was still derived from the parents.

The results showed no subgroup differences in parent-rated adaptive functioning between the different targets of parent-mediated interventions ($p = 0.58$).

For the primary outcome parent-rated adaptive functioning there was low certainty in the effect estimates due to rating down for serious risk of bias due to lack of blinding of participants and outcome assessors, as well as serious risk of imprecision due to few participating children. In conclusion, PMIs may slightly improve parent-rated adaptive functioning.

Only 2 studies of PMIs focusing on language reported clinician-rated adaptive functioning (33, 49), and the studies found no effect of PMIs [SMD −0.45 (95% CI: −0.87, −0.03) (**Figure 5**) corresponding to a MD on CGI severity scale: −0.36 (95% CI: −0.70, −0.02)]. The degree of heterogeneity was low ($I^2 = 0\%$). There was very low certainty in the evidence on clinician-rated adaptive functioning due to rating down for serious risk of bias due to problems with lack of blinding of participants and outcome assessors and very serious risk of imprecision due to few participating children and wide confidence intervals. Thus, it is uncertain if the PMIs increase the clinician-rated adaptive functioning.

Synthesis of the Results on Secondary Outcomes

A single study (44) reported on parent-rated adaptive functioning after 6 months of follow-up on Vineland Adaptive Behavior Scales Daily Living subscale. This study did not report an end of treatment effect, thus was included in the meta-analysis of the primary outcome (**Figure 4**). The study showed significant improvement in the daily living subdomain of VABS [effect size −0.62 (95% CI: −1.10, −0.13)] and the socialization subdomain

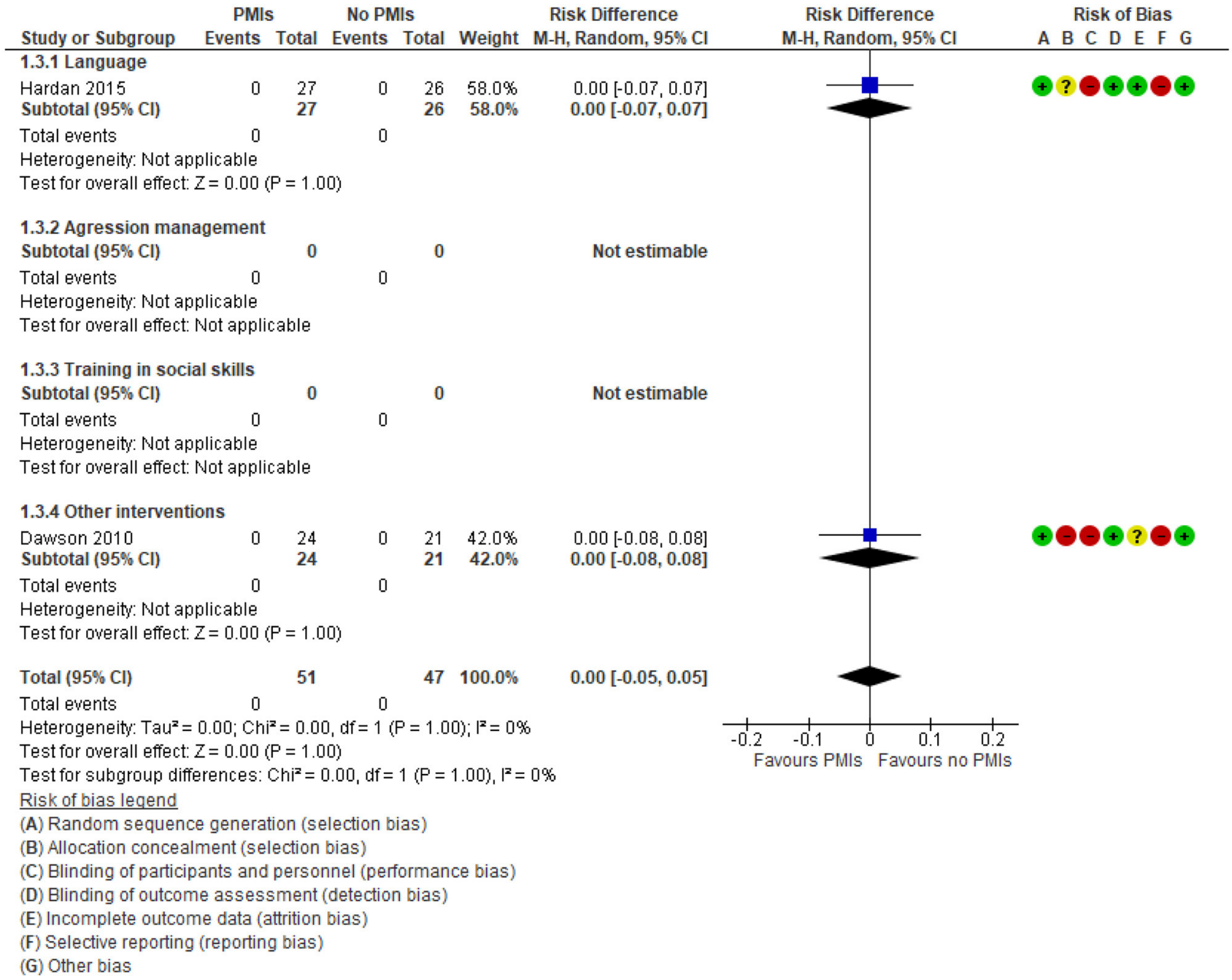


FIGURE 6 | Forest plot of comparison: PMI vs. no PMI, outcome: adverse effects.

[effect size−0.60 (95% CI: −1.09, −0.12)] in the PMI group compared to a psychoeducative group (44). Adverse effects were only reported in 2 of 30 studies (29, 33) and reported no adverse effects in any of the two groups (**Figure 6**). One of the studies compared the Early Start Denver Model to treatment as usual (29), and the other compared Pivotal Response Training to 12 sessions of psychoeducation (33). There was low certainty in the evidence due to rating down for very serious risk of imprecision because of few participating children and few studies reporting adverse effects. Thus, PMIs may not cause substantial adverse effects.

Seven studies reported the effect of PMIs on parent-rated core symptoms of ASD (30, 31, 33, 35, 43, 44, 49). No relevant effect was found [SMD: 0.06 (95% CI: −0.18, 0.30)] (**Figure 7**). The degree of heterogeneity was low for the parent-rated outcome (I^2 = 20%). The results showed no subgroup differences between the different targets of PMIs, e.g., language and disruptive behavior ($p = 0.91$). There was low certainty in the evidence due to rating down for serious risk of bias because of lack of blinding of participants and outcome assessors, as well as serious risk of imprecision due to few participating children. Thus, PMIs may result in little or no clinical relevant change in parent-rated autism core symptoms.

Nine studies reported a small effect of PMIs on clinician-rated core symptoms of ASD [SMD: −0.35 (95% CI: −0.71, 0.02)] (**Figure 8**) (25, 28, 29, 32, 35, 39, 48, 50, 52). The degree of heterogeneity was considerable for the clinician-rated outcome ($I^2 = 69\%$). The results showed no subgroup differences between the different targets of PMIs, e.g., language and disruptive behavior ($p = 0.67$). There was low certainty in the evidence due to rating down for serious risk of bias because of lack of blinding of participants and outcome assessors, as well as serious risk of imprecision due to few participating children. Thus, PMIs may slightly improve clinician-rated autism core symptoms.

Regarding parent-rated disruptive behavior, there was a moderate and clinically relevant effect of PMIs [SMD: −0.55

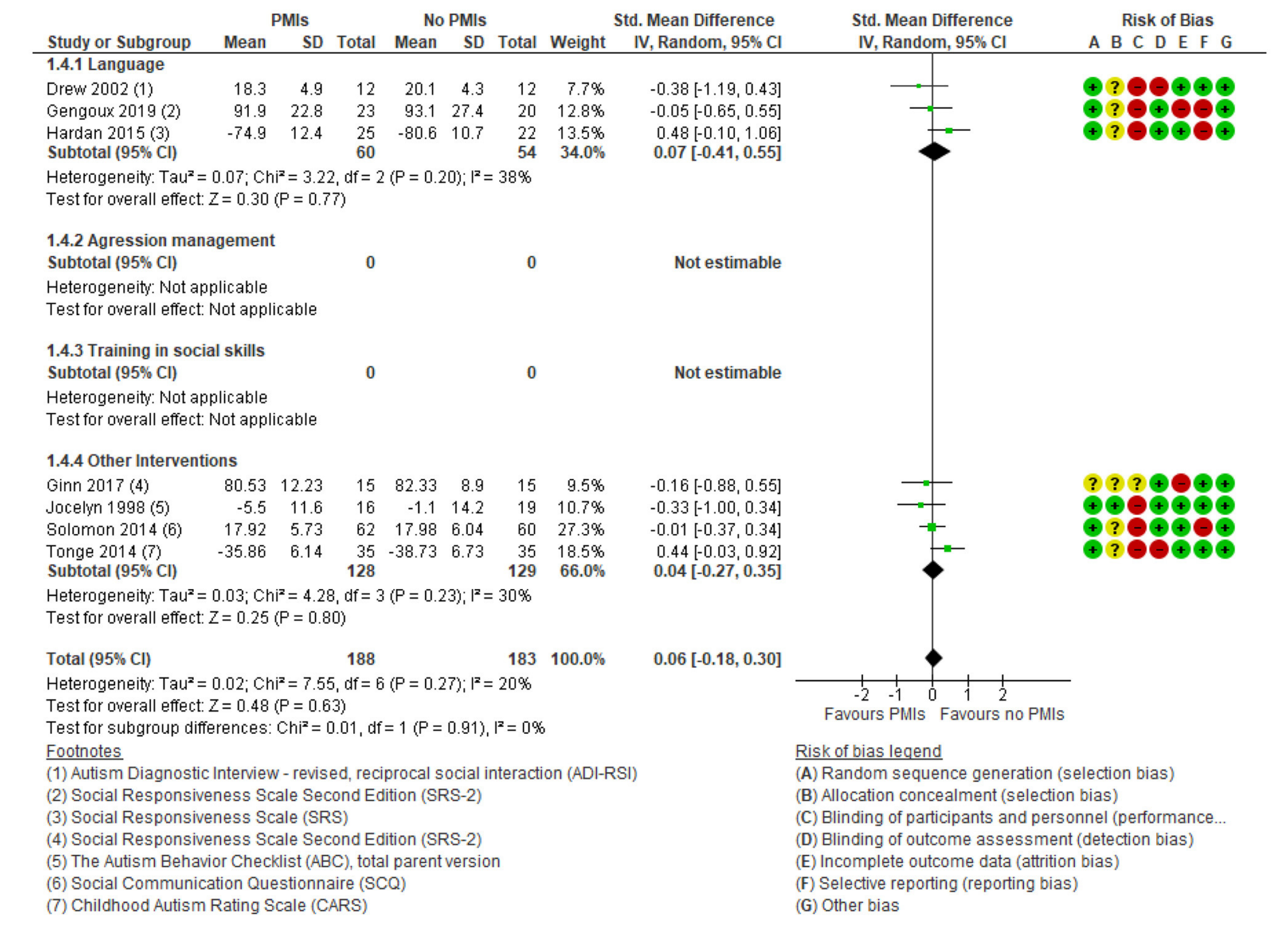


FIGURE 7 | Forest plot of comparison: PMI vs. no PMI, outcome: autism core symptoms, parent-rated.

(95% CI: −0.74, −0.36)] (**Figure 9**). None of the language interventions reported on this outcome. There was a low degree of heterogeneity ($I^2 = 26\%$), and the results showed no subgroup differences between the different targets of PMIs ($p = 0.53$). There was moderate certainty in the evidence due to rating down for serious risk of bias because of lack of blinding of participants and outcome assessors. Thus, PMIs probably improves parent-rated disruptive behavior considerably.

Parental well-being showed a small and not clinically relevant effect of PMIs [SMD: −0.16 (95% CI: −0.32, −0.01)] (**Figure 10**). There was a low degree of heterogeneity ($I^2 = 6\%$), and the results showed no subgroup differences between the different targets of PMIs ($p = 0.64$). There was low certainty in the evidence due to rating down for very serious risk of imprecision because of few participating children and wide confidence intervals (**Supplementary Table 5**). Thus, PMIs may result in little or no clinically relevant change in parental well-being.

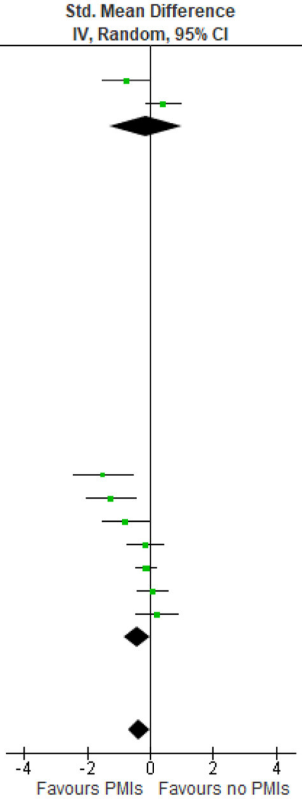
None of the included studies reported on child anxiety or parent-rated quality of life of the child.

DISCUSSION

The current systematic review identified 30 RCTs of PMIs for children and adolescents with ASD. The results showed a clinically relevant effect on parent-rated adaptive functioning but no effect when the outcome was rated by a clinician. Moreover, PMIs may be a valuable treatment for disruptive behavior in children and adolescents with ASD. There was no effect on core symptoms of ASD (both parent- and clinician-rated), parent-rated adaptive functioning after 6 months or adverse effects. No studies reported on anxiety or parent-rated quality of life of the child. The certainty of the effect estimates reported in the studies was moderate to very low due to serious risk of bias and very serious risk of imprecision; thus, the effect of PMIs on children and adolescents with ASD is still uncertain. A qualitative synthesis of the studies revealed significant variability across studies.

Meanwhile, previous reviews (10, 13–16) presented evidence in favor of PMIs and emphasized the positive effect of PMIs on joint attention and social interaction in the parent-child dyad,

Study or Subgroup	PMIs Mean	PMIs SD	PMIs Total	No PMIs Mean	No PMIs SD	No PMIs Total	Weight	Std. Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F G
1.5.1 Language									
Aldred 2004 (1)	11.8	6.4	14	16.1	4.4	14	9.7%	-0.76 [-1.53, 0.01]	? ? - + + + +
Carter 2011 (2)	15.56	4.56	25	13.6	4.89	25	12.2%	0.41 [-0.15, 0.97]	+ ? - - + - +
Subtotal (95% CI)			**39**			**39**	**21.8%**	**-0.14 [-1.29, 1.00]**	
Heterogeneity: Tau² = 0.56; Chi² = 5.77, df = 1 (P = 0.02); I² = 83%									
Test for overall effect: Z = 0.25 (P = 0.80)									
1.5.2 Agression management									
Subtotal (95% CI)			**0**			**0**		**Not estimable**	
Heterogeneity: Not applicable									
Test for overall effect: Not applicable									
1.5.3 Training in social skills									
Subtotal (95% CI)			**0**			**0**		**Not estimable**	
Heterogeneity: Not applicable									
Test for overall effect: Not applicable									
1.5.4 Other interventions									
Vernon 2019 (3)	4.92	1.51	12	7.82	2.18	11	7.9%	-1.50 [-2.45, -0.56]	+ ? - - - + +
Pajareya 2011 (4)	-2.9	2	15	-0.8	1.2	16	9.6%	-1.25 [-2.03, -0.47]	? - - + + + +
Valeri 2019 (5)	4.9	1.2	15	6	1.5	15	9.9%	-0.79 [-1.53, -0.04]	? - - + + + +
Dawson 2010 (6)	7	1.9	24	7.3	1.8	21	11.8%	-0.16 [-0.75, 0.43]	+ - - + ? - +
Green 2010 (7)	15.7	6	77	16.5	5.7	75	15.1%	-0.14 [-0.45, 0.18]	+ + - + + ? +
Brian 2017 (8)	6.9	2.07	30	6.72	2.56	32	12.9%	0.08 [-0.42, 0.57]	+ ? - - + - +
Jocelyn 1998 (9)	-11.6	18.1	16	-15.1	15.5	19	10.9%	0.20 [-0.46, 0.87]	+ + - + + + +
Subtotal (95% CI)			**189**			**189**	**78.2%**	**-0.41 [-0.81, -0.01]**	
Heterogeneity: Tau² = 0.19; Chi² = 19.05, df = 6 (P = 0.004); I² = 69%									
Test for overall effect: Z = 2.00 (P = 0.05)									
Total (95% CI)			**228**			**228**	**100.0%**	**-0.35 [-0.71, 0.02]**	
Heterogeneity: Tau² = 0.20; Chi² = 25.91, df = 8 (P = 0.001); I² = 69%									
Test for overall effect: Z = 1.88 (P = 0.06)									
Test for subgroup differences: Chi² = 0.19, df = 1 (P = 0.67), I² = 0%									



Footnotes
(1) Autism Diagnostic Observation Schedule (ADOS), total score
(2) ADOS total score
(3) ADOS-2 CSS (Calibrated severity score)
(4) Childhood Autism Rating Scale (CARS)
(5) ADOS-2 CSS
(6) ADOS-2 CSS
(7) ADOS total score
(8) ADOS-2 CSS
(9) The Autism Behavior Checklist, rated by psychologist

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance...
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

FIGURE 8 | Forest plot of comparison: PMI vs. no PMI, outcome: autism core symptoms, clinician-rated.

which was not among the prespecified outcomes of this review (10, 15, 16).

This meta-analysis suggests a clinically relevant effect of PMIs for children and adolescents with ASD on parent-rated adaptive functioning, which was not found in the review and meta-analysis by Oono et al. (10). This may be explained by the inclusion of more studies in our review compared to Oono et al. (10) and thus an increase in power. This is a strong indicator of the efficacy of PMIs, since none of the interventions directly affects adaptive functioning, and the positive outcome on adaptive functioning could be a cascading effect of the PMIs.

The results from the meta-analysis align with results from previous reviews regarding favorable results of child disruptive behavior (14, 15). Interestingly, interventions targeting behavior as well as social communication and joint attention for younger children demonstrated positive effects of PMIs on disruptive behavior (50).

Previous reviews have also identified minor improvements in core symptoms of ASD in children participating in PMIs (10, 13), which was not confirmed in this meta-analysis. However, the clinician-rated core symptom measures favored of the PMIs, with a non-significant but clinically relevant effect.

As early interventions have been developed for children with ASD over the past several years (69), it is expected that most studies target younger children when searching for PMIs. This was confirmed in the current review, where only two of 30 included studies targeted children 5 years of age and older (38, 42), although the age range of the study population in this review 18 months to 17 years. The age range was suggested by the scientific committee, and interest associations which were both appointed by the

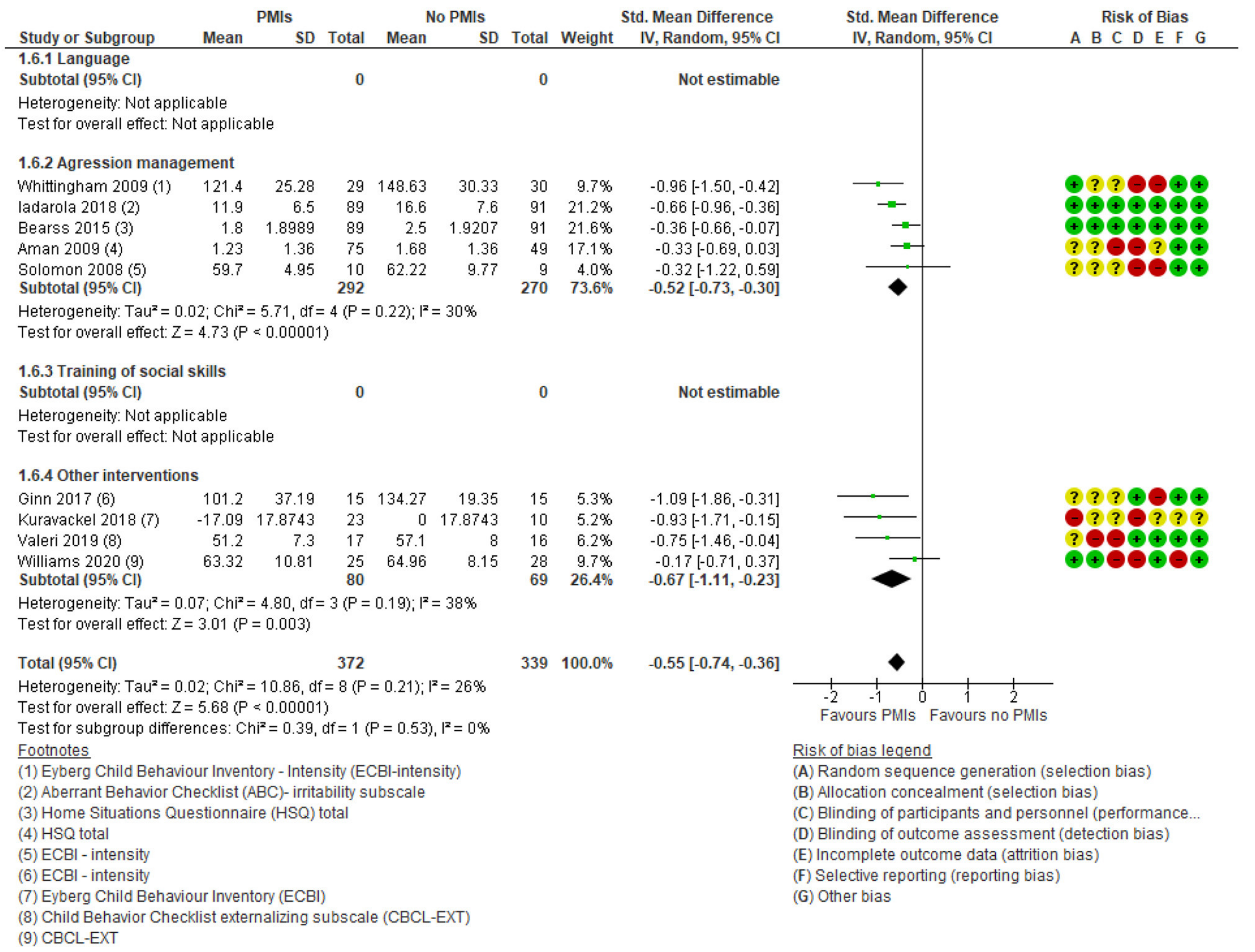


FIGURE 9 | Forest plot of comparison: PMI vs. no PMI, outcome: disruptive behavior, parent-rated.

Danish Health Authority to develop national Clinical Practice Guidelines in Denmark. The inclusion of both children and adolescents was relevant for most of the frameworks in the guideline development and was therefore applied to all of the PICOs.

Typically, interventions targeting social communication are recommended to younger children. This underlines the necessity of using interventions appropriate for the child's age and developmental stage. With respect to the remaining secondary outcomes, a clinically relevant effect regarding clinician rated core symptoms of ASD was seen in favor of PMIs. Moreover, the interventions targeting conduct problems were provided to younger children with ASD aged 2–9 years of age (27, 34, 45); interestingly, some of the studies extended the intervention to be applied to children 4 and 5 years of age to 12 and 13-year-old children (26, 42), suggesting that these kinds of interventions are effective at improving positive behavior in both younger and older children.

Strengths and Limitations of the Included Studies

A critical limitation of the included studies is that different outcome measures were used to assess the same effect; and when they used the same assessment tools, they were administered differently. For example, the Vineland Adaptive Behavior Scale (VABS) was used to assess adaptive functioning, and it was administered either as an interview or a parent-reported questionnaire (70). Another limitation is a generally small sample size in several studies.

Strengths and Limitations of the Methodology of the Present Systematic Review and Meta-Analysis

A major strength of this systematic review and meta-analysis is that it was performed according to principles described in GRADE and PRISMA as well as the PICO framework.

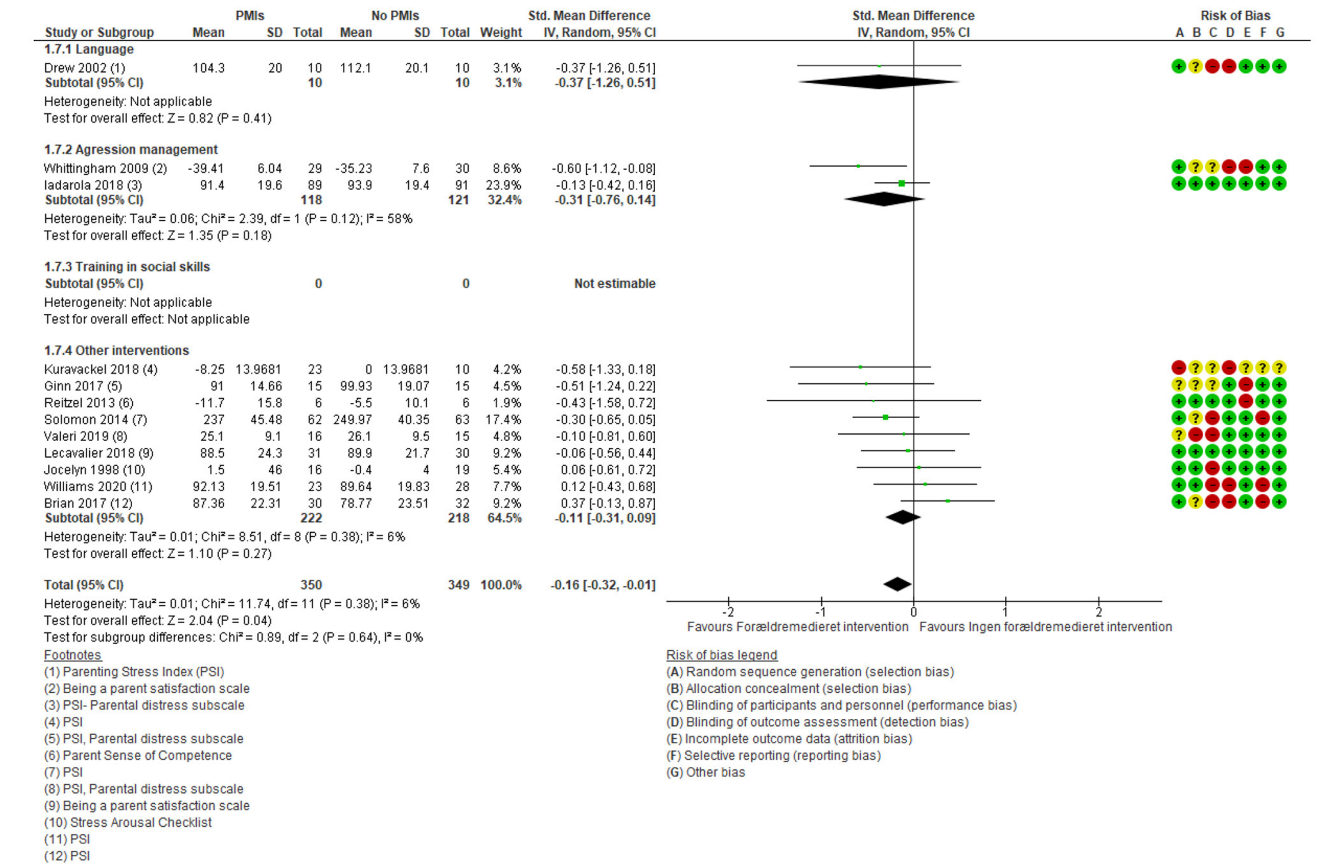


FIGURE 10 | Forest plot of comparison: PMI vs. no PMI intervention, outcome: parental well-being.

However, from a resource saving perspective, we chose a stepwise literature search by initially searching for existing reviews to identify eligible studies, followed by a search for primary studies based on the latest search date of an existing high-quality systematic review, and finally screening reference lists of included studies and conferring content experts (working group at the Danish Health Authority). *Post-hoc*, we identified three articles with a total of 307 participants (71–73) (**Supplementary Table 6**) that were not identified in any of the included reviews by consulting content experts or in the reference list of the included studies. Since the ability to identify relevant studies is mainly dependent on the scope and search quality of the existing reviews, we acknowledge that our search may have been limited regarding both search specificity (recall) and sensitivity (precision). However, the results did not change substantially when performing *post-hoc* sensitivity analysis and including results from the unidentified studies. However, the increased power strengthened the positive results of PMIs on both parent-rated adaptive functioning [SMD: 0.27 (95% CI: 0.02, 0.52)] and clinician-rated autism core symptoms [SMD: −0.34 (95% CI: −0.64, −0.03)] (**Supplementary Table 7**).

Future Research

To estimate the effect of PMIs, further research with large high-quality RCTs investigating manualized interventions and following standardized principles for trial design, content and reporting is needed. Interventions previously investigated in RCTs need replication studies to build on the evidence of the intervention. In future research, it could be interesting to investigate the association between contextual factors, such as age and effect size, to address which children are most likely to benefit from PMIs. A need for measurement consistency still remains and is recommended in future research, to improve comparison between studies. Furthermore, there is a need to assess a core outcome set to investigate the importance of anxiety, parent-rated adaptive functioning after a minimum of 6 months and parent-rated child's quality of life.

CONCLUSION

When PMIs are delivered to children with ASD, it is recommended to use manualized interventions targeting autism spectrum disorders, and the characteristics of the included PMIs are that the child should be directly or indirectly involved in the intervention. However, the parents are the primary participants in the treatment and must actively train the different skills included in the intervention, both during the sessions and/or at home between sessions. The intervention must be adapted to the age and development of the child.

Based on the current evidence, there appears to be a benefit of providing PMIs to parents of children and adolescents with ASD concerning adaptive functioning and disruptive behavior reported by the parents. Perhaps by enhancing the parents' understanding and management of their child's pervasive disorder, it seems that the parents are empowered, which is supported by the trend toward improving parental well-being. As expected, there were minor differences between the intervention and control groups in changing core symptoms of ASD. PMIs may slightly improve clinician-rated autism core symptoms. Even though there were few reports on adverse effects, any adverse effects of the PMIs were considered insignificant and few. Adverse effects should be included in future studies. However, since the evidence base's certainty is low, the limitations of the current literature hinder the possibility of drawing any solid conclusions, and more well-designed, high-quality clinical trials of sufficient duration are required.

AUTHOR CONTRIBUTIONS

MR, JR, BP, CK, ST, and MH: methodology. MR, JR, BP, CK, and MH: data curation. MH: formal analysis, visualization, supervision, and project administration. All authors investigation, resources, writing—original draft preparation, writing—review and editing, funding acquisition, and read and agreed to the published version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.773604/full#supplementary-material

Supplementary Table 1 | PRISMA checklist.

Supplementary Table 2 | Search description.

Supplementary Table 3 | Characteristics of excluded studies.

Supplementary Table 4 | Characteristics of the included studies.

Supplementary Table 5 | Summary of findings table.

Supplementary Table 6 | Characteristics of *post-hoc* identified studies.

Supplementary Table 7 | *post-hoc* analyses.

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Effects of Creative Movement Therapies on Social Communication, Behavioral-Affective, Sensorimotor, Cognitive, and Functional Participation Skills of Individuals With Autism Spectrum Disorder: A Systematic Review

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Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder affecting multiple developmental domains including social communication, behavioral-affective, sensorimotor, and cognitive systems. There is growing evidence for the use of holistic, whole-body, Creative Movement Therapies (CMT) such as music, dance, yoga, theater, and martial arts in addressing the multisystem impairments in ASD. We conducted a comprehensive quantitative and qualitative review of the evidence to date on the effects of CMT on multiple systems in individuals with ASD. The strongest evidence, both in terms of quantity and quality, exists for music and martial arts-based interventions followed by yoga and theater, with very limited research on dance-based approaches. Our review of 72 studies ($N = 1,939$ participants) across participants with ASD ranging from 3 to 65 years of age suggests that at present there is consistent evidence from high quality studies for small-to-large sized improvements in social communication skills following music and martial arts therapies and medium-to-large improvements in motor and cognitive skills following yoga and martial arts training, with insufficient evidence to date for gains in affective, sensory, and functional participation domains following CMT. Although promising, our review serves as a call for more rigorous high-quality research to assess the multisystem effects of CMT in ASD. Based on the existing literature, we discuss implications of our findings for autism researchers and also provide evidence-based guidelines for clinicians to incorporate CMT approaches in their plan of care for individuals with ASD.

Keywords: creative movement, music, dance and movement, yoga, theater, martial arts, autism spectrum disorder (ASD), interventions

INTRODUCTION

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder that affects multiple domains including the social communication, behavioral-affective, sensorimotor, and cognitive systems. Currently, around 1 in every 54 children in the United States qualify for a diagnosis of ASD (1) and boys are almost four times more likely to be diagnosed with ASD than girls of the same age (2). The hallmark impairments in ASD include poor reciprocal social interactions, difficulties with verbal and non-verbal communication, and restricted and repetitive behaviors and interests (3). For instance, children with ASD have difficulties in responding to social stimuli, sharing their play with peers and caregivers, developing and maintaining relationships, as well as understanding body language, gestures, and facial expressions of others (4–8). In terms of behavioral-affective impairments, children demonstrate repetitive and stereotyped behaviors such as finger flicking and hand flapping, highly circumscribed and restricted interests, insist on sameness relative to daily routines/schedules, demonstrate extreme distress to small changes in daily routines, and difficulties with transitions between activities (2, 9). Moreover, children may also have sensory symptoms including hypo- and hyper-sensitivity to sensory input and unusual responses to sensory stimuli in multiple domains including auditory, tactile-proprioceptive, vestibular, olfactory, and visual senses (9–12). In addition, children may also demonstrate disruptive behaviors such as aggression, tantrums, defiance, and self-injurious behaviors, as well as increased levels of negative affect (10, 11, 13, 14). Moreover, children with ASD also demonstrate cognitive difficulties such as attentional deficits, impaired decision-making, and impaired executive functioning (i.e., working memory, cognitive flexibility, self-control, generativity, and planning), with deficits being more pronounced during open-ended compared to structured settings (15–17).

Besides the diagnostic symptoms, children with ASD also exhibit a variety of other impairments within the sensorimotor domain that may lead to significant challenges in their activities of daily living (18–26). Although the exact prevalence estimates of motor impairments in ASD vary widely across studies from around 35% to over 85%, there is a growing consensus that children diagnosed with ASD exhibit motor impairments in gross and fine motor skills (e.g., bilateral coordination, gait and postural stability, handwriting, manual dexterity skills, and visuomotor control), as well as socially-embedded motor skills, including imitation, praxis (performance of skilled functional movement sequences/gestures), and interpersonal synchrony (ability to synchronize movements with those of another person) (19, 22, 27–38). Several studies have documented the association between motor impairments and severity of core autism symptoms in social communication, repetitive behaviors, and cognitive domains (22, 39–47). Moreover, sensorimotor difficulties could limit children's social participation and affect their activities of daily living including self-care, mobility, and leisure (41, 48–51). In short, children with ASD have multisystem impairments that need to be addressed through holistic evidence-based interventions (22, 24, 52–54).

Current standard interventions for ASD focus primarily on addressing the core social communication and behavioral impairments. Some popular evidence-based approaches include Applied Behavioral Analysis (ABA) (55), Treatment and Education of Autism and related Communication Handicapped Children (TEACHH) (56), Picture Exchange Communication System (PECS) (57), as well as developmental approaches such as Floor time (58), Social Communication, Emotional Regulation and Transactional Support Model (SCERTS) (59), Early Start Denver Model (ESDM) (60), and Pivotal Response Training (PRT) (61, 62). ABA-based approaches are considered the gold standard treatment for ASD and use principles of operant conditioning and intensive structured task practice to promote social communication and behavioral skills (55, 63–68). Similarly, the TEACHH approach uses visual cues to promote learning through picture schedules and also provides guidelines to increase structure and consistency in the environment, supplies-used, and therapists working with children with ASD (56, 69). Conventional therapies are usually very structured, adult-driven, and use a more sedentary approach (67, 70, 71). On the other hand, developmental approaches facilitate age-appropriate developmental skills such as joint attention, play, and imitation using child-preferred, play-based therapeutic activities within naturalistic settings (67, 70, 72). However, interestingly, both conventional and developmental approaches do not focus on addressing the sensorimotor impairments that are clearly highly prevalent in ASD (22, 46). This highlights a dire need to expand therapeutic interventions to address not just the core impairments but also the multiple co-morbidities in ASD.

Over the past several years, there has been a growing interest in exploring the effects of novel, alternative and integrated behavioral treatment approaches in addressing the multisystem impairments in ASD (27, 73–84). These holistic, whole-body movement-based, multisystem treatment approaches include but are not limited to structured physical activity, music therapies, yoga, martial arts, dance, and theater-based interventions (53, 73, 85–89). For the purpose of this review, we use the term "Creative Movement Therapy (CMT)" as an umbrella term that encompasses alternative behavioral interventions including music, dance, yoga, martial arts, and theater. The rationale for grouping these interventions together is that all these approaches use movement to integrate the social, emotional, cognitive, and physical aspects of the individual. Approaches involving CMT differ from conventional ASD interventions in that they are based in whole-body movement and promote self-expression (e.g., theater), creativity (e.g., innovative ways of moving body and using props in dance and theater), and improvisation (e.g., music making using instruments, moving to the rhythm of music). These interventions typically encourage child-led activities, playful exploration, and are therefore inherently more enjoyable and motivating for children with ASD (53, 90). From a theoretical perspective, CMT approaches are grounded in the ecological Dynamical Systems Theory (DST) (91, 92) and the Shared Affective Motion Experience (SAME) theory (93). The DST emphasizes that basic perception-action cycles of bodily movement form the basis for higher-order social communication and cognitive skills (82). Similarly, the SAME theory suggests that music- and movement-based experiences are multimodal in nature and activate similar "mirror" networks in the brain of participants, thereby forming the basis for social, emotional, and motoric connectedness between them (83). This is especially crucial for individuals with ASD given their deficits in multimodal integration stemming from long-distance brain under-connectivity (94–96).

In addition, given their very nature, CMT interventions are known to have multisystem effects on the sensorimotor domains as well as on the social communication, cognitive/attentional, and behavioral/affective domains in individuals with ASD. For instance, practicing simple and complex movement sequences during choreographed dance routines provides opportunities to promote rhythmic synchronization, multi-limb coordination, balance, gait, and postural control in participants (85). On the other hand, music-based group activities provide a medium for children with ASD to connect with social partners, improve communication abilities, and lead to greater positive affect/engagement (4, 6, 53, 93, 97–103). Similarly, short bouts of exercise that incorporate self-discipline, goal-oriented behavior, multistep action sequences, and sustained focus, as seen with any martial arts-based techniques, could enhance cognitive abilities such as executive functioning in children with ASD (104).

Although the preliminary evidence is promising, currently, it is unclear if CMT approaches can be considered as evidence-based interventions in ASD. Therefore, this review aims to synthesize the literature to date on the effects of CMT on social communication, behavioral-affective, cognitive, sensorimotor, and functional/participation skills of individuals with ASD across the lifespan (note that for the purpose of the review, we excluded studies that focused on structured physical activity, animal-assisted therapies, or technology-based interventions given the clear differences in the key intervention components of CMT approaches compared to the above-mentioned approaches). A few previous reviews have assessed the effects of CMT in children with ASD (75, 76, 78, 105). However, most of them have been restricted to examining the effects of a single type of CMT in individuals with ASD. It would be crucial to compile information on different CMT approaches to compare and contrast the differential effects of these approaches on multiple systems in ASD. Moreover, except a couple of reviews by Zou et al. and Geretsegger et al., none of the other reviews conducted a risk of bias analysis for the reviewed studies or calculated effect size (ES) estimates based on data reported in the reviewed literature (75, 105). Assessing methodological quality of studies through a risk of bias analysis enables researchers to estimate the level of confidence in study findings and guides interpretation of study results. Similarly, ES estimates from individual studies indicate the magnitude of the treatment effect and are thus crucial to evaluate the clinical utility of specific treatment approaches. We address these gaps in the literature by providing a comprehensive review of empirical reports studying the effects of CMT approaches through August 2021 in children with ASD. Specifically, we (i) summarize the narrative literature and compare the efficacy of different types of CMT in addressing multisystem impairments in individuals with ASD, and (ii) provide quantitative ES estimates for outcome measures addressed using CMT approaches to objectively evaluate the clinical importance of CMT for individuals with ASD.

METHODS

Search Protocol

We reviewed literature from four different electronic databases related to allied health, psychology, physical therapy/kinesiology, and education, namely, PubMed (1950–2021), PsycINFO (1969–2021), Scopus (1966–2021), and CINAHL (1937–2021). The combination of key terms used included, (a) "*music*," "*dance*," "*yoga*," and "*play*," (b) "*intervention*," "*therapy*," and (c) "*autism*" (please see **Appendix 1** for details of search strategy). We also conducted additional hand searches of reference sections of included studies and previous review papers to identify missed literature through August 2021.

Eligibility Criteria

We included studies published in peer-reviewed journals that assessed the effects of creative movement and play-based therapies in individuals with ASD using experimental or quasi-experimental, longitudinal study designs. Studies were excluded based on the following criteria: (a) only included individuals with other developmental disabilities such as Cerebral Palsy, Down's Syndrome, Attention Deficit Hyperactivity Disorder, Intellectual disability, Spina Bifida, Dyslexia, Learning Disability, etc. [note that studies ($N = 5$) that recruited mixed samples i.e., individuals with ASD and individuals with other developmental diagnoses were included since we wanted the review to be comprehensive and inclusive of all studies that recruited samples of individuals with ASD], (b) review papers, case-studies, qualitative studies, purely narrative reports, observational studies or reports describing the protocol for a future study, (c) interventions directed solely toward parents/primary caregivers of individuals with ASD, (d) studies that used structured physical activity, animal-assisted therapies, or technology-based interventions in ASD, (e) reports in languages other than English, and (f) gray literature including theses and dissertations.

Data Extraction and Evaluation

After screening 2,643 articles using our eligibility criteria [PubMed (1,354), PsycINFO (821), Scopus (267), and CINHAL (201)] and removing duplicates, 72 articles qualified for our review. Two trained research assistants and the last author screened titles and abstracts of the 2,643 articles based on our eligibility criteria. When necessary, full texts of articles were reviewed to assess eligibility of the study (see **Figure 1** for details of search process). All three coders agreed in their ratings for 90% of studies. Disagreements between coders for study inclusion were resolved through discussions and consensus scoring.

Risk of Bias Assessment

We employed the Physiotherapy Evidence Database (PEDro) scale and the NIH quality assessment tool (106, 107) to assess risk of bias in reviewed studies. The PEDro scale was used to evaluate the internal and external validity of randomized controlled trials (RCTs) and controlled clinical trials (CCT's) included within our

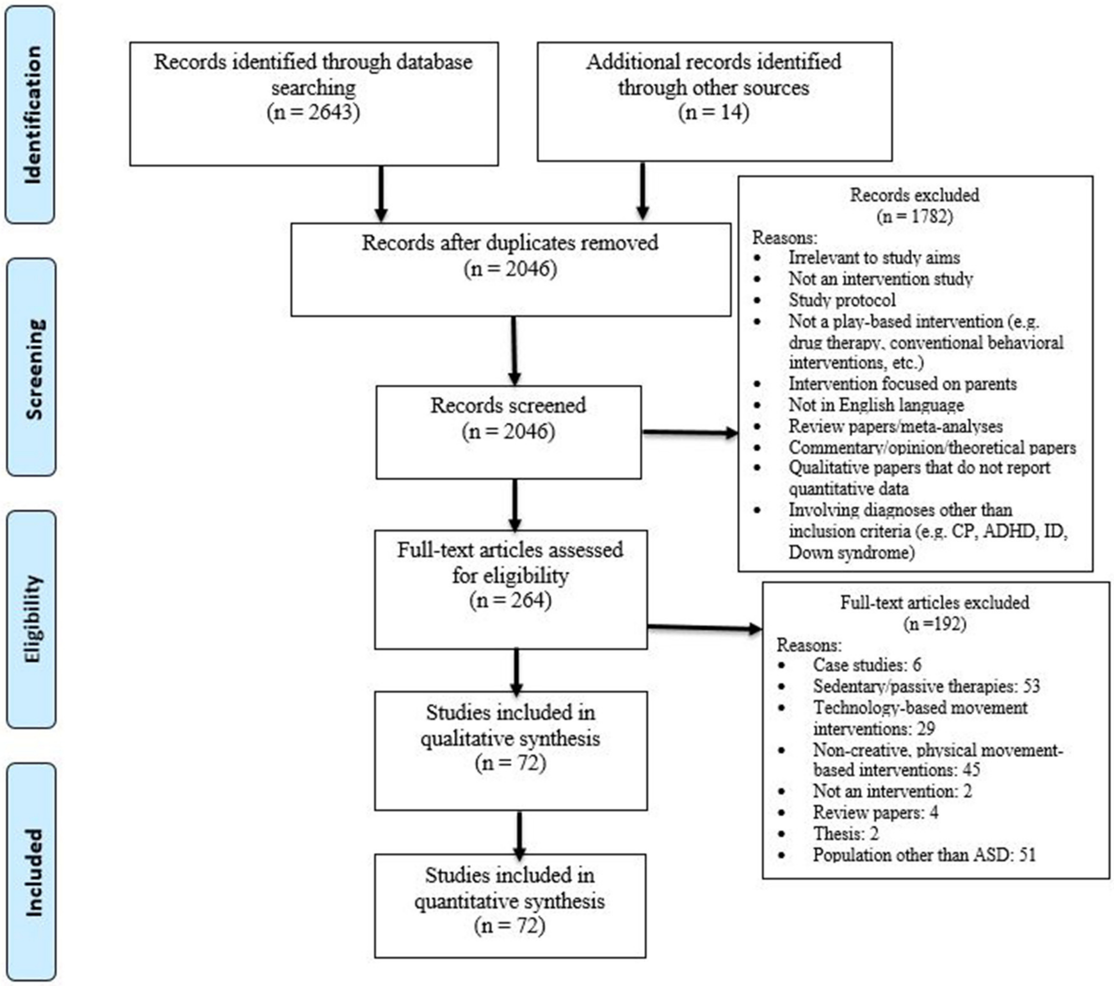

FIGURE 1 | PRISMA flow diagram of search strategy and study selection process.

review. The PEDro has a total of 11 items which are scored on a dichotomous scale (No = 0, Yes = 1) of which 10 items are scored for each RCT/CCT to obtain a study score out of a maximum possible score of 10 (first item on the PEDro is not included in the total score) (106). Studies with a PEDro score ≥ 6 are classified as having low risk of bias. For single group pre-post designs, we used the NIH quality assessment tool to assess risk of bias (107). The NIH tool comprises 12 items that are scored on a dichotomous scale (No = 0, 1 = Yes) to assess internal validity of reviewed studies. Questions 6, 7, 9, and 10 include multiple questions per item. For these questions, if studies satisfied all criteria listed in the item, we gave them full points (score of 1). However, if studies satisfied some but not all criteria, a partial score of 0.5 was awarded for the item. The original tool recommends raters to categorize studies based on their risk of bias into categories of "good," "fair," and "poor" with studies rated as "good" having low risk of bias and studies rated as "poor" having high risk of bias (106). We classified studies with total scores ≥ 9 as "good," studies with total scores ≤ 6 as "poor," and all other studies as having "fair" quality. In addition to the above-mentioned tools, we also used the Levels of evidence as outlined by Sackett et al. (108) to classify all the 72 studies. This grading, based on study design, ranges from Levels I-V. We only included studies from Levels I up to III in our review. Level I is the highest level of evidence and includes systematic reviews, meta-analyses, and RCT's with a PEDro score of ≥ 6, Level II includes RCT's with a PEDro score < 6 and all CCT's, whereas Level III includes single group before-after (pre-post) study designs.

Study Coding Procedures

We coded each study in the review for sample and study characteristics, methodological quality, intervention characteristics (*FITT*: Frequency, Intensity, *T*ime, *T*ype), assessments used, dependent variables, and treatment effects (see **Appendix 2** for coding details). In addition to a narrative description of studies, we also report on quantitative ES from reviewed studies along with their confidence intervals to obtain estimates of the true magnitude of treatment effects following CMT in individuals with ASD. For parametric data, when adequate data were provided in the original report, we calculated ES i.e., standardized mean difference (d) values (109–111). For papers that reported non-parametric statistics, ES were calculated using U- and z- statistics (112). In studies where the original report did not provide estimates of central tendency and variability of measured outcomes, we calculated ES using parameter estimates (F- and t-values) and p-values. We acknowledge that these estimates are more inaccurate compared to ES estimates calculated using measures of central tendency and spread within the sample (see **Tables 4A–C** for details); however, we wanted to provide readers with ballpark estimates of ES. We classified ES according to Cohen's conventions as small (0.1–0.3), medium (0.3–0.49), or large (0.5 and above) (113). We also report 95% confidence intervals (CI) around ES estimates to identify robust, statistically significant effects of CMT in ASD (114, 115). Specifically, if a CI does not include 0, it implies a truly significant non-zero treatment effect at the 5% significance level. For the purpose of reliability, all authors as well as 2 undergraduate students coded a subset of the 72 studies using a detailed coding form. Intra-rater reliability of over 99% and inter-rater reliability of over 90% were achieved through consensus coding on scores that coders disagreed on. Following reliability, rest of the papers were divided and coded by the first and last authors.

RESULTS

Description of Studies

All 72 studies reviewed were published between 1994 and 2021 although only 25% of the studies specifically mentioned the year of data collection in the published report. Out of the 72 studies that we reviewed, 25 used music therapy approaches, 11 studies employed yoga-based interventions, 16 studies assessed the efficacy of martial arts-based interventions, 12 studies employed theater-based interventions, 7 studies assessed the effects of dance, and lastly, 1 study employed a combination of music and dance therapies. Of these studies, 30 were conducted in the US, 8 studies were from Iran, 6 from India, 4 from Germany, 3 each from UK and South Korea, 2 each from Hong Kong, Italy, Australia, and Brazil, 1 study each conducted in the Netherlands, Portugal, Greece, Spain, Portugal and Spain, France and Canada, and finally three studies that were subsets of the same larger study (98, 116, 117) were conducted simultaneously across multiple countries of the world including Norway, Austria, Australia, Israel, Brazil, Italy, UK, Korea, and USA. Several research groups reported on the exact same sample or on subsets of overlapping samples across multiple papers. Specifically, 4 of the music therapy studies by Srinivasan et al., 2 music studies by Kim et al., 2 yoga-based studies by Radhakrishna et al., 3 martial arts studies by Bahrami et al., and 2 by Phung et al. reported data from the same sample across multiple papers (4, 6, 27, 86, 101, 104, 118–123). Furthermore, 3 music therapy papers (98, 116, 117) reported on samples collected as part of the same, large-scale international study, 3 theater-papers reported on data collected across multiple cohorts by Corbett et al. (124–126) and 2 more martial arts studies had an overlap in reported samples (127, 128).

Sample Characteristics

The 72 studies had a total sample size of 1,939 participants with ASD. Among the studies that did provide gender-related data (total $N = 1{,}573$), there were 1,338 males and 235 females. Sixty-six studies were conducted in children between 3 and 21 years, 5 studies included both children and adults, and only 1 study was conducted purely in adults with ASD (see **Table 1**). Specifically, the ages of participants across CMT approaches were as follows: music (3–38 years), yoga (3–23 years), martial arts (5–17 years), theater (6–21 years), and dance (8–65 years), indicating that within the studies that met our inclusion criteria, music, yoga and dance approaches were the three types of CMT approaches that have been implemented in adults with ASD. All studies provided interventions to individuals with ASD only, except one study that provided training to both individuals with ASD and their caregivers (146). All studies reported that participants did not have prior exposure to CMT.

Sixty-seven studies recruited only individuals with ASD and the remaining 5 studies included children with ASD as well as children with other diagnoses including ADHD, anxiety disorder, learning disability, sensory processing disorder, and emotional and behavioral disorder. Across studies, the diagnosis of ASD was confirmed using multiple measures including standardized tests, physician report and parent-report questionnaires (see **Table 1**). Specifically, 41 studies employed gold standard measures such as the Autism Diagnostic Observation Schedule (ADOS), Autism Diagnostic Interview-Revised (ADI-R), Gilliam Autism Rating Scale (GARS), and Childhood Autism Rating Scale (CARS) to confirm ASD diagnosis, 19 studies relied on physician diagnosis made using criteria listed in the Diagnostic and Statistical Manual of Mental Disorders (DSM) or the International Classification of Disease (ICD), and 12 studies did not provide details of methods used to confirm participants' ASD diagnosis (see **Table 1**). In terms of intellectual functioning of participants, only 27 of the 72 studies reported on assessing Intellectual Quotient (IQ) scores using various scales such as Wechsler Abbreviated Scale of Intelligence-2nd edition (WASI-2) or the PsychoEducational Profile (PEP). Overall, only five studies included children with mild intellectual disability in their sample, with the remaining studies including participants without any accompanying intellectual disability (101, 117, 119, 150, 170). Although a vast majority of included studies did not report on socioeconomic status, the remaining studies primarily included participants from middle and upper-middle class families.

Study sample sizes across the different CMT interventions were as follows: 764 participants in music therapy interventions (455 received experimental intervention and 309 received control interventions), 317 in yoga therapy (184 in experimental group and 133 controls), 326 in martial arts (176 in experimental group and 150 control group participants), 246 participants in theater training (162 received experimental intervention and 84 were in control group; 1 theater study ($N = 8$) did not provide the distribution of the sample into the intervention groups), 262 participated in dance-based studies (139 received experimental group intervention and 123 received a control intervention), and 16 participated in combined music and dance intervention (8 in experimental and 8 in control group). There was great

TABLE 1 | Study and sample characteristics.

References	Study location	Study design	Final sample size (EG, CG)	Age [M (SD); range]	Diagnosis of subjects	Measures used to establish diagnosis	Duration in weeks (frequency of sessions/week)	Session time in minutes (format—I/G)	Intervention type	Intervention provider	C-group intervention
Music/rhythm therapy											
Edgerton et al. (129)	USA	Reversal	11 (11,0)	6–9	ASD	ND	10 (1)	30 (I)	Nordoff-Robin's IMT	SI	NA
Hartshorn et al. (130)	USA	CCT	76 (38,38)	5; 3–7	ASD	ND	8 (2)	30 (G)	Music/Rhythm-based MT	SI	WLC
Boso et al. (131)	Italy	Pre-post	8 (8,0)	30.2 (5.5); 23–38	ASD	CARS, DSM-IV	52 (1)	60 (G)	Active MT	LC	NA
Kim et al. (119)	South Korea	RCT	10 (5,5)	4.22 (12.1); 3–6	ASD	CARS, ADOS, DSM-IV	12 (1)	30 (I)	IMT	SI	Cross-over design: toy play and MT
Kim et al. (101)											
Gattino et al. (132)	Brazil	RCT	24 (12,12)	9.8 (1.4); 6.8–12.2	AD, AS, PDD-NOS	CARS-BR, ADI-BR, DSM-IV TR	16 (1)	30 (I)	RMT	SI	Routine clinical activities
Hillier et al. (133)	USA	Pre-post	22 (22,0)	18; 13–29	AD, AS, PDD-NOS	DSM-IV	8 (1)	90 (I)	Soundscape- MT program	SI	NA
Wan et al. (134)	USA	Pre-post	6 (6,0)	6.7 (1.2); 5–9	ASD	CARS, DSM-IV	8 (1)	45 (I)	AMMT	LC	NA
Thompson et al. (135)	Australia	RCT	21 (11,10)	3–5	ASD	DSM-IV-TR	16 (1)	30–40 (not clear)	Family centered MT-based movement therapy + Early intervention	SI	Regular EI
LaGasse (136)	USA	RCT	17 (9,8)	7.6 (1.1); 6–9	ASD	CARS	5 (2)	50 (not clear)	MT	SI, O (support staff)	No-music social skills intervention
Ghasemtabar et al. (137)	Iran	CCT	27 (13,14)	7–12	ASD	CARS	6 (2)	30 (G)	MT	SI	NIC
Srinivasan et al. (27)	USA	RCT	36 (12,12,12)	7.7 (2.2); 5–12	ASD	ADOS-2, SCQ	8 (4)	45 (I)	RI	LC, CG, O (model)	Academic sedentary activities, Robot-mediated interactions
Srinivasan et al. (118)											
Srinivasan et al. (4)											
Srinivasan et al. (6)											
Bieleninik et al. (116)	Australia, Austria, Israel, Brazil, Italy Norway, UK, Korea, USA	RCT	314 (165,149)	5.4 (0.9); 4–6	ASD	ADOS, ADI-R, ICD-10	20 (1-low intensity; 3-high intensity)	30 (low); 60 (high); (I)	IMT + standardized care	SI, LC	Enhanced standard care

(Continued)

TABLE 1 | Continued

References	Study location	Study design	Final sample size (EG, CG)	Age [M (SD); range]	Diagnosis of subjects	Measures used to establish diagnosis	Duration in weeks (frequency of sessions/week)	Session time in minutes (format—I/G)	Intervention type	Intervention provider	C-group intervention
Mossler et al. (117)	Australia, Austria, Brazil, Israel, Italy, Korea, Norway, UK and USA	Pre-post	101 (101,0)	5.4 (0.3); 4–7	ASD	ADOS, ADI-R, Physician report	20 (1-low intensity; 3-high intensity)	30 (low); 60 (high); (I)	IMT	SI	NA
Dvir et al. (98)	Israel, Austria and Norway	Pre-post	21 (21,0)	5.33 (0.72); 4.1–6.9	ASD	ADOS, ADI-R, Physician report	20 (61,2,3)	30 (I)	MT	SI	NA
Yoo & Kim (138)	South Korea	Pre-post	8 (8,0)	10.8; (3.4)	ASD	KCARS, DSM-IV	8	30 (I)	RI	SI	NA
Willemin et al. (139)	USA	Pre-post	14 (14,0)	10; 5–14	ASD	ND	4 (2)	60 (I)	Drumtastic®-drumming program	LC, SI	NA
Lowry et al. (140)	UK	CCT	18 (12,6)	7–8	O	ND	5 (2)	30 (not clear)	Rock drumming	SI	School-based educational program
Stephen (141)	India	CCT	30 (15,15)	ND	ASD	ND	12	ND	ND	ND	WLC
Schmid et al. (142)	USA	Pre-post	64 (64,0)	8.04 (1.62); 5–11	ASD	ASD diagnosis on IEP	16 (1)	45 (G)	Voices together MT	SI	NA
Rabeyron et al. (143)	France	RCT	36 (19,17)	4–7	ASD	CARS	8 (1)	30 (G)	IMT	SI	Music listening
Cibrian et al. (144)	USA	RCT	22 (11,11)	5.72 (1.2)	ASD	DSM-V	8 (1)	(G)	NMT using bendable sound prototype	SI, O (school psychology teachers)	NMT using tambourines
Yoga/mindfulness-based therapy											
Radhakrishna et al. (120)	India	CCT	12 (6,6)	8–14	ASD	ICD-10	82 (2)	1 (I)	IAYT + ABA	SI, CG	ABA training
Radhakrishna et al. (121)	India	Pre-post	6 (6,0)	12.7; 8–14	ASD	CARS, DSM-IV TR	40 (5)	45 (not clear)	IAYT	LC, CG	NA
Rosenblatt et al. (145)	USA	Pre-post	24 (24,0)	8.9; 3–16	ASD	70%-physician-provided diagnosis 30%-ND	8 (1)	45 (G)	Relaxation response based-yoga	SI	NA
Koenig et al. (88)	USA	CCT	46 (24,22)	5–12	ASD	ND	16 (5)	15–20 (G)	GRTL Yoga	LC	Standard morning activity at school
de Bruin et al. (146)	Netherlands	Pre-post	21 children with 26 parents (EG: 21	Children—15.8 (2.7); 11–23, Fathers—53.1 (4.4); 48–61,	AD, AS, PDD-NOS, O	AODS-G, DSM-IV TR	9 (1)	90 (G)	*MYmind*—Mindfulness training	LC	NA

(Continued)

TABLE 1 | Continued

References	Study location	Study design	Final sample size (EG, CG)	Age [M (SD); range]	Diagnosis of subjects	Measures used to establish diagnosis	Duration in weeks (frequency of sessions/week)	Session time in minutes (format—I/G)	Intervention type	Intervention provider	C-group intervention
			children with 26 parents, CG: 0)	Mothers—49.8 (5.6); 40–56							
Narasingharao et al. (147)	India	CCT	61 (32,29)	5–16	ASD	ICD-10	24 (5)	75 (G)	Yoga	SI, CG	Regular school curriculum
Sotoodeh et al. (148)	Iran	RCT	29 (15,14)	11.2 (2.9); 7–15	ASD	ADI-R, DSM-V	8 (3)	30 (I)	Yoga	SI	NIC
Litchke et al. (149)	USA	Pre-post	5 (5,0)	10.4 (1.8); 8–13	AS, PDD-NOS	ND	4 (2)	1 (G)	Teen yoga warriors—multimodal mandala yoga	LC, O (graduate student)	NA
Kaur & Bhat (150)	USA	RCT	23 (11,12)	5–13	ASD	SCQ, ADOS, Medical Records	8 (4)	40–45 (Expert); (I); 20–25 (Parent)	Creative yoga	LC, O (under-graduate student)	Academic sedentary activities
Vidyashree et al. (151)	India	RCT	35 (15,20)	9.6 (2.4); 8–14	ASD	ND	12	40 (not clear)	Yoga	SI	Routine rehabilitation therapy
Tanksale et al. (152)	Australia	RCT	61 (31,30)	9.42 (1.34); 8–12	ASD	ADOS	6 (1)	60 (G)	Yoga therapy	LC, O (parent, psychology student volunteers)	WLC
Martial art											
Bahrami et al. (122)	Iran	RCT	30 (15,15)	9.1 (3.3); 5–1	ASD	GARS, DSM-IV TR	14 (4)	30 (I)	Heian Shodan Kata technique	SI	Educational intervention
Movahedi et al. (153)			26 (13,13)	9.03 (3.3); 5–16				30, 90 (I, G)			
Bahrami et al. (86)			30 (15,15)	9.1 (3.3); 5–16				30, 90 (I, G)			
Chan et al. (154)	Hong Kong	RCT	40 (20,20)	6–17	AD, PDD-NOS	ADI-R, DSM-IV TR	4 (2)	60 (G)	Nei Yang Gong-Mind-body exercise	LC	PMR
Chan et al. (155)	Hong Kong	RCT	48 (18,17,13)	5–17	AD, PDD-NOS	ADI-R, DSM-IV TR	4 (2)	60 (G)	Chanwuyi- Mind-body exercise	LC	PMR, NIC
Figueiredo et al. (156)	Portugal and Spain	Pre-post	8 (8,0)	8.5 (1.6); 7–12	ASD, AS, O	ND	6–18 (1)	30–45 (not clear)	Karate	ND	NA
Kim et al. (157)	USA	CCT	14 (8,6)	8–14	ASD	Physician report	8 (2)	50 (not clear)	Taekwondo	SI	NIC

(Continued)

TABLE 1 | Continued

References	Study location	Study design	Final sample size (EG, CG)	Age [M (SD); range]	Diagnosis of subjects	Measures used to establish diagnosis	Duration in weeks (frequency of sessions/week)	Session time in minutes (format—I/G)	Intervention type	Intervention provider	C-group intervention
Phung & Goldberg (104)	USA	RCT	34 (14,20)	9.3 (1.1); 8–11	ASD	SCQ, ADOS-2, Clinician Report	13 (2)	45 (G)	Mixed martial arts	SI, O (peers, under-graduate students)	WLC
Phung et al. (123)											
Sarabzadeh et al. (158)	Iran	RCT	18 (9,9)	6–12	ASD	GARS, Physician Report	6 (3)	60 (not clear)	Tai Chi Chuan	SI	NIC
Garcia et al. (127)	USA	Pre-post	14 (14,0)	12.3 (3.4); 8–17	ASD, O	Physician report	8 (1)	45 (G)	Judo	SI, O (graduate student)	NA
Rivera et al. (128)	USA	Pre-post	33 (33,0)	12;67 (2.99); 8–17	ASD	Physician report	8 (1)	45	Judo	SI	NA
Ansari et al. (159)	Iran	RCT	30 (15,15)	8–14	ASD	Physician report	10 (2)	60	Kata technique	SI	Aquatic therapy, WLC
AdibSaber et al. (160)	Iran	RCT	20 (10,10)	8–14	ASD	GARS-2	10 (2)	60 (G)	Heian Shodan Kata technique	ND	Maintained regular program and activity levels
Greco & de Ronzi (161)	Italy	RCT	28 (14,14)	9.25 (1); 8–11	ASD	ADOS-2	12 (2)	45 (G)	Karate	SI	WLC
Tabeshian et al. (162)	Canada	RCT	23 (12,11)	9.6 (1.4); 6–12	ASD	Physician report	12 (3)	45 (G)	Tai Chi Chuan	SI	WLC
Theater/dramatic training											
Lerner et al. (163)	USA	CCT	17 (9,8)	11–17	AD, AS	DSM-IV TR	6 (5)	300 (G)	SDARI	SI	NIC
Lerner & Mikami (164)	USA	RCT	13 (7,6)	ND	AD, AS, PDD-NOS	SCQ, LC	4 (1)	90 (G)		SI	Skill-streaming
Corbett et al. (124)	USA	Pre-post	8 (8,0)	11.3 (4); 6–17	AD, PDD-NOS	ADOS-G, DSM-IV TR	12 (1-4)	120 (I)	SENSE Theater	CG, O (peers)	NA
Corbett et al. (126)	USA	Pre-post	11 (11,0)	12.1; (8–17)	AD, AS, PDD-NOS	ADOS-G, DSM-IV	2 (5)	240 (I, G)		LC, O (peers)	NA
Corbett et al. (165)	USA	RCT	30 (17,13)	8–14	ASD	ADOS, DSM-V	10 (1)	240 (I, G)		T, O (peers)	NIC
Corbett et al. (87)											
Ioannou et al. (125)	UK	RCT	77 (44,33)	8–16	ASD	ADOS-2, physician report	10 days	240 (G)	SENSE Theater	O (peers)	WLC

(Continued)

TABLE 1 | Continued

References	Study location	Study design	Final sample size (EG, CG)	Age [M (SD); range]	Diagnosis of subjects	Measures used to establish diagnosis	Duration in weeks (frequency of sessions/week)	Session time in minutes (format—I/G)	Intervention type	Intervention provider	C-group intervention
Guli et al. (166)	USA	CCT	34 (18,16)	10.9; 8–14	ASD, O	DSM-IV TR	Fall: 8 (2) Spring: 12 (1)	Fall: 90 Spring: 120 (G)	SCIP	SI	WLC
Kim et al. (167)	USA	Pre-post	18 (18,0)	15	ASD	ND	5 (5)	4 (G)	Theater	SI	NA
Reading et al. (168)	USA	CCT	16 (8,8)	17–21	ASD	ND	10 (1)	2 (G)	Theater	SI	NIC
Naniwadekar et al. (169)	India	CCT	8 (ND)	ND	ASD	ND	ND	ND (G)	Drama	SI	Story telling using flash cards and video
Beadle-Brown et al. (170)	UK	Pre-post	22 (22,0)	7–13	ASD	ADOS	10 (1)	45 (I)	"Imagining Autism" —Drama	SI	NA
Dance therapy											
Arzoglou et al. (85)	Greece	CCT	10 (5,5)	16.8 (EG), 16.6 (CG)	ASD	DSM-IV	8 (3)	35–45 (I, G)	Greek traditional dance	ND	Physical education at school
Koehne et al. (171)	Germany	CCT	51 (27,24)	18–55	AD, AS	ADOS, ADI-R, DSM-IV/ICD-10	10 (1)	90 (G)	Synchrony-based DMT	ND	Movement intervention without imitation or synchronization
Koch et al. (77)	Germany	CCT	31 (16,15)	22 (7.7); 16–47	ASD, AD, AS	ICD-10	7 (1)	60 (G)	M-DMT	SI	WLC
Hildebrandt et al. (172)	Germany	RCT	43 (31,12)	22.5 (7.75); 14–65	ASD	ICD-10	10 (1)	60 (G)		SI	WLC
Mastrominico et al. (173)	Germany	RCT	56 (35,21)	22.5 (8.5); 14–52	ASD	ICD-10, SANS	10 (1)	60 (G)		SI	WLC
Souza-Santos et al. (174)	Brazil	Cross-over	45 (15,15,15)	7 (1.1)	ASD	CARS, DSM-V	12 (2)	60 (not clear)	Dance + EAT	SI	CG1: EAT, CG2: EAT and Dance
Aithal et al. (175)	UK	Cross-over	26 (10,16)	10.65; 8–13	ASD	DSM-V	5 (2)	40 (G)	Dance movement psychotherapy	SI	Standard care
Miscellaneous: dance and music therapy											
Mateos-Moreno & Atencia-Doña (176)	Spain	CCT	16 (8,8)	ND	ASD	CARS, DSM-IV	17 (2)	60 (G)	Dance + Music (combined)	SI, O (graduate student)	NIC

ABA, Applied Behavioral Analysis; AD, Autistic Disorder; ADI-R, Autism Diagnostic Interview-Review; ADI-BR, Brazilian version of ADI-R; ADOS, Autism Diagnostic Observation Schedule; AMMT, Auditory-motor Mapping Training; ASD, Autism Spectrum Disorder; AS, Asperger's Syndrome; CARS, Childhood Autism Rating Scale; CARS-BR, Brazilian version of CARS; KCARS, Korean version of CARS; CCT, Controlled Clinical Trial; CG, Control Group; Cg, Caregiver; DMT, Dance Movement Therapy; DSM, Diagnostic and Statistical Manual of Mental Disorders; EAT, Equine-assisted therapy, EG, Experimental group; ESDM, Early Start Denver Model; G, Group therapy; GARS, Gilliam Autism Rating Scale; GRTL, Get Ready To Learn; I, Individual therapy; IAYT, Integrated approach to Yoga Therapy; ICD, International Classification of Diseases; IEP, Individualized Education Program; IMT, Improvisational Music Therapy; LC, Licensed Clinician; M-DMT, Manualized Dance Movement Therapy; MT, Music Therapy; NA, Not Applicable; ND, Not Defined; NMT, Neurologic Music Therapy; NS, Not specified; NIC, No Intervention Control; O, Others; PDD, Pervasive Developmental Disorder; PDD-NOS, Pervasive Developmental Disorder-Not Otherwise Specified; PMR, Progressive muscle relaxation; RCT, Randomized Controlled Trial; RI, Rhythm Intervention; RMT, Relational Music Therapy; SANS, Scale for Assessment of Negative Symptoms; SCIP, Social Competence Intervention Program SCQ, Social Communication Questionnaire; SDARI, Socio-dramatic Affective Relational Intervention; SENSE, Social Emotional NeuroScience Endocrinology; SI, Specialized Instructor; T, Teacher; WLC, Waitlist Control.

variability in sample sizes across individual studies. The largest sample size studies for different CMT approaches included 364 participants for music therapies (116), 61 participants for yoga therapy (147, 152), 57 participants for dance therapy (173), 48 participants for martial arts (155), 77 participants for theater–based interventions (125), and 56 participants for dance and other combined therapies (173).

Study Characteristics

Out of the 72 studies, 34 studies were RCTs, 17 were CCTs, 18 were pre-post designs, 2 studies were cross-over designs, and 1 study employed a reversal design. We scored the PEDro scale for the 52 clinical trials (16 music, 7 yoga, 13 martial arts, 8 theater, 7 dance, and 1 combined dance and music intervention) and the NIH quality assessment tool for the 20 single group pre-post design studies (9 music, 4 yoga, 3 martial arts, 4 theater) reviewed to assess risk of bias (see **Tables 2A**,**B**). The clinical trials included in the review employed the following control groups: waitlist control, ABA therapy, routine or enhanced standard-of-care, seated play, school-based educational programming, social skills training, physical education training, robotic therapy, equine-assisted therapy, or no intervention. In terms of fidelity of implementation of training procedures, of the total 72 studies, around 25% ($N = 18$) used and provided details of specific checklists employed to monitor the consistency of treatment implementation, another 22% ($N = 16$) provided brief details of some form of fidelity checks, and 51% ($N = 38$) of studies did not provide any information on intervention fidelity. In terms of intervention implementation, music therapy and yoga therapy-based studies were almost equally split between an individualized vs. group-based format (Music: 13 out of 25 studies and yoga: 5 out of 11 studies provided individualized intervention), whereas martial arts (12 out of 16 studies), theater (10 out of 12 studies), dance (6 out of 7 studies), and combination-based approaches frequently employed group-based implementation with group sizes varying between 3 and 12 participants (see **Table 1**).

Risk of Bias

Controlled Intervention Studies

Out of the 52 clinical trials, 50% studies ($N = 26$) had a high risk of bias (PEDro scores < 6). No study satisfied all the 11 criteria (see **Table 2A**). Among factors contributing to risk of bias, few studies concealed allocation of subjects to intervention groups ($N = 8$), and blinding of subjects ($N = 1$), therapists ($N = 9$), and assessors ($N = 20$) were ensured to a varying extent by reviewed studies. Although not as frequent, other factors associated with risk of bias included random subject allocation ($N = 36$ satisfied the criterion) and baseline similarity of groups on key prognostic measures ($N = 33$ satisfied the criterion) (see **Table 2A**).

Single Group Pre-post Designs

Based on the NIH quality assessment tool rating used for assessing the 20 pre-post designs, 1 study was rated as "poor" indicating high risk of bias, 12 studies were "fair" indicating moderate risk of bias, and 7 studies were rated as "good" indicating low risk of bias. Specifically, none of the studies measured outcomes multiple times at pretest and posttest to get stable estimates of child performance, and all but three studies did not discuss power analyses to justify the choice of sample sizes. Another area of concern included blinding of assessors which was ensured in only 3 studies. Finally, 50% studies ($N = 10$) did not report on validity and reliability of assessed outcome measures, with 30% of the remaining studies ($N = 6$) reporting on only one but not both these measures (see **Table 2B**).

Intervention Characteristics

The mean duration of studies that provided music-based interventions was 12 weeks (SD = 9.73, Range = 4–52 weeks), with a mean frequency of around 2 sessions/week (SD = 1.3, Range = 2–5 times), and each session lasting around 40 min (SD = 14.9, Range = 30–90 min, see **Table 1** for details). Studies that provided yoga therapy had the longest mean intervention duration of 20 weeks (SD = 23.99, Range = 4–82 weeks) with a mean frequency of around 3 times per week (SD = 1.81, Range = 1–5 times) for around 50 min per session (SD = 19.9, Range = 20–90 min). Martial arts and theater-based studies had similar intervention characteristics, i.e., average intervention duration ranged around 10 and 8 weeks respectively (Martial arts: SD = 3.44, Range = 4–14 weeks; Theater: SD = 3.38, Range = 4–12 weeks) and average frequency was around 2 sessions/week (Martial arts: SD = 1.01, Range = 1–4 times; Theater: SD = 1.86, Range = 1–5 times). However, the 2 CMT types differed greatly in terms of average session duration, with theater interventions (Mean ∼175 min/session, SD = 90.56, Range = 60–300 min) lasting on an average for much longer time compared to martial arts interventions (Mean ∼50 min/session, SD = 9.2, Range = 30–60 min). Lastly, interventions focusing on dance therapy had an overall mean duration of 9.5 weeks (SD = 1.76, Range = 7–12 weeks), with a mean frequency of around 1–2 sessions per week (SD = 0.78, Range = 7–12 weeks), and each session lasting for around 60 min (SD = 16.02, Range = 40–90 min).

In terms of intervention providers, most of the CMT approaches were provided by either licensed clinicians or specialized instructors trained in the CMT approach ($N = 62$). Fifteen studies (6 music, 3 yoga, 2 martial arts, 3 theater, 1 music and dance combined) asked teachers, caregivers, support staff, models, students or peers, etc. to assist in the intervention delivery process (see **Table 1**). Only 2 theater studies by Corbett et al. had teaching staff and peers deliver the intervention independently of clinicians after conducting a 2-day intensive training seminar (87, 165). Several papers mentioned using conventional ASD treatment strategies while providing CMT interventions to children with ASD. Common training strategies were based on principles of conventional ASD treatments such as ABA, TEACHH, and PECS and specifically included the use of picture schedules/visual cues, incremental prompting (verbal, gestural, modeling, hand-on-hand assistance), reinforcement schedules, structured and predictable training routines, motivational strategies, activities designed keeping in mind the participant's sensory needs, and the use of non-competitive, goal-directed, and child-led activities to ensure child compliance. Although a total of 15 studies (2 music, 2 yoga, 5 martial arts, 4 theater, 1 dance, 1 music and dance) mentioned progression in training across intervention weeks,

TABLE 2A | PEDro scoring for RCT/CCT.

References	Eligibility criteria specified**	Random subject allocation	Concealed allocation	Baseline similarity of groups	Blinding: subjects	Blinding: therapists	Blinding: assessors	Measures of key outcomes	Intent to treat	Between group analyses	Point estimates and variability measures	Total (ROB)
Music												
Hartshorn et al. (130)												4 (H)
Kim et al. (119)												6 (L)
Kim et al. (101)												4 (H)
Gattino et al. (132)												8 (L)
Thompson et al. (135)												7 (L)
LaGasse (136)												6 (L)
Ghasemtabar et al. (137)												5 (H)
Srinivasan et al. (27)												7 (L)
Srinivasan et al. (118)												7 (L)
Srinivasan et al. (4)												7 (L)
Srinivasan et al. (6)												7 (L)
Bieleninik et al. (116)												8 (L)
Stephen (141)												4 (H)
Lowry et al. (140)												5 (H)
Rabeyron et al. (143)												5 (H)
Cibrian et al. (144)												4 (H)
Yoga/mindfulness-based therapy												
Radhakrishna et al. (120)												1 (H)
Koenig et al. (88)												4 (H)
Narasingharao et al. (147)												2 (H)
Sotoodeh et al. (148)												6 (L)
Kaur & Bhat (150)												6 (L)
Vidyashree et al. (151)												4 (H)
Tanksale et al. (152)												6 (L)
Martial arts												
Bahrami et al. (122)												5 (H)
Movahedi et al. (153)												5 (H)
Bahrami et al. (86)												5 (H)
Chan et al. (154)												8 (L)
Chan et al. (155)												6 (L)
Kim et al. (157)												4 (H)

(Continued)

TABLE 2A | Continued

References	Eligibility criteria specified**	Random subject allocation	Concealed allocation	Baseline similarity of groups	Blinding: subjects	Blinding: therapists	Blinding: assessors	Measures of key outcomes	Intent to treat	Between group analyses	Point estimates and variability measures	Total (ROB)
Phung & Goldberg (104)	■	■		■				■	■	■	■	6 (L)
Phung et al. (123)	■	■				■		■	■	■	■	6 (L)
Sarabzadeh et al. (158)	■	■		■		■	■	■	■	■	■	8 (L)
Ansari et al. (159)	■	■		■				■	■	■	■	6 (L)
AdibSaber et al. (160)	■	■						■	■	■	■	5 (H)
Greco & de Ronzi (161)	■	■	■	■		■	■	■	■	■	■	9 (L)
Tabeshian et al. (162)	■	■		■		■	■	■	■	■	■	8 (L)
Theater/dramatic training												
Lerner et al. (163)	■			■		■		■	■	■	■	6 (L)
Lerner & Mikami (164)	■	■		■		■		■	■	■	■	7 (L)
Guli et al. (166)	■	■	■	■			■	■	■	■	■	8 (L)
Corbett et al. (165)	■	■	■	■			■	■	■		■	7 (L)
Corbett et al. (87)	■							■	■	■	■	4 (H)
Ioannou et al. (125)	■	■						■	■	■	■	5 (H)
Reading et al. (168)	■						■	■	■	■	■	5 (H)
Naniwadekar et al. (169)	■							■	■	■	■	4 (H)
Dance therapy												
Arzoglou et al. (85)	■							■	■	■	■	4 (H)
Koehne et al. (171)	■			■	■		■	■	■	■	■	7 (L)
Koch et al. (77)	■			■				■	■	■	■	5 (H)
Hildebrandt et al. (172)	■	■		■			■			■	■	5 (H)
Mastrominico et al. (173)	■	■		■					■	■	■	5 (H)
Souza-Santos et al. (174)	■	■		■				■	■		■	5 (H)
Aithal et al. (175)	■	■	■	■				■	■	■	■	7 (L)
Miscellaneous interventions												
Mateos-Moreno & Atencia-Doña (176)	■							■	■	■	■	4 (H)

***Item 1 is not included in PEDro total score calculation.*

Gray shaded cells indicate that the criterion has been fully satisfied (receives a score of 1 point for that item) and blank cells indicate that the criterion has not been satisfied (receives a score of 0 points for that item). Total scores are calculated by summing the number of gray shaded cells (except criterion 1) for each individual study.

ROB, Risk of bias, H, High risk of bias, L, Low risk of bias. ROB rating based on PEDro scores (i.e., Low risk = scores ≥ 6, High risk = scores < 6).

TABLE 2B | NIH quality assessment tool for before-after (pre-post) study design.

References	Study objective	Eligibility criteria	Sample represen -tation	Eligible partici- pants enrolled	Sample size/power analysis	Intervention description	Outcome measures specified	Blinding: assessors	Intent to treat	Statistical tests used	Multiple assessments of outcome measures	Group/ individual level analysis	Total and ROB
Music therapy													
Edgerton et al. (129)													8 (M)
Boso et al. (131)													8 (M)
Hillier et al. (133)													8.5 (M)
Wan et al. (134)													8 (M)
Yoo and Kim (138)													8.5 (M)
Willemin et al. (139)													8 (M)
Schmid et al. (142)													9.5 (L)
Dvir et al. (98)													9.5 (L)
Mossler et al. (117)													11 (L)
Yoga therapy													
Radhakrishna et al. (121)													7 (M)
Rosenblatt et al. (145)													9 (L)
de Bruin et al. (146)													9 (L)
Litchke et al. (149)													8 (M)
Martial arts													
Figueiredo et al. (156)													6 (H)
Garcia et al. (127)													9 (L)
Rivera et al. (128)													8 (M)
Theater													
Corbett et al. (124)													8 (M)
Corbett et al. (126)													8 (M)
Kim et al. (167)													7.5 (M)
Beadle-Brown et al. (170)													10.5 (L)

Gray shaded cells indicate that the criterion has been fully satisfied (receives a score of 1 point for that item), cells with diagonal stripes indicate that the criterion was partially satisfied (receives a score of 0.5) and blank cells indicate that the criterion has not been satisfied (receives a score of 0 points for that item). Total scores are calculated by summing the number of gray shaded cells (except criterion 1) for each individual study.

ROB, Risk of bias; H, High risk of bias; M, Moderate risk of bias; L, Low risk of bias. Risk of bias rating based on scoring on ratings on NIH quality assessment tool for pre-post designs (i.e., Low risk = scores ≥ 9, High risk = scores ≤ 6, Moderate risk = scores of 6.1–8.9).

only four of these studies (1 music, 1 yoga, 1 martial art, 1 theater) discussed specific principles of treatment progression over the course of the program. The remaining 57 studies provided no information on treatment principles and progression.

Common music therapy training approaches evaluated included Improvisational Music Therapy (IMT) and Relational Music Therapy (RMT). Similarly, yoga-based training approaches included Mandala Yoga and Mindfulness training, Relaxation Response-based training, and ABA based-integrated Yoga training. Common martial art approaches included Kata, Judo, Karate, Tai chi, and Taekwondo. Theater-based studies used programs such as the Social Emotional NeuroScience Endocrinology (SENSE) Theater, Social Competence Intervention Program (SCIP), and Socio-dramatic Affective Relational Intervention (SDARI). Lastly, Dance Movement Therapy (DMT) and traditional Greek dance were some of the approaches used in dance-based studies (see **Table 1**).

In terms of the location of intervention delivery, 5 studies (all music) delivered interventions at the child's home, 13 studies (4 music, 4 yoga, 2 martial arts, 1 theater, 1 dance, 1 music and dance) delivered interventions at the child's school, 30 studies (10 music, 1 yoga, 8 martial arts, 7 theater, 4 dance) provided intervention at other indoor settings such as a community center, YMCA, etc., 3 studies (1 music, 1 martial art, 1 theater) provided intervention either at the child's school or a community center, 2 studies (both yoga-based involving the same sample) conducted their intervention in a calm and open outdoor setting, and 19 of the remaining studies (5 music, 4 yoga, 5 martial arts, 3 theater, 2 dance) did not provide any specific information on where the intervention was provided.

Outcomes Measures and Treatment Effects

Of the 72 studies reviewed, 31 reported within-group changes, 31 reported between-group differences, and 10 studies reported both between- and within-group changes. Studies used a combination of tests and measures including standardized tests, self-/parent-/teacher-reported questionnaires, video coding, and observational measures to assess the impact of CMT on multiple domains including social communication, behavioral-affective, sensorimotor, cognitive, functional skills, and quality of life (see **Tables 3A–C**, **6**). Twenty-eight studies (16 music, 3 yoga, 1 martial arts, 6 theater, 1 dance, 1 combined music and dance) reported on the inter- and intra-reliability of the assessments employed. In terms of reporting treatment effects, 28 studies reported ES for the assessed outcomes (see **Tables 4A–C**). We were able to use data from the original papers to calculate ES in 64 out of the total 72 studies (i.e., 89% studies). **Tables 4A–C** provides a comparison between ES we calculated based on data provided in the paper and ES estimates reported in the original paper, and also discusses the level of agreement between both sets of estimates. **Table 6** displays our results to indicate the number of studies stratified by CMT approach where calculated ES were statistically significant (i.e., CI did not include 0). Below, we provide a narrative description of the types of measures employed and summarize the salient treatment effects from the studies included in our review across the developmental domains. Please note that each section discusses the results reported in the original papers assessing those domains followed by a summary of the results from our own ES calculations for the specific domain.

Social Communication

A total of 47 studies i.e., 17 Level I (7 music, 1 yoga, 3 martial arts, 4 theater, 2 dance), 15 Level II studies (6 music, 1 yoga, 2 martial arts, 4 theater, 1 dance, 1 music and dance combined) and 15 Level III studies (7 music, 2 yoga, 2 martial arts, 4 theater) assessed changes in social communication skills following CMT (refer to section Risk of Bias Assessment for definition of levels; see **Table 6**). The social communication outcome measures employed included standardized tests such as the ADOS, CARS, and GARS, observational measures such as the ESCS and JTAT, parent/teacher-report questionnaires such as the ATEC, SRS, VABS, and SSRS, as well as video-based coding measures of joint attention, verbalization, and turn taking (see **Tables 3A–C**). All except one Level II study (121) reported quantitative data on social communication outcomes following CMT interventions. Using data from original reports, we were able to calculate a total of 91 ES, specifically, 38 ES from 12 out of the total 17 level I studies, 21 ES from 11 out of total 15 level II studies, and 32 ES from 9 out of the total 15 level III studies.

Of the 17 Level I studies, three studies reported no significant changes (1 martial arts, 1 theater, 1 dance) and 14 studies (7 music, 1 yoga, 2 martial arts, 3 theater, 1 dance) reported positive effects with small to large effect sizes (ES: 0.09–4.06) within their original report. Out of the 38 ES we calculated, CI for 14 ES from 9 studies did not include 0 (5 Music, 1 yoga, 2 martial arts, 1 theater). The largest multi-site study in our review that included 364 children from 9 countries was the only study that reported only small improvements on the social affect sub-domain of the ADOS (ES: 0.03–0.2) and the social motivation and autistic mannerisms subscales of the SRS (ES: 0.04–0.02) in the experimental group following a 20-week improvisational music therapy program compared to a comparison group that received a standard-of-care intervention; however, these findings were not statistically significant at the between-group level (116).

Among all 15 Level II studies, improvements of medium sizes (ES: 0.22–0.79) in social communication outcomes were reported in the original papers by music (6), yoga (1), martial arts (2), theater (4), dance (1) and combined music and dance (1) interventions, but out of the 21 ES we calculated, only 6 ES from 3 studies (2 martial arts, 1 theater) were statistically significant (CI did not include 0). In terms of the level III studies, only 3 of the 15 studies reported small to large ES on the ADOS and SRS following theater (2) and yoga (1) interventions (see **Tables 4B,C**). Similarly, despite large mean ES (0.88–3.04) estimates, only 6 out of the 32 ES we calculated from the 3 Level III studies did not include 0 (2 music and 1 theater).

Overall, out of the 91 calculated ES across 47 studies, 26 ES from 15 studies (∼32% studies) were statistically significant (CI did not include 0) and indicated effects that were varying in magnitude from small to large (see **Tables 4A–C**, **6**). Specifically, there is moderately strong evidence for beneficial effects of music (5 Level I and 2 Level III studies) followed by martial arts

TABLE 3 | Study-wise dependent variables and results.

References	Domains tested	Study design	Type of effect reported	Type of assessment	Measures	Measures/variables showing improvement
(A) Music/rhythm therapy						
Edgerton et al. (129)	Other (musical and non-musical communication abilities)	W	W	Questionnaire	CRASS	Total CRASS scores
Hartshorn et al. (130)	Social, behavioral, and sensory	B	B	Video coding	Stereotypies, compliance, on-task behavior, eye contact, response to teacher	Wandering, negative response to touch, resisting teacher, on-task passive behavior
Boso et al. (131)	Behavioral and other (severity of illness and music skills)	W	W	Standardized scale, questionnaire	CGI-S, CGI-I, BPRS, musical skills	BPRS and music skills (except complex rhythmic patterns) from PRE to POST
Kim et al. (119)	Social communication and behavioral	B	B	Standardized scale, video coding	PDDBI-C, ESCS, Video coding (eye contact and turn taking)	PDDBI-C, ESCS (RJA, IJA), eye contact and turn taking during sessions
Kim et al. (101)	Social and behavioral	B	B	Video coding	Episodes of joy, compliance, and initiation of engagement	All variables
Gattino et al. (132)	Social communication	B	B	Standardized scale	CARS-BR	Nonverbal communication scores on CARS-BR in EG.
Hillier et al. (133)	Social and behavioral	W	W	Questionnaire	IPR (participant and parent), RSES, STAI-C	All variables
Wan et al. (134)	Communication	W	W	Video coding	Video coding of child's vocal output	All variables
Thompson et al. (135)	Social communication	B	B	Video coding, questionnaire	VSEEC, SRS, Mac-CDI, PCRI, MTDA	VSEEC
			W			MTDA
LaGasse (136)	Social communication	B	B	Video coding, questionnaire	SRS, ATEC, and video coding (eye gaze, JA, communication and withdrawal behaviors)	ATEC (parent and teacher- main effect), eye gaze and joint attention toward persons
			W			SRS
Ghasemtabar et al. (137)	Social	B	B	Questionnaire	SSRS	SSRS—social skills and functioning
Srinivasan et al. (27)	Behavioral	B	B	Video coding, questionnaire	RBS-R, video coding (positive, negative and greater interested affect)	Positive affect (mid and late)
			W			EG: RBS-R (lower negative behaviors from early to mid and late sessions, lower negative and greater interested affect from early to late sessions)
Srinivasan et al. (118)	Motor	B	W	Standardized scale, video coding	BOT-2, video coding (imitation and interpersonal synchrony)	EG: BCC, imitation, IPS CG: FMCC, imitation
Srinivasan et al. (4)	Social	B	B	Standardized scale, video coding	JTAT, video coding (spontaneous and responsive social attention)	Attention to targets: EG—greater attention to social partners and CG—greater attention to objects in the early, middle, and late sessions, Increased Spontaneous and Responsive Attention (EG)
			W			JTAT (EG)
Srinivasan et al. (6)	Social communication	B	W	Standardized scale, video coding	JTAT, video coding (response to social bids, verbalization and vocalization)	Increase in response to social bids from early to mid and late sessions, respectively, in EG and CG; socially-directed verbalization increased in EG, self-directed verbalization greater in CG, JTAT in EG

(Continued)

TABLE 3 | Continued

References	Domains tested	Study design	Type of effect reported	Type of assessment	Measures	Measures/variables showing improvement
Bieleninik et al. (116)	Social, QOL, other (cost-effectiveness and parent reported adverse events)	B	B	Standardized scale, questionnaire	ADOS, SRS (parent), QOL, cost-effectiveness scores	QOL (5M), ADOS—social affect (5M), SRS—motivation (5M) (as) and mannerisms (Baseline to 2M, 5M, and 12M) (as)
Mossler et al. (117)	Social communication	W	W	Standardized scale, questionnaire	ADOS, AQR, SRS	Attunement with therapist associated with changes in SRS total and cognition sub-scale scores at 5M (as)
Dvir et al. (98)	Social communication and motor	W	W	Standardized scale, video coding	ADOS-2, movement analysis, attunement analysis	Attunement parameters: AI and TAI, ADOS-CS (5M)
Yoo & Kim (138)	Social and motor	W	W	Observational assessment, video coding, questionnaire	K-SSRS, imitation, drumming, video coding (eye gaze and joint action synchronous movement), social validity	K-SSRS (total scores, self-control and cooperation subscales)
Willemin et al. (139)	Social and behavioral	W	W	Questionnaire	SPRS, fun-o-meter, smiley-o-meter, PANAS-C	SPRS, smiley-o-meter, fun-o-meter
Lowry et al. (140)	Social, motor, and other (program effectiveness and feasibility)	B	B	Standardized scale, video coding, questionnaire	MABC-2, drumming skills, SDQ, staff interview	Drumming (peer drum and EBD control at posttest and FUP) and SDQ (EBD drum- total difficulties and hyperactivity)
Stephen (141)	Social communication	B	B	Questionnaire	SSRS	EG: social skills
Schmid et al. (142)	Social communication	W	W	Video coding, questionnaire	DUACS, PDDBI, spoken language questionnaire	Language levels, empathy, social pragmatic problems, social awareness problems
Rabeyron et al. (143)	Social communication, behavioral	B	B	Standardized scale, questionnaire	CGI, ABC, CARS	CGI, CARS total, ABC total, lethargy, stereotypy
Cibrian et al. (144)	Motor and others (engagement with music)	B	B	Questionnaire, video coding	Bendable sound survey, DCDQ, strength, reaction time	DCDQ scores, control of movement, fine motor skills, strength, reaction time
(B) Yoga/mindfulness and martial arts-based interventions						
Yoga/mindfulness-based therapy						
Radhakrishna et al. (120)	Social communication, behavioral and motor	B	W	Observational assessment, questionnaire	ARI-E2 checklist, ITB, RSB	Qualitative improvements noted on all variables but details per outcome measure not provided
Radhakrishna et al. (121)	Motor	W	W	Observational assessment, questionnaire	ITB, parent-reported improvements using custom rating scale	ITB—improved imitation skills in GM, oro-facial, breathing, complex motor, and vocalization domains. Qualitative improvements in JA, object use, play, compliance, and language
Rosenblatt et al. (145)	Behavioral	W	W	Questionnaire/interview	BASC-2, ABC	BASC-2 (total sample—BSI; latency group—BSI, internalizing), ABC (latency group—irritability) (as)
Koenig et al. (88)	Behavioral	B	B	Video coding, questionnaire	ABC-C (parent and teacher), video coding (off-task behaviors and Teacher redirection)	ABC-C (teacher- total, irritability/agitation/crying, lethargy/social withdrawal and hyperactivity/non-compliance), Off-task behaviors, Teacher redirection
de Bruin et al. (146)	Social, behavioral, QOL, and others (self-reported anxiety and worry, mindful awareness, parental stress)	W	W	Questionnaire	Children: AQ, MAAS, PSWQ, RRS, WHO-5, parents rating children: SRS, AQ, parents rating themselves: FFMQ, WHO-5, IM-P, PSI-C, parenting scale	Children: WH0-5, RRS, parent rating children: SRS, parents rating themselves: FFMQ, WHO-5 (as)

(Continued)

TABLE 3 | Continued

References	Domains tested	Study design	Type of effect reported	Type of assessment	Measures	Measures/variables showing improvement
Narasingharao et al. (147)	Behavioral and others (GI and sleep problems)	B	W	Questionnaire	Custom questionnaire	Custom questionnaire (sleep, food, digestion, behavior (except savant ability)
Sotoodeh et al. (148)	Social communication, motor, and cognitive	B	B	Questionnaire	ATEC	ATEC (total scores, sociability, sensory/cognitive awareness, and healthy/physical behavior subscales)
Litchke et al. (149)	Social and behavioral	W	W	Video coding, questionnaire	TSSA, MFMS	TSSA (total, response to initiation, initiating interaction, affective understanding and perspective taking), MFMS (positive mood) (as)
Kaur & Bhat (150)	Motor	B	W	Standardized scale, video coding	BOT-2, video coding (% imitation error)	BOT-2 (EG: BC subtest, CG: FMI and FMP subtests), % imitation error EG: early-mid and early-late, CG: early-late, CG: showed positive correlation between IQ levels and BOT-2 FMI scores, % imitation error CG: mid-late (as)
Vidyashree et al. (151)	Others (HR variability)	B	W	ECG	ECG recording in Lead II	ECG (EG): Reduction in HR and pNN50%, Increase in mean RR, SDNN, RMSSD.
Tanksale et al. (152)	Cognitive and others (sleeping quality, anxiety, goal attainment scale, and emotion awareness)	B	B	Questionnaires	BRIEF-2, children's sleep habits questionnaire, anxiety scale for children with ASD-parent and self-report, GAS, emotional awareness questionnaire	BRIEF-2 (GEC and organization of material subscale at posttest and FUP, the self-monitor, working memory and task monitor subscale scores at posttest), children's Sleep Habits questionnaire (bedtime resistance, sleep onset delay, sleep breathing disorder), emotion awareness (verbal sharing and willingness to understand emotions), anxiety scale
Martial arts						
Bahrami et al. (122)	Behavioral	B	W	Standardized scale	GARS (stereotypy)	GARS (stereotypy- pre to post and FUP)
Movahedi et al. (153)	Social	B	W	Standardized scale	GARS (social interaction)	GARS (social interaction—pre to post and FUP)
Bahrami et al. (86)	Communication	B	W	Standardized scale	GARS (communication)	GARS (communication—pre to post and FUP)
Chan et al. (154)	Social communication, behavioral, cognitive	B	B	Computerized test, questionnaires, observational assessments, and EEG	Neuropsychological measures, ATEC, custom questionnaire, Go-No-Go test, EEG	Neuropsychological measures (TOL-rule violation), custom questionnaire (temper outburst), Neuropsychological measures [TOL-initial time (as)]
			W			ACC (EG: No-Go part of Go-No-Go Test), Main Effect of time-Neuropsychological measures (EG: CCTT-T2, FPT), ATEC (EG: sensory/cognitive awareness, sociability, health/physical behavior subscales) [TOL-initial time (as)]
Chan et al. (155)	Cognitive	B	W	Computerized test, EEG	Memory functions and EEG measures	Memory functions (visual scanning and semantic clustering), EEG measures (Theta coherence in left fronto-posterior region, left to right fronto-posterior region, frontal and posterior scalp). Increased theta

(Continued)

TABLE 3 | Continued

References	Domains tested	Study design	Type of effect reported	Type of assessment	Measures	Measures/variables showing improvement
						source activity in BL prefrontal cortex, left parietal cortex and medial and inferior temporal cortex in EG. In CG, increased source activity in left medial and inferior temporal cortex
Figueiredo et al. (156)	Social and behavioral	W	W	Questionnaire	Conner's scale (parent), SDQ	Conner's scale—parent (oppositional, DSM-IV total and defiant/aggressive behaviors), SDQ (peer relationship)
Kim et al. (157)	Motor	B	B	Posturography	Static balance test, functional balance test	Static balance test (single leg—R (eyes closed)
			W			EG: static balance test [single leg—L (eyes open), double leg—unstable surface (eyes closed) (as)], Functional balance test (step-quick turn to R (as)
Phung & Goldberg (104)	Cognitive	B	B	Questionnaire, computerized tests	Hearts and flowers executive functioning test, BRIEF-2	% accuracy scores on congruent and mixed blocks of the Hearts and flowers test, BRIEF-2 (global executive, behavior, and emotion regulation index)
Phung et al. (123)	Social communication	B	B	Questionnaire	SSIS	EG: SSIS
Sarabzadeh et al. (158)	Motor	B	B	Standardized scale	MABC-2	MABC-2 (total, ball skills, and balance)
			W			EG: MABC-2 (total, ball skills, and balance)
Garcia et al. (127)	Motor and others (continued participation in a similar program)	W	W	Physical activity monitoring using actigraph	MVPA	Increase in % time spent and increase in number of minutes (as) spent in MVPA/day
Rivera et al. (128)	Social communication	W	W	Questionnaire	ABC, Parent perspective questionnaire	–
Ansari et al. (159)	Motor	B	B	Qualitative measures	Static and Dynamic balance	EG: static and dynamic balance with greater improvements in kata group than aquatic training group compared to the control group
AdibSaber et al. (160)	Others (sleep habits)	B	B	Questionnaire	Sleep habits questionnaire	EG: sleep resistance, sleep duration, sleep anxiety, night time awakening, parasomnia, and daytime sleepiness
Greco & de Ronzi (161)	Social communication and cognitive	B	B	Questionnaire	SSIS-RS, BRIEF	EG: SSIS-RS (Social skills, problem behaviors scale), BRIEF (behavior regulation index, emotion regulation index, cognitive regulation index, global executive functioning composite)
Tabeshian et al. (162)	Behavior	B	B	Standardized scale	GARS-2	EG: GARS-2 stereotypy (pre-post)
			W			
(C) Theater/dramatic, dance-based, and miscellaneous interventions						
Theater/dramatic training						
Lerner et al. (163)	Social communication and behavioral	B	B	Questionnaire, computerized tests	EDI, SRS, SSRS, BDI-Y, satisfaction survey, CBCL, DANVA-2	Time 1–7: all measures, time 1–5: EDI (non-verbal communication), CBCL (Internalizing), SSRS (overall), DANVA-2 (child faces, postures)
Lerner & Mikami (164)	Social	B	B	Video coding, questionnaire	SRS, SSRS (parent and teacher), SIOS, Socio-metrics (child's social and friendship preferences)	SIOS: positive and negative interactions, socio-metrics: social preference (as), reciprocal friendship nominations. SSRS-T (social skills)

(Continued)

TABLE 3 | Continued

References	Domains tested	Study design	Type of effect reported	Type of assessment	Measures	Measures/variables showing improvement
Corbett et al. (124)	Social, behavioral, sensory problems and other (stress levels)	W	W	Standardized scale, questionnaire	NEPSY, SRS, SSS, SSP, ABAS, cortisol levels	NEPSY (Faces, ToM), cortisol (beginning of first and last, from pre-post for first and second rehearsal
Corbett et al. (126)	Social and others (stress levels)	W	W	Standardized scale, video coding, questionnaire	NEPSY, SRS, PSI, Parent/Child Dysfunction scale, ABAS, Companionship scale, PIP, cortisol levels	NEPSY (delayed memory for faces and memory for faces immediate v/s delayed), SRS (total, social awareness, social cognition), ABAS (home living, self-care), PSI (parent/child relationship), Cortisol (Theater 1 Camp—Play 2 and Theater Last Day—Play 2), Companionship scale (active involvement), NEPSY-(immediate memory for faces) (as)
Corbett et al. (165)	Social communication	B	B	Standardized scale, video coding, questionnaire	SRS, ABAS, NEPSY, PIP, ERP	NEPSY (MFD, MFI, TOM), ABAS (social- posttest), SRS (communication—at posttest and FUP), PIP (Group Play), ERP
Corbett et al. (87)	Social, behavioral, and others (stress levels)	B	B	Video coding, questionnaire	STAI-C, PIP, cortisol levels	STAI-C (trait), cortisol levels (beginning—end of first and middle days of intervention), PIP (as)
Ioannou et al. (125)	Social communication and others (anxiety levels)	B	B	Video coding, questionnaire	PIP, STAI- C	EG: PIP (solicited and unsolicited play) (as), STAI-C (trait anxiety)
Guli et al. (166)	Social communication, behavioral, and others (data collected on parent interview regarding efficacy of treatment)	B	B	Observational assessment, questionnaire, computerized tests	BASC, DANVA-2, observed social interactions	Social interaction—increase in positive interactions and decrease in solitary play
Kim et al. (167)	Social and behavioral	W	W	Observational assessment, questionnaire	RSE, EQ/SQ, resiliency scale, SCRETS	RSE (self-esteem−2 items), EQ/SQ (empathy−2 items), Resiliency scale (Comfort and Support from others−2 and 1 item, respectively, composite measures−3 items)
Reading et al. (168)	Social communication	B	B	Questionnaire	Rating of social behaviors	Scores on Social responsiveness, perspective of others, and participation and cooperation subscales increased from pretest to posttest in EG but not in CG.
Naniwadekar et al. (169)	Social communication	B	B	Questionnaire	ACPC-DD	ACPC-DD (social communication and emotion domains)
			W			EG and CG: ACPC-DD (social communication, and emotion domains)
Beadle-Brown et al. (170)	Social communication and behavioral	W	W	Standardized scale, questionnaire	ADOS-2, VABS-2, Ekman, parent/teacher rating of intervention	ADOS (reciprocal social interaction—module 3 (pre-post), total-module 3 (pre-post, pre-FUP, post-FUP), VABS (communication, socialization—pre-post), Ekman (pre-FUP) (pre-post- (as), ADOS-2 [total (pre-post and pre-FUP)] (as)
Dance therapy						
Arzoglou et al. (85)	Motor	B	W	Standardized scale	KTK (Korperkoordinationstest fur Kinder)	EG: KTK (total, backward walking, obstacle clearance on 1 leg, jumping sideways and sideways movement and repositioning), CG: No improvements

(Continued)

TABLE 3 | Continued

References	Domains tested	Study design	Type of effect reported	Type of assessment	Measures	Measures/variables showing improvement
Koehne et al. (171)	Social and Behavioral	B	B	Standardized scale, video coding, questionnaire, computerized test	MET, IRI, Automation imitation paradigm, Finger tapping test of synchrony, ASIM	Emotion inference on MET, automatic imitation on automatic imitation paradigm, reduction in asynchrony on finger tapping test with virtual human-like partner, improvements in spontaneous imitation/synchronization and reciprocity/dialogue on ASIM in EG but not CG
Koch et al. (77)	Social, behavioral, and sensory	B	B	Video coding, questionnaire	HSI, QMT, SA-Q, EES-SF, FBT (Social skills)	All the variables except Empathy (EES-SF)
Hildebrandt et al. (172)	Behavioral	B	B	Standardized scale	SANS	SANS total score and all 5 subscales (affective blunting, alogia, avolition, anhedonia, attention)
Mastrominico et al. (173)	Behavioral	B	B	Questionnaire	CEEQ	–
Souza-Santos et al. (174)	Self-care skills and others (social participation and autism severity)	B	B	Standardized scale, questionnaire	CARS, FIM, WHODAS	CARS (all groups), WHODAS (dance+EAT)
			W			FIM—communication and psychosocial domains (dance), WHODAS (dance and dance+EAT)
Aithal et al. (175)	Social communication and behavior	B	B	Questionnaire	SCQ, SDQ	SCQ (social communication), SDQ (emotional social well-being)
Miscellaneous: dance and music therapy						
Mateos-Moreno & Atencia-Doña (176)	Social, behavioral, and motor	B	B	Standardized scale	ECA-R	ECA-R (overall score), factor 1 (interaction disorder), function of imitation, emotion, instinct and regulation/behavior variability disorders)

EG, Experimental Group; CG, Control Group; ES, Effect Size; NA, Not Applicable; B, Between-group; W, Within-group; N, No; Y, Yes; CI, Confidence Interval; FUP, Follow-up; CRASS, Checklist for Communicative Responses/Acts Score Sheet; CGI-S, Clinical Global Impressions-Severity; CGI-I, Clinical Global Impressions-Improvement; BPRS, Brief Psychiatric Rating Scale; PDDBI-C; Pervasive Developmental Disorder Behavior Inventory-C; ESCS, Early Social Communication Scales; RJA, Responding to Joint Attention; IJA, Initiation of Joint Attention; CARS-BR, Childhood Autism Rating System-Brazilian version; IPR, Index of Peer Relations; RSES, Rosenberg Self-Esteem Scale; STAI-C, State Trait Anxiety Inventory (State and trait scales); VSEEC, Vineland Social-Emotional Early Childhood Scales; SRS, Social Responsiveness Scale; Mac-CDI, MacArthur Bates Communicative Development Inventories; PCRI, Parent-Child Relationship Inventory; MTDA, Music Therapy Diagnostic Assessment; ATEC, Autism Treatment and Evaluation Checklist; JA/ JTAT, Joint Attention; SSRS, Social Skills Rating System; RBS, Repetitive Behavior Scale; BOT-2, Bruininks-Oseretsky Test of Motor Performance-2nd Edition; FMCC, Fine Manual Control Composite; FMP, Fine Motor Precision; FMI, Fine Motor Integration; BCC, Body Coordination Composite; IPS, Interpersonal Synchrony; ADOS, Autism Diagnostic Observational Schedule; QOL, Quality Of Life; K-SSRS, Social Skills Rating System-Korean Version; SPRS, Social and Parent Relationship Scale; PANAS-C, Positive and Negative Affect Schedule for Children; MABC-2, Movement Assessment Battery 2nd Edition; SDQ, Strengths and Difficulties Questionnaire; AQR, Assessment of the Quality of the Relationship, DUACS, Duke University Autism Communication and Socialization; DCDQ, Developmental Coordination Disorder Questionnaire; AI, Attunement Index, TAI, Therapist Attunement Index. ARI-E2, Autism Research Institutes form E2 Checklist; ITB, Imitation Test Battery; RSB, Repetitive and Stereotyped Behavior Test Battery; GM, Gross Motor BASC-2, Behavior Assessment System for Children-Second Edition; ABC-C, Aberrant Behavior Checklist-Community; AQ, Autism Questionnaire; MAAS, Mindful Assessment and Awareness Scale; PSWQ, Penn State Worry Questionnaire; RRS, Ruminative Response Scale; WHO-5, World Health Organization-Five Well Being Index; FFMQ, Five Facet Mindfulness Questionnaire; IM-P, Interpersonal Mindfulness in Parenting Scale; PSI-C, Parenting Stress Index-Competence Scale; TSSA, Treatment and Research Institute for ASD Social Skills Assessment; MFMS, Modified Facial Mood Scale; EEG, Electroencephalogram; GARS, Gilliam Autism Rating Scale; NEPSY, Neuropsychological Measures; TOL, Tower of London; CCTT-T2, Children Color Trail Test; FPT, Five Point Test; BL, Bilateral; DSM, Diagnostic and Statistical Manual of Mental Disorders; BRIEF-2, Behavior Rating Inventory of Executive Function-2nd Edition; MVPA, Moderate to Vigorous Physical Activity; SSIS-RS, Social Skills Improvement System Rating Scale; GAS, Goal Attainment Scale; GEC, Global Executive Composite; EDI, Emory Dyssemia Index; BDI-Y, Beck Depression Inventory-Youth; CBCL, Child Behavior Checklist; DANVA-2, Diagnostic Analysis of Non-verbal Accuracy-2; SIOS, Social Interaction Observation System; MF, Memory for Faces; MFI, Memory for Faces Immediate; MFD, Memory for Faces Delayed; TOM, Theory of Mind; SSS, Stress Survey Schedule; SSP, Short Sensory Profile; ABAS, Adaptive Behavior Assessment System; PSI, Parent Stress Inventory; PIP, Peer Interaction Paradigm; ERP, Event Related Potential; EQ/SQ, Empathy/Systemizing Quotient; SCERTS, Social Communication, Emotional Regulation and Transactional Support Model; ACPC-DD, Activity Checklist for Preschool Children with Developmental Disability; VABS-2,Vineland Adaptive Behavior Scales; KTK, Korperkoordinationstest fur Kinder; MET, Multifaceted Empathy Test; IRI, Interpersonal Reactivity Index; ASIM, Assessment of Spontaneous Interaction in Movement; HIS, Heidelberg State Inventory; QMT, Questionnaire for Movement Therapy; SA-Q, Self-Awareness Questionnaire; EES, Emotional Empathy Scale; FBT, Fragebogen fuer Bewegungstherapie; SANS, Severity of Negative Symptoms; CEEQ, Cognitive and Emotional Empathy Questionnaire; CARS; Childhood Autism Rating System; FIM, Functional Independence Measure; WHODAS, WHO Disability Assessment Scale; ECA-R, Evaluation of Autistic Behavior-Revised Version; EAT, Equine Assisted Therapy; SCQ, Social Communication Questionnaire; SDQ, Strengths and Difficulties Questionnaire; STAI-C, State Trait Anxiety Scale for Children.

TABLE 4 | Study-wise list of reported and calculated effect sizes.

References	Reported ES	Magnitude of reported ES	Type of effect calculated	Magnitude of calculated ES	CI range for ES	# of ES per measure where CI doesn't include 0	Agreement between reported and calculated ES	Comments
(A) Music/rhythm therapies								
Music/rhythm therapy								
Edgerton et al. (129)	N	None	W	CRASS (3): 1.13–2.01	CRASS (3): 0.23–3.28	CRASS: 3 (total gain, musical vocal behavior, non-musical speech production)	NC	The paper reported significant findings for only total CRASS scores that was confirmed by our ES calculations. Non-parametric statistics used for all outcomes but no parameter estimates provided. Hence, ES calculated using provided Means and SDs
Hartshorn et al. (130)	N	None	B	Wandering (1): −1.28, Responding to touch negatively (1): 0.59, On-task passive behavior (1): 4.11, Resisting teacher (1): −1.57	Wandering (1): −1.77 to −0.78, Responding to touch negatively (1): 0.13–1.05, On-task passive behavior (1): 3.32–4.91, Resisting teacher (1): −2.08 to −1.06	Wandering: 1, Responding to touch negatively: 1, On-task passive behavior: 1, Resisting teacher: 1	NC	–
Boso et al. (131)	N	None	W	BPRS (3): −2.53 to −2.28, Music Skills (15): 0.16–2.66	BPRS (2): −4.54–0.63, Music Skills (15): −0.81–4.75	BPRS: 1 (T1–T2 and T1–T3), Music Skills: 3 (T1–T2 and T1–T3: singing a short melody, singing a long melody, playing the C scale on a keyboard)	NC	Non-parametric statistics used for all outcomes but no parameter estimates provided. Hence, ES calculated using provided Means and SDs
Kim et al. (119)	Y	PDDBI-C (clinician) (1): 0.79, ESCS (1): 0.97	B	ESCS (1): 1.91, Eye Contact (1): 4.06, Turn Taking (1): 4.06	ESCS (1): 0.41–3.41, Eye Contact (1): 1.89–6.23, Turn Taking (1): 1.89–6.23	ESCS: 1, Eye Contact: 1, Turn taking: 1	Fair	Calculated ES using *p*-values only
Kim et al. (101)	N	None	B	Joy (2): 0.47–0.55, Emotional Synchronicity (2): 0.51–0.54, Initiation of Engagement (1): 0.79, Initiation of Interaction (1): −0.30, Compliant Response (1): 0.11, No response (1): −0.64	Joy (2): −0.78–1.81, Emotional Synchronicity (2): −0.74–1.80, Initiation of Engagement (1): −0.49–2.08, Initiation of Interaction (1): −1.55–0.93, Compliant Response (1): −1.12–1.35, No response (1): −1.90–0.63	Joy: 0, Emotional Synchronicity: 0, Initiation of engagement: 0, Initiation of Interaction: 0, Compliant response: 0, No response: 0		
Gattino et al. (132)	Y	CARS-BR (1): −2.22	B	CARS-BR (1): −2.30	CARS-BR (3): −3.33 to −1.27	CARS-BR: 1 (non-verbal communication in autistic disorder)	Good	–

(Continued)

TABLE 4 | Continued

References	Reported ES	Magnitude of reported ES	Type of effect calculated	Magnitude of calculated ES	CI range for ES	# of ES per measure where CI doesn't include 0	Agreement between reported and calculated ES	Comments
Hillier et al. (133)	N	None	W	IPR-participant (1): 0.42, IPR-parent (1): 0.33, RSES (1): 0.40, STAI-C (2): 0.45–0.48	NA	NA	NC	Non-parametric statistics used. ES calculated using *Z* values provided in the paper
Wan et al. (134)	N	None	W	IPA (1): 1.38–2.36	IPA (3): −0.33–4.92	IPA: 0	NC	Non-parametric statistics used for all outcomes but no parameter estimates provided. Hence, *p*-values used for ES calculations
Thompson et al. (135)	Y	VSEEC (1): 1.96	B	VSEEC (1): 1.97	VSEEC (1): 0.93–3.02	VSEEC: 1	Fair	–
	N	None	W	MTDA (1): −1.37	MTDA (1): −2.37 to −0.38	MTDA: 1		
LaGasse (136)	N	None	B	Eye gaze (1): 0.91, JA w/child (1): 1.24, JA w/adult (1): −0.02	Eye gaze (1): −0.08–1.91, JA w/child (1): 0.20–2.28, JA w/adult (1): −0.97–0.93	Eye gaze: 0, JA w/child: 1, JA w/adult: 0	NC	–
	N	None	W	SRS (1): −1.00	SRS (1): −2.00 to −0.01	SRS: 1	NC	
Ghasemtabar et al. (137)	N	None	B	SSRS-P (2): 0.47–0.59	SSRS-P (1): −0.29–1.36	SSRS-P: 0	NC	–
Srinivasan et al. (27)	Y	RMB (1): 0.5; Negative Affect (1): −0.32; Interested Affect (1); 0.43	W	RMB (2): −0.50 to −0.66; Negative Affect (1): −0.32; Interested Affect (1): 0.43	RMB (2): −1.37–0.18; Negative Affect (1): −0.97–0.32; Interested affect (1): −0.23–1.09	RMB: 0; Negative affect: 0; Interested affect:	Good	–
Srinivasan et al. (118)	Y	BOT (1): 0.6; Imitation (1): −0.65; IPS (1): 0.23	W	Imitation (1): −0.65; IPS (1): 0.23	Imitation (1): −1.35–0.05; IPS (1): −0.41–0.87	Imitation: 0; IPS: 0		
Srinivasan et al. (4)	Y	Social attention (3): 1.09–4.5; Spontaneous and responsive attention (6): 0.23–3.09	B	None	NA	NA		
	Y	JTAT (1): 0.55; Social Attention (9): 1.03–2.04	W	JTAT (1): 0.94	JTAT (1): 0.15–1.72	JTAT: 1		

(Continued)

TABLE 4 | Continued

References	Reported ES	Magnitude of reported ES	Type of effect calculated	Magnitude of calculated ES	CI range for ES	# of ES per measure where CI doesn't include 0	Agreement between reported and calculated ES	Comments
Srinivasan et al. (6)	Y	Spontaneous verbalization (3): 0.51–0.61;	B	Spontaneous verbalization (1): 0.91	Spontaneous verbalization (1): 0.07–1.76	Spontaneous verbalization: 1	Calculated ES for JTAT and other outcome measures based on *p*-values reported in the paper. Hence, poor agreement between calculated and reported ES	
	Y	JTAT (1): 0.55; Response to social bids (2): 1.18–1.67; Verbalization with social partners (4): 0.67–1.07	W	JTAT (1): 0.94; Response to social bids (2): 1.20–1.70;	JTAT (1): 0.15–1.72 Response to social bids (2): 0.32–2.75;	JTAT: 1; Response to social bids: 2		
Bieleninik et al. (116)	N	None	B	ADOS (6): −0.03–0.2; SRS (6): −0.04–0.02	ADOS (6): −0.25–0.44; SRS (6): −0.28–0.26	ADOS: 0, SRS: 0	NC	No significant differences found in ADOS and SRS scores from baseline to post-test or at FUP
Mossler et al. (117)	N	None	W	Couldn't calculate ES	NA	NA	NA	–
Dvir et al. (98)	N	None	W	AI (1): −0.26, TAI (1): −0.27, ADOS-2 (1): 0.20	ADOS-2 (1): −0.13–0.54	ADOS-2: 0	NC	Non-parametric statistics i.e., Wilcoxon's signed rank test used and *Z*-scores reported. Thus, the Kerby's formula of r = Z/(sqrt)N was used (*N* = number of observations made and r = ES estimate)
Yoo & Kim (138)	N	None	W	SRS-K (3): 1.35–1.63	SRS-K (3): 0.12–3.07	SRS-K: 3 (total, cooperation and self-control)	NC	Non-parametric statistics used for all outcomes but no parameter estimates provided. Hence, ES calculated using provided Means and SDs
Willemin et al. (139)	Y	Smiley 8 (1): −0.25, Fun-O-Meter (1): −0.36	W	Smiley 8 (2): −0.55, Fun-O-Meter (2): −0.56	Smiley 8 (2): −1.17–0.06, Fun-O-Meter (2): −1.18–0.06	Smiley 8: 0, Fun-O-meter: 0	Good agreement between ES calculated through the *p* and *F* values provided. But poor agreement between calculated and reported ES	ES calculated and triangulated using p and *t*-values
Lowry et al. (140)	N	None	B	SDQ (3): 0.73–0.90	NA	NA	NC	Non-parametric statistics (Mann-Whitney *U*-test) used and *U*-values were provided in the paper. ES calculation based on formula, ES = U/n1+n2 (n1 and n2 = sample sizes of the 2 Groups being compared)
Stephen (141)	N	None	B	SSRS (1): 0.60	SSRS (1): −0.12–1.34	SSRS: 0	NC	–

(Continued)

TABLE 4 | Continued

References	Reported ES	Magnitude of reported ES	Type of effect calculated	Magnitude of calculated ES	CI range for ES	# of ES per measure where CI doesn't include 0	Agreement between reported and calculated ES	Comments
Schmid et al. (142)	N	None	W	DUACS (1): 0.78, PDDBI subscales (7): −0.23–0.23	DUACS (1): 0.49–1.07, PDDBI subscales (7): −1.51–0.48	DUACS: 1, PDDBI subscales: 1 (associative learning skills)	NC	–
Rabeyron et al. (143)	Y	CGI (1): −0.8, CARS (1): 0.22, ABC (3): −0.31–0.02	B	CGI (1): −1.05, CARS (1): −0.13, ABC (3): −0.46 to −0.26	CGI (1): −1.74 to −0.35, CARS (1): −0.79–0.52, ABC (3): −1.12–0.39	CGI: 1, CARS: 0, ABC: 0	Poor	–
Cibrian et al. (144)	N	None	B	Couldn't calculate ES	NA	NA	NA	–
(B) Yoga/mindfulness and martial arts-based interventions								
Yoga/mindfulness-based therapy								
Radhakrishna et al. (120)	N	None	W	None	NA	NA	NA	NA
Radhakrishna et al. (121)	N	None	W	None	NA	NA	NA	NA
Rosenblatt et al. (145)	N	None	W	BASC (2): 0.43–0.49; Aggregate BASC and ABC (4): 0.60–0.88	BASC (2): 0.050–19.83; Aggregate BASC and ABC (4): 0.01–1.52	BSI: 2 (BSI, atypicality); Aggregate BASC and ABC: 4 (irritability-atypicality, irritability-BSI, irritability-depression, irritability- externalization	NC	Study conducted overall sample analysis as well as sub-group analysis for 5–12-year-olds. BASC improvements were seen in analysis for total sample and the sub-group. Aggregate of ABSC and ABC improved in sub-group only.
Koenig et al. (88)	Y	Teacher ABC (4): 0.53–1.19	B	Teacher ABC (4): 0.50–0.65	Teacher ABC (4): −0.08–1.24	Teacher ABC: 1 [total (*F*-value)]	Poor agreement for teacher-ABC (lethargy, total), good agreement for teacher- ABC (irritation, stereotypic behavior, hyperactivity, inappropriate speech)	ES calculated and triangulated using *p* and *F* values
de Bruin et al. (146)	Y	WHO (2): 0.55–0.63; RRS (1): −0.92; SRS (4): −0.4−0.17;	W	Couldn't calculate ES	NA	NA	NA	-
Narasingharao et al. (147)	N	None	W	EG: SQ (15): 0.28–0.64, FQ (16): 0.48–0.63, BQ (29): 0.50–0.62	NA	NA	NA	Non-parametric statistics i.e., Wilcoxon's signed rank test used and *Z*-scores reported. Thus, the Kerby's formula of r = Z/(sqrt)N was used (*N* = number of observations made and r = ES estimate)
Sotoodeh et al. (148)	N	None	B	ATEC (4): 1.42–2.66	ATEC (4): 0.39–3.93	ATEC: 4 (sociability, sensory/cognitive/ awareness, health/physical/behavior and total)	NC	ES calculated and triangulated using *p* and *F* values

(Continued)

TABLE 4 | Continued

References	Reported ES	Magnitude of reported ES	Type of effect calculated	Magnitude of calculated ES	CI range for ES	# of ES per measure where CI doesn't include 0	Agreement between reported and calculated ES	Comments
Litchke et al. (149)	N	None	W	TSSA (4): −3.04–0.92	TSSA (4): −7.17–2.64	TSSA: 0	NC	ES calculated and triangulated using *t*- and *p*-values except for Total scores where Means and SD were provided
Kaur & Bhat (150)	N	None	B	None			Poor	
	Y	EG: BOT-2 (1): 0.56, % Imitation (2): 0.96–1.48, CG: BOT-2 (2): 0.3–0.32, % Imitation (1): 0.83	W	EG: BOT-2 (1): 0.96, % Imitation (2): 0.76–0.76, CG: BOT-2 (2): 0.66–0.66, % Imitation (1): 0.77	EG: BOT-2 (1): 0.12–1.81, % Imitation (2):−0.011 to 1.55, CG: BOT-2 (2):−0.04–1.37, % Imitation (1):−0.011–1.55	EG: BOT-2: 1 (Bilateral coordination), % Imitation: 0, CG: BOT-2: 0, % Imitation: 0		*p*-values used for calculation of ES
Vidyashree et al. (151)	N	None	B	Couldn't calculate ES	NA	NA	NA	NA
	N	None	W	Couldn't calculate ES	NA	NA		
Tanksale et al. (152)	Y	BRIEF-2 (10): −0.69 to −0.37, Children's sleep habits questionnaire (4): −0.48–0.33, Emotion awareness (3): −0.52–0.59, Anxiety (1): −0.43	B	BRIEF-2 (10): −0.64 to −0.34, Children's sleep habits questionnaire (4): 0.5–0.59, Emotion awareness (3): 0.51–0.73, Anxiety (1): 0.56	BRIEF-2 (10): −1.16–0.15, Children's sleep habits questionnaire (4): −0.004–1.1, Emotion awareness (3): 0.002–1.25, Anxiety (1): 0.05–1.08	BRIEF-2: 2 (FUP: GEC, self-monitor) Children's sleep habits questionnaire: 3 (bedtime resistance, sleep onset delay, sleep breathing disorder), Emotion awareness: 3, Anxiety: 1	Good	–
Martial Arts								
Bahrami et al. (122)	N	None	B	GARS (2): −0.66 to −0.47	GARS (2): −0.14–0.24	GARS: 0	NC	Paper reported significant within-group effects confirmed by our ES calculations. Between-group comparisons were not significant
	N	None	W	GARS (2): −0.73 to −0.60	GARS (2): −1.35 to −0.003	GARS: 2 (Stereotypy: pre-post and pre-FUP)		
Movahedi et al. (153)	N	None	B	GARS (2): −1.10 to −0.78	GARS (2): −1.93–0.01	GARS: 1 (Social Interaction: pre-post)	NC	
	N	None	W	GARS (2): −1.13 to −0.82	GARS (2): −1.93 to −0.11	GARS: 2 (Social Interaction: pre-post and pre-FUP)		
Bahrami et al. (86)	N	None	B	GARS (2): −0.75 to −0.64	GARS (2): −1.49–0.090	GARS: 1 (Communication: pre-post)	NC	
	N	None	W	GARS (2): −0.81 to −0.70	GARS (2): −1.45 to −0.07	GARS: 2 (Communication: pre-post and pre-FUP)		

(Continued)

TABLE 4 | Continued

References	Reported ES	Magnitude of reported ES	Type of effect calculated	Magnitude of calculated ES	CI range for ES	# of ES per measure where CI doesn't include 0	Agreement between reported and calculated ES	Comments
Chan et al. (154)	Y	Neuropsychological measures (1): 0.84, Custom questionnaire (3): 0.86	B	Neuropsychological measures (1): 0.20, Custom questionnaire (1): 0.73	Neuropsychological measures (1):−0.42–0.822, Custom questionnaire (2): 0.09–1.37	Neuropsychological measures: 0, Custom questionnaire: 1 (temper outburst (*t*-value)	Between-group ES show good agreement. Within-group ES for EG show poor agreement	Paper reported only within-group effects. ES calculated and triangulated using *p* and *t* values
	Y	Neuropsychological measures (2): 0.80–0.83, ATEC (3): 0.2 −0.68	W	Neuropsychological measures (2):−0.4–0.57, ATEC (3):−0.33 to −0.25, ACC (2): 0.06	Neuropsychological measures (2):−0.88–1.07, ATEC (3):−0.82–0.22, ACC (2):−0.39–0.52	Neuropsychological measures: 1 (FPT), ATEC: 0, ACC: 0		
Chan et al. (155)	Y	Memory (2): 0.57–0.73	W	Memory (2): 0.55 −0.70; EEG (6): 0.42–0.68	Memory (2): 0.02–1.26: EEG (6):−0.03–1.24	Memory: 2; EEG: 4	Good agreement for memory scores	ES calculated and triangulated using *p* and *t* values
Figueiredo et al. (156)	N	None	W	SDQ (1): 0.87, Connors scale for parents (3): 0.87–0.97	SDQ (1):−0.16–1.90, Connors Scale for Parents (3):−0.15–2.04	SDQ: 0, Connor's Scale: 0	NC	Non-parametric statistics used for all outcomes but no parameter estimates provided. Hence, *p*-values used for ES calculations
Kim et al. (157)	Y	Single Leg R (eyes closed) (1): 0.5	B	Single Leg R (eyes closed) (1): Could not calculate	NA	NA	NC	The SD for control group was reported as 0 in the original paper; hence ES could not be computed
	N	None	W	Single leg L (eyes open) (1): −0.522	Single leg L (eyes open) (1): −1.42–0.37	Single leg L (eyes open): 0		
Phung & Goldberg (104)	Y	Hearts and flowers accuracy % (2): 0.83–1.01, BRIEF-2 (2):−0.88 to −0.67	B	Hearts and flowers accuracy % (2): 0.442–0.72, BRIEF-2 (3):−0.55 to −0.45	Hearts and flowers accuracy % (2):−0.24–1.42, BRIEF-2 (2):−2.25–0.23	Hearts and flowers accuracy %: 1 (congruent), BRIEF-2: 0	Poor	–
Phung et al. (123)	Y	SSIS (2): −1.61–1.19	B	SSIS (2): −1.13–0.63	SSIS (2): −1.86–1.33	SSIS: 1 (problem behaviors)	Fair	
Sarabzadeh et al. (158)	N	None	B	MABC-2 (3): −3.61 to −3.14	MABC-2 (3): −5.11 to −1.76	MABC: 3 (total, ball skills and balance)	NC	Paper reported significant between- and within-group effects. We report only between-group ES
Garcia et al. (127)	Y	MVPA (% activity) (1): 0.97	W	MVPA (% activity) (1): 0.54	MVPA (% activity) (1): −0.076–1.16	MVPA (% activity): 0	Poor	Non-parametric statistics used for all outcomes but no parameter estimates provided. Hence, *p*-values used for ES calculations
Rivera et al. (128)	N	None	W	ABD (6): −0.29–0.01	ABC (6): −0.71–0.42	ABC: 0	NC	No improvements reported by paper, confirmed by our ES calculations

(Continued)

TABLE 4 | Continued

References	Reported ES	Magnitude of reported ES	Type of effect calculated	Magnitude of calculated ES	CI range for ES	# of ES per measure where CI doesn't include 0	Agreement between reported and calculated ES	Comments
Ansari et al. (159)	N	None	B	Static balance (1): 2.3, dynamic balance (1): 5.34	Static balance (1): 1.17–3.44, dynamic balance (1): 3.46–7.21	Static balance: 1, dynamic balance: 1	NC	–
AdibSaber et al. (160)	N	None	B	Sleep questionnaire (6): −3.87 to −1.41	Sleep questionnaire (6): −5.35 to −0.43	Sleep questionnaire: 6 (total score, sleep duration, sleep anxiety, night time awakening, parasomnia, daytime sleepiness)	NC	–
Greco & de Ronzi (161)	Y	SSIS-RS (2): 2.64–2.85, BRIEF (4): 0.97–1.63	B	SSIS-RS (2):−0.92–1.15, BRIEF (4):−0.46 to −0.33	SSIS-RS (2):−1.7–1.95, BRIEF (4):−4.19–0.41	SSIS-RS: 1 (social skills)	Poor.	Reported ES larger in magnitude than calculated ES.
Tabeshian et al. (162)	N	None	B	GARS (1): −0.49	GARS (1): −1.17–0.17	GARS: 0	NC	–
(C) Theater/dramatic, dance-based, and miscellaneous interventions								
Theater/dramatic training								
Lerner et al. (163)	Y	None	B	Couldn't calculate ES	NA	NA	NA	–
	N	None	W	Couldn't calculate ES	NA	NA		
Lerner & Mikami (164)	Y	SIOS (2):−0.98 to −1.17, SSRS-T (1): 0.59	B	SIOS (2):−2.02 to −1.88, SSRS-T (1): 0.33	SIOS (2):−2.36–0.57, SSRS-T (1):−0.76–1.43	SIOS: 0, SSRS-T: 0	Poor	–
	Y	CG: Sociometrics (1): 0.7	W	CG: Sociometrics (1): 1.16	CG: Sociometrics (1): −0.38–2.72	Sociometrics: 0		
Corbett et al. (124)	Y	NEPSY (2): 1.44–1.68	W	NEPSY (2): 0.35–0.429, Cortisol (3): −2.55 to −1.69	NEPSY (2):−0.50–1.30, Cortisol (3):−4.55 to −0.22	NEPSY: 0, Cortisol (3): 3	Poor	Significant differences found between cortisol levels measured before and after the first and middle rehearsals and also those taken at the beginning of D1 and D3 sessions
Corbett et al. (126)	Y	NEPSY (2): −0.99 to −0.89, SRS (3): 0.23–1.46, ABAS (2): −0.34 to −0.29, PSI (1): 0.71, Cortisol (5): −0.72–1.24	W	NEPSY (2): 0.78–0.89, SRS (3):−3.30 to −0.26, ABAS (2): 0.31–0.36, PSI (1):−0.60, Companionship scale (1): 0.56, Cortisol (5): 0.73–0.84	NEPSY (2): 0.002–1.72, SRS (3):−3.27–0.4, ABAS (2):−0.36–1.05, PSI (1):−1.34–0.13, Companionship scale (1):−0.16–1.29, Cortisol (5):−0.03–1.65	NEPSY: 2 (MFD and MFD), SRS: 1 (social cognition), ABAS: 0, PSI: 0, Companionship scale: 0, Cortisol: 3	Good agreement overall except for ABAS communication and play-based cortisol levels	Non-parametric statistics used for all outcomes but no parameter estimates provided. Hence, *p*-values used for ES calculations for cortisol levels measured at different times. Reductions in cortisol levels during play between D1 and D2 and between D2 to end of training

(Continued)

TABLE 4 | Continued

References	Reported ES	Magnitude of reported ES	Type of effect calculated	Magnitude of calculated ES	CI range for ES	# of ES per measure where CI doesn't include 0	Agreement between reported and calculated ES	Comments
Corbett et al. (165)	N	None	B	ABAS (1): 0.75, SRS (2):−0.83, PIP (1): 0.74, NEPSY (3): 0.73 −0.97, ERP (1): 0.90	ABAS (1): 0.004–1.49, SRS (2):−2.58 to −0.08, PIP (1): 0.002–1.49, NEPSY (3):−0.01–1.73, ERP (1): 0.15–1.66	ABAS: 1 (social), SRS: 1 (communication), PIP: 1 (group play), NEPSY: 2 (MFD, TOM), ERP: 1 (social brain)	Good agreement for all except SRS communication	–
Corbett et al. (87)	N	None	W	STAI-C (1): −0.49, Cortisol (2): −0.61 to −0.58	STAI-C (1): −1.04–0.04, Cortisol (2): −1.17 to −0.02	STAI-C: 0, Cortisol: 2	NC	Reductions in cortisol levels during play from beginning to the end of first and middle days of intervention
Ioannou et al. (125)	N	None	B	PIP (4): 0.47–0.66, STAI-C (2): 0.02–0.63	PIP (4): 0.01–1.14, STAI-C (2): −0.44–1.11	PIP: 4 (solicited and unsolicited group and self-play), STAI-C: 1 (trait anxiety)	NC	–
Guli et al. (166)	Y	None	B	Observed behaviors (2): −0.54–0.68	Observed behaviors (2): −1.59–1.66	Observed behaviors: 0	NC	Non-parametric statistics used for all outcomes but no parameter estimates provided. Hence, Means and SDs used for ES calculations
Kim et al. (167)	N	None	W	RSE (2): −0.47–0.5, EQ/SQ (2): 0.30–0.40, Comfort with others (2): 0.75 −0.4, Support from others (1): −0.46, Composite measures (3): 0.34–0.58	RSE (2): −1.01–1.02, EQ/SQ (2): −0.20–0.91, Comfort with others (2): −0.11–1.31, Support from others (1): −0.98–0.05, Composite measures (3): −0.16–1.12	RSE: 0, EQ/SQ: 0, Comfort with others: 1 (I can meet new friends easily), Support from others: 0, Composite measures: 2 (self-esteem and comfort with others)	NC	Non-parametric statistics used for all outcomes but no parameter estimates provided. Hence, Means and SDs used for ES calculations
Reading et al. (168)	N	None	B	Couldn't calculate ES	NA	NA	NC	Main effect of group X time provided, thus ES could not be calculated
Naniwadekar et al. (169)	N	None	B	Communication (1): −1.01	Communication (1): −2.49–0.45	Communication: 0	NC	–
	N	None	W	Communication (1): 1.07	Communication (1): −3.50–0.19	Communication: 1		
Beadle-Brown et al. (170)	Y	ADOS-2 (1): 1.96, VABS (2): 3.42–6.07, Ekman (1): 2.12	W	ADOS-2 (4): 0.17–0.55, VABS (2): 0.51–0.62	NA	NA	Poor	Non-parametric statistics i.e., Wilcoxon's signed rank test used and *Z*-scores reported. Thus, the Kerby's formula of r = Z/(sqrt)N was used (*N* = number of observations made and r= ES estimate)

(Continued)

TABLE 4 | Continued

References	Reported ES	Magnitude of reported ES	Type of effect calculated	Magnitude of calculated ES	CI range for ES	# of ES per measure where CI doesn't include 0	Agreement between reported and calculated ES	Comments
Dance therapy								
Arzoglou et al. (85)	N	None	B	KTK (5): 0.88–2.63	KTK (5): −0.32–4.32	KTK: 0	NC	Paper reported significant differences between groups, but ES calculations suggest no significant between or within-group differences
Koehne et al. (171)	Y	None	B	MET (1): 0.31, AIP (1): 0.56, asynchrony test (1): −0.42, ASIM (2): 0.71–1.21	MET (1): −0.23–0.866, AIP (1): −0.004–1.12, asynchrony test (1): −1.106–0.26, ASIM (2): −0.12–2.1	MET: 0, AIP: 0, asynchrony test: 0, ASIM: 1 (reciprocity/dialogue	Fair	–
	N	MET (1): 0.58, AIP (1): 0.47, Asynchrony test (1): −0.63, ASIM (2): 1.27–1.25	W	MET (1): 0.76, AIP (1): 0.42, Asynchrony test (1): −0.34, ASIM (2): 0.41–1.28	MET (1): −0.11–0.68, AIP (1): −0.341–0.44, Asynchrony test (1): −0.83–0.14, ASIM (2): −0.13–0.96	MET: 0, AIP: 0, asynchrony test: 0, ASIM: 1 (reciprocity/dialogue)		
Koch et al. (77)	Y	QMT (1): 0.62, SOA (1): 0.72, HSI (1): 0.68, FBT (1): 0.67	B	QMT (1): 0.59, SOA (1): 0.63, HSI (1): 0.68, FBT (1): 0.54	QMT (1): −0.12–1.31, SOA (1): −0.09–1.35, HSI (1): −0.04–1.40, FBT (1): −0.16–1.26	QMT: 0, SOA: 0, HSI: 0, FBT: 0	Fair	–
Hildebrandt et al. (172)	N	None	B	SANS (6): −0.47 to −0.01	SANS (6): −0.97–0.48	SANS: 0	NC	The study had a lot of missing data but ES calculations using full sample vs. completed cases only did not reveal substantial differences in magnitude and direction of ES and their CIs. Hence, estimates from full sample are reported
Mastrominico et al. (173)	N	None	B	IRI/SPF-E (1): 0.03, CEEQ (6): −0.17–0.23	IRI/SPF-E (1): −0.58–0.57, CEEQ (6): −0.71–0.78	IRI/SPF-E (1): 0, CEEQ (6): 0	NC	No improvements reported by paper, confirmed by our ES calculations
Souza-Santos et al. (174)	N	None	B	CARS (1): −2.63 (dance-EAT), –d.36 (dance-dance and EAT), 1.26 (EAT-dance and EAT)	CARS (1): −3.60 to −1.65 and –n.15 to −0.56 and 0.48–2.05	CARS: 1 (dance, equine and dance+equine)	NC	Non-parametric statistics used for all outcomes but no parameter estimates provided. Hence, *p*-values used for ES calculations for WHODAS and FIM
	N	None	W	CARS (1): −4.72 (dance-EAT), –d.72 (dance-dance and EAT), −2.09 (EAT-dance and EAT), FIM (2): 0.64–0.73, WHODAS (1): 0.91	CARS (1): −6.82 to −1.04, FIM (2): 0.02–1.35, WHODAS (1): 0.24–1.59	CARS: 1 (between all 3 groups), FIM: 2 (communication, psychosocial adjustments in dance group), WHODAS: 1 (dance+equine)		

(Continued)

TABLE 4 | Continued

References	Reported ES	Magnitude of reported ES	Type of effect calculated	Magnitude of calculated ES	CI range for ES	# of ES per measure where CI doesn't include 0	Agreement between reported and calculated ES	Comments
Aithal et al. (175)	Y	SCQ (2): 0.09–1.523, SDQ (2): 0.02–1.127	B	SCQ (2): 0.33–0.48, SDQ (2): 0.22–0.68	SCQ (2): −1.28–0.45, SDQ (2): −1.49–0.56	SCQ: 0, SDQ: 0	Poor	
Miscellaneous: dance and music therapy								
Mateos-Moreno & Atencia-Doña (176)	Y	Overall score on ECA-R (1): 2.04, Interaction disorder (1): 1.18, Function of imitation (1): 2.35, Function of emotion (1): 1.41, Function of instinct (1): 1.88, Function of behavior (1): 2.37	B	Interaction disorder (1): 0.5, Function of imitation (1): 0, Function of emotion (1): 1, Function of instinct (1): 0.5, Function of behavior (1): 0	NA	NA	Poor	Non-parametric statistics i.e., Wilcoxon's signed rank test used and *Z*-scores reported. Thus, the Kerby's formula of r = Z/(sqrt)N was used (*N* = number of observations made and r = ES estimate)

Effect size (ESs) have been calculated and reported only for variables and measures where significant effects were reported in the original study. Effect sizes have been reported as absolute values in terms of magnitude only (for instance, for some variables a negative ES implies improvement. The numbers in parentheses reported next to the measure in columns 4–6 indicate the number of effect sizes calculated per measure. In case of multiple effect sizes calculated per measure, an ES range has been reported. Whenever possible, an attempt was made to triangulate ES values (for instance, if the study provide p-, t-, and/or F-values, ESs were calculated using all methods and checked for agreement). In addition, we have also reported Confidence intervals (CI) for effect sizes. In cases where multiple effect sizes have been calculated per outcome measure, CI ranges have been reported. Lastly, we have also mentioned the number of statistically significant effect sizes (CI do not include 0) per outcome measure for each study. In papers that used multiple control groups, results are reported only from the ASD groups that received creative movement interventions.
EG, Experimental Group; CG, Control Group; ES, Effect Size; NA, Not Applicable; NC, No Comparison Possible Since Original Paper did not report effect size estimates; B, Between-group; W, Within-group; N, No; Y, Yes; CI, Confidence Interval; FUP, Follow-up; CRASS, Checklist for Communicative Responses/Acts Score Sheet; CGI-S, Clinical Global Impressions-Severity; CGI-I, Clinical Global Impressions-Improvement; BPRS, Brief Psychiatric Rating Scale; PDDBI-C, Pervasive Developmental Disorder Behavior Inventory-C; ESCS, Early Social Communication Scales; RJA, Responding to Joint Attention; IJA, Initiation of Joint Attention; CARS-BR, Childhood Autism Rating System-Brazilian version; IPR, Index of Peer Relations; RSES, Rosenberg Self-Esteem Scale; STAI-C, State Trait Anxiety Inventory (State and Trait scales); VSEEC, Vineland Social-Emotional Early Childhood Scales; SRS, Social Responsiveness Scale; Mac-CDI, MacArthur Bates Communicative Development Inventories; PCRI, Parent-child Relationship Inventory; MTDA, Music Therapy Diagnostic Assessment; ATEC, Autism Treatment and Evaluation Checklist; JA/ JTAT, Joint Attention; SSRS, Social Skills Rating System; RBS, Repetitive Behavior Scale; BOT-2, Bruininks-Oseretsky Test of Motor Performance-2nd Edition; FMCC, Fine Manual Control Composite; FMP, Fine Motor Precision; FMI, Fine Motor Integration; BCC, Body Coordination Composite; IPS, Interpersonal Synchrony; ADOS, Autism Diagnostic Observational Schedule; QOL, Quality Of Life; K-SSRS, Social Skills Rating System-Korean Version; SPRS, Social and Parent Relationship Scale; PANAS-C, Positive and Negative Affect Schedule for Children; MABC-2, Movement Assessment Battery 2nd Edition; SDQ, Strengths and Difficulties Questionnaire; AI, Attunement Index, TAI, Therapist Attunement Index; DUACS, Duke University Autism Communication and Socialization; ARI-E2, Autism Research Institutes form E2 Checklist; ITB, Imitation Test Battery; RSB, Repetitive and Stereotyped Behavior Test Battery; GM, Gross Motor BASC-2, Behavior Assessment System for Children-Second Edition; ABC-C, Aberrent Behavior Checklist-Community; AQ, Autism Questionnaire; MAAS, Mindful Assessment and Awareness Scale; PSWQ, Penn State Worry Questionnaire; RRS, Ruminative Response Scale; WHO-5, World Health Organization-Five Well Being Index; FFMQ, Five Facet Mindfulness Questionnaire; IM-P, Interpersonal Mindfulness in Parenting Scale; PSI-C, Parenting Stress Index-Competence Scale; TSSA, Treatment and Research Institute for ASD Social Skills Assessment; MFMS, Modified Facial Mood Scale; EEG, Electroencephalogram; GARS, Gilliam Autism Rating Scale; NEPSY, Neuropsychological Measures; TOL, Tower of London; CCTT-T2, Children Color Trail Test; FPT, Five Point Test; BL, Bilateral; DSM, Diagnostic and Statistical Manual of Mental Disorders; BRIEF-2, Behavior Rating Inventory of Executive Function-2nd Edition; MVPA, Moderate to Vigorous Physical Activity; SSIS-RS, Social Skills Improvement System Rating Scale; GEC, Global Executive Composite; EDI, Emory Dyssemia Index; BDI-Y, Beck Depression Inventory-Youth; CBCL, Child Behavior Checklist; DANVA-2, Diagnostic Analysis of Non-verbal Accuracy-2; HSI, Heidelberger State Inventory; SIOS, Social Interaction Observation System; SSRS-T, SSRS Teacher Version; MF, Memory for Faces; MFI, Memory for Faces Immediate; MFD, Memory for Faces Delayed; TOM, Theory of Mind; SSS, Stress Survey Schedule; SSP, Short Sensory Profile; ABAS, Adaptive Behavior Assessment System; PSI, Parent Stress Inventory; PIP, Peer Interaction Paradigm; ERP, Event Related Potential; EQ/SQ, Empathy/Systemizing Quotient; SCERTS, Social Communication, Emotional Regulation and Transactional Support Model; ACPC-DD, Activity Checklist for Preschool Children with Developmental Disability; VABS-2,Vineland Adaptive Behavior Scales; KTK, Korperkoordinationstest fur Kinder; MET, Multifaceted Empathy Test; IRI, Interpersonal Reactivity Index; ASIM, Assessment of Spontaneous Interaction in Movement; HIS, Heidelberg State Inventory; QMT, Questionnaire for Movement Therapy; SA-Q, Self-awareness Questionnaire; EES, Emotional Empathy Scale; FBT, Fragebogen fuer Bewegungstherapie; SANS, Severity of Negative Symptoms; CEEQ, Cognitive and Emotional Empathy Questionnaire; CARS; Childhood Autism Rating System; FIM, Functional Independence Measure; WHODAS, WHO Disability Assessment Scale; EAT, Equine Assisted Therapy; ECA-R, Evaluation of Autistic Behavior-Revised Version; SCQ, Social Communication Questionnaire.

(2 Level I and Level II studies each), with limited insufficient evidence for yoga (1 Level I study), and theater (1 Level I, 1 Level II, and 1 Level III study) interventions in promoting social communication outcomes (see **Table 6**). One salient finding from our ES calculations is that although all 12 theater studies assessed social communication skills, only 3 of these studies (25%) showed significant improvement (CI of ES did not include 0) in social communication despite the heavy emphasis on peer-mediated social skill training in theater-based interventions (see **Table 6**). Taken altogether, our review suggests that there is *moderate evidence* from multiple Level I studies for *small-to-large-sized improvements* in *social communication* skills following mainly music and martial arts-based approaches.

Behavioral—Affective

Twenty-one papers in our review assessed *behavioral* outcomes i.e., 8 Level I (2 music, 1 yoga, 1 martial arts, 3 theater, 1 dance), 9 Level II studies (3 music, 2 yoga, 1 martial art, 1 theater, 1 dance, and 1 combined dance and music), and 4 Level III studies (1 yoga, 1 martial arts, and 2 theater). Behavioral states were assessed using standardized scales such as the GARS, Scale for Assessment of Negative Symptoms (SANS), and Pervasive Developmental Disorder Behavioral Inventory-Children (PDDBI-C), video-based coding of on- and off- task behaviors and the amount of redirection required during training sessions, as well as using questionnaire-based measures such as the Child Behavior Checklist (CBCL), Aberrant Behavior Checklist (ABC-C), and Autism Treatment and Evaluation Checklist (ATEC) (see **Tables 3A–C**). A total of 18 studies reported significant effects of CMT on behavioral skills, with the remaining 3 theater-based studies (87, 124, 166) reporting non-significant effects. Only 6 of the 18 studies that reported positive effects of CMT provided ES estimates in their original report ranging from small to large in magnitude. Furthermore, we were able to calculate a total of 39 ES from 14 studies, specifically, 8 ES from 5 out of the total 8 Level I studies, 20 ES from 6 out of the total 9 Level II studies, and 11 EFs from 3 out of the total 4 Level III studies. Our own calculations based on these papers suggested mostly medium effects for CMT (note that we obtained large ES estimates for 2 studies where *F*-values were used to calculate ES; however, these measures are more imprecise compared to ES calculations using means and SD/SE values).

As an example of positive intervention effects, Hartshorn et al. (130) reported significant, large improvements in on-task behaviors (ES: 1.28–4.11) from an early to a late training session following their Level II 8-week music and movement intervention compared to a no-intervention control group (130). Similarly, following a Level II, 14-week, Kata martial art intervention, the experimental group showed significant, medium-sized improvements on the stereotypy subscale (ES: 0.47–0.66) of the GARS compared to a control group, with gains retained at 1 month follow-up (122). Hildebrandt et al. conducted a Level II RCT to assess the effectiveness of a 10-week manualized dance movement therapy intervention on negative symptoms using the standardized, clinician-rated SANS scale in 78 individuals with ASD. The authors concluded that although the results did not reach statistical significance at the between-group level, they found promising trends for greater symptom reduction (ES: 0.008–0.47) in the experimental group compared to the waitlist control group in overall negative symptoms as well as most subscales of the SANS (177). Overall, out of the 39 total calculated ES across 14 studies, 17 estimates calculated from 7 studies (∼50% studies), specifically, 2 music (Level II), 3 yoga (1 each of Levels I, II, and III), 1 martial art (Level III), and 1 theater-based (Level I) intervention were statistically significant (CI did not include 0). Although the present state of the literature is insufficient to systematically evaluate the differing effects of various types of CMT, there is currently *some consistent evidence* for *medium-sized, positive effects* of CMT in reducing *behavioral* symptoms in individuals with ASD.

A total of 20 studies, i.e., 5 Level I (1 music, 3 theater, 1 dance), 6 Level II (1 music, 1 yoga, 1 theater, 2 dance, 1 music and dance combined), and 9 Level III (3 music, 2 yoga, 4 theater) studies assessed *affective* outcomes using questionnaires such as the Empathy/Systemizing Quotient (EQ/SQ), Brief Psychiatric Rating Scale (BPRS) Positive and Negative Affect Schedule (PANAS-C), and a computerized test such as the Multifaceted Empathy Test (MET) (see **Tables 3A–C**). We found that only 4 out of the 20 studies (1 yoga, 2 theater, and 1 dance) reported non-significant effects, with majority of the remaining studies suggesting small to medium-sized improvements. From the studies that reported training-related affective improvements, we were able to calculate a total of 57 ES, with 5 ES calculated from 4 out of the total 5 level I studies, 34 ES obtained from 3 out of the total 6 level II studies, and 18 ES from 4 out of the total 9 level III studies assessing changes in affective states following CMT.

Among the 5 Level I studies that indicated positive effects following CMT (1 music, 1 dance, 3 theater), largest ES estimates were reported by the 2 studies by Corbett et al. that found improvements in affect/emotion recognition and a reduction in anxiety (ES: 0.49–0.97) following a 10-week Social Emotional NeuroScience Endocrinology (SENSE) theater intervention in 8–14-year-old children with ASD (87, 165). While the Level I dance study by Koehne et al. (171) found significant improvements in emotion interference and empathy (ES: 0.31) on a computerized Multifaceted Empathy Test (MET) following a 10-week imitation- and synchronization-based group DMT in youth and adults with ASD, the single Level I music-based study by Srinivasan et al. (118) reported only within-group improvements (ES: 0.32–0.43) in levels of negative and interested affect in the group receiving rhythm therapy.

Of the 6 Level II studies (1 music, 1 yoga, 1 theater, 2 dance, and 1 combined music and dance), a majority of the studies reported small to medium positive effects on empathy, emotional synchronicity, joy, and overall psychological well-being inclusive of anxiety, depressed affect, tension, and vitality (ES: 0.31–0.68). For example, Kim et al. used a within-subject comparison cross-over design for improvisational music therapy and toy play sessions in 10 children with ASD and found that children showed greater frequencies of joyful events and mirrored emotional synchronicity (ES: 0.47–0.55) with the therapist during music therapy sessions compared to toy play sessions (101). The 9 Level III pre-post designs provided the largest variations in ES estimates ranging from small to large (0.3–1.12) across multiple studies for multiple outcomes related to anxiety, self-esteem, empathy, resiliency, emotion recognition, and enjoyment during sessions. However, out of the total 57 calculated ES across all affective outcomes from 11 studies, only 3 ES—from one Level III music and one Level I theater-based intervention (∼18% studies) had a CI that did not include 0. Moreover, similar to social communication outcomes, although a majority of theater-based studies assessed affective outcomes, our calculations suggest that only 1 study found significant, non-zero effects of the intervention on affective outcomes. Overall, our review suggests that although individual studies concluded *small-to-large*-sized positive effects, there is at present *insufficient evidence* supporting the beneficial effects of CMT on *affective* outcomes in ASD.

Taken altogether, we found only limited evidence from 26% studies (8 out of 31 studies) that were mainly Level II and Level III studies with high risk-of-bias for beneficial effects of yoga, music, martial arts, theater, and dance on behavioral-affective outcomes in ASD (see **Table 6**).

Sensorimotor

Of the three studies that assessed *sensory* skills using either questionnaires (Short sensory Profile, Questionnaire of movement therapy) or video coding-based measures, 2 Level II studies reported moderate-sized positive effects following dance and music interventions on children's body awareness and their negative response to touch (77, 130), with the 3rd theater-based study (Level III) reporting non-significant effects (124). We could calculate only 2 ES from 2 out of 2 Level II studies of which only 1 ES from a Level II music study did not include 0. Specifically, an 8-week intervention of music-based movement therapy led to improvements in children's negative response to touch (ES: 0.59) during training sessions compared to a waitlist control group (130). Although Koch et al., reported moderate improvements in awareness of body movement (ES: 0.62) after a 7-week long manualized DMT intervention, the CI of the calculated ES included 0 [(77); see **Tables 4A–C**]. Given the few studies that have assessed effects of CMT on sensory outcomes, at present, there is *insufficient evidence* to make definitive conclusions on the effects of CMT approaches on *sensory* outcomes in ASD.

Fifteen studies that assessed *motor* outcomes, i.e., 5 Level I (1 music, 2 yoga, 2 martial arts), 6 Level II studies (2 music, 1 yoga, 1 martial arts, 1 dance, 1 music and dance combined), and 4 Level III studies (2 music, 1 yoga, 1 martial arts) used standardized tests such as the Bruininks-Oseretsky Test of Motor Performance-2nd Edition (BOT-2), Movement Assessment Battery-2nd Edition (MABC), and the Korperkoordinationstest fur Kinder (KTK), questionnaires such as the ATEC and imitation test battery, as well as observation-based quantitative measures such as posturography, and video-coding for imitation and interpersonal synchrony. Out of the 8 studies that reported ES estimates, five studies (1 music, 1 yoga, 2 martial arts, 1 music and dance combined) reported medium-to-large positive effects of CMT and 3 music-based studies (1 Level I, 1 Level II, and 1 Level III; see **Tables 2A,B**) reported non-significant effects on motor skills following intervention (120, 138, 140). However, even among the clinical trials, 3 studies (27, 150, 157) reported only within-group effects suggesting that the positive effects were perhaps not robust enough to attain statistical significance at the between-group level. We were able to calculate a total of 18 ES, i.e., 10 ES from 4 out of the total 5 Level I studies, 5 ES from 1 out of the total 6 Level II studies and 3 ES from 2 out of the total 4 Level III studies assessing motor outcomes.

Large effects were obtained from the Level I study by Sarabzadeh et al. (158) on ball skills and balance subscales (ES: 3.14–3.16) assessed using the standardized MABC-2 test after a 6-week Tai Chi Chuan martial arts-based intervention. Similarly, the single Level II dance intervention that assessed motor outcomes reported improvements in the Korperkoordinations test fur Kinder (KTK) test (ES: 0.88–2.63), a measure of neuromuscular coordination including balance and agility, following an 8-week traditional Greek dance program in 5 children with ASD (85). Of the 3 studies that employed quantitative measures to assess motor outcomes, Garcia et al. in a Level III study reported large improvements in moderate-to-vigorous physical activity levels (MVPA) (ES: 0.97) using Actigraph GT9X accelerometers following a judo intervention in children with ASD (127). The other Level I and II studies reported improved static and dynamic balance and reduced postural sway during an eyes closed single leg balance task, respectively (ES: 0.5–5.34), following a 10-week Kata and an 8-week Taekwondo intervention in children with ASD, respectively (157, 159). Overall, out of the 18 ES calculated from 7 studies, CI for 8 ES calculated from 4 Level I studies (2 yoga, 2 martial arts) and 1 Level II study (music) did not include 0 (∼71% studies). Therefore, there seems to be *limited, yet very promising* evidence from mainly Level I studies for *medium-to-large sized improvements* in *motor* outcomes following martial arts and yoga-based interventions in ASD.

Therefore, altogether across the sensorimotor domain, there is limited evidence from around 28% studies (5 out of 18 studies, i.e., 4 Level I and 1 Level II) which showed improvements in assessed outcomes following predominantly yoga and martial arts interventions (see **Table 6**).

Cognitive

The 6 Level I studies (2 yoga, 4 martial arts) that assessed cognition used EEG measures to record neural activity, computerized tests such as the Go-No-Go and the Hearts and flowers test, as well as questionnaires such as the ATEC to report medium to large ES for improvements in executive functioning, visual memory, cognitive awareness, and brain activation patterns following CMT (104, 148, 152, 154, 155, 161) (see **Tables 3A,B**, **6**). For instance, Chan et al. reported large improvements in self-control (ES: 0.84), indicated by a reduction in the # of rule violations during a Tower of London task following a Nei Yang Gong martial arts intervention compared to a control group that received progressive muscle relaxation (154). Similarly, following a 13-week mixed martial arts intervention, Phung and Goldberg reported improvements in accuracy (ES: 0.83–1.01) on the computerized Hearts and Flowers executive functioning test (104). Of the 22 ES we could calculate from the 6 studies, the CI of 14 ES from 4 Level I studies (2 yoga, 2 martial arts) did not include zero (∼66% studies) (see **Table 6**). We found some disagreements between reported and calculated ES (see **Tables 4A–C** for details) (104, 154); however, our overall assessment suggests *limited promising evidence* for *medium-to-large sized improvements* in *cognitive* skills following martial arts and yoga-based interventions.

Functional Skills and Quality of Life

Three studies assessed activities of daily living and QOL using self- and family-report questionnaires such as the World Health Organization-Five Well-being Index (WHO-5), the WHO Disability Assessment Scale (WHODAS) and the Functional Independence Measure (FIM). Of these, 1 study each of Level I and II, respectively (1 music and 1 dance + EAT) [(116, 174); see **Tables 3A–C**, **6**] reported non-significant between-group effects on QOL and functional participation, whereas a single Level III study found medium-sized within-group improvements in QOL following a yoga-based intervention (146). Specifically, de Bruin et al., reported medium-sized improvements in QOL in adolescents with ASD measured on the WHO-5 well-being index (ES: 0.55–0.63) following a 9-week mindfulness training intervention (146). Although Souza-Santos et al., reported non-significant between-group differences, they found within-group improvements in the dance and combined dance and equine-assisted therapy intervention groups on the Functional Independence Measure (FIM) and WHO Disability Assessment Scale (WHODAS) (174). Based on reported data, we could only calculate 6 within-group ES from a single Level II study. Our calculations confirmed the findings from Souza-Santos et al. (174) with within-group ES estimates ranging from 0.64 to 0.73 and their CI not inclusive of 0. However, overall, at present, there is *insufficient evidence* to indicate any benefits from CMT on *functional participation and QOL* of individuals with ASD.

Other Domains

Sixteen (4 Level I, 6 Level II, 6 Level III) out of the 72 papers assessed effects of CMT on other domains including, (1) physiological parameters such as sleep, gastrointestinal (GI) problems, heart rate variability, and cortisol levels, (2) training-specific skills such as musical abilities and mindful awareness, and (3) cost effectiveness of provided interventions and parent-reported adverse effects (see **Tables 3A–C**, **6**). A combination of quantitative measures such as ECG recordings and salivary cortisol levels, standardized tests, and patient/caregiver-report questionnaires were used to assess these miscellaneous outcomes. For instance, Corbett et al. assessed the effects of theater-based interventions on salivary cortisol levels, a marker for physiological stress, in 3 separate studies, 2 of which were Level III pre-post designs and one was a Level I RCT (87, 124, 126). While theater interventions had large within-group effects (ES: 0.73–2.55) for reducing cortisol levels in participants during and after the intervention (124, 126), the effects were not strong enough to attain significance at the between-group level (87). A single Level II study also reported significant medium-sized effects (ES: 0.3–0.64) on a questionnaire-based assessment of sleep and GI problems in children with ASD following a 90-day yoga training program (147). Two Level III studies that assessed training-specific musical skills reported mostly large effects (ES: 1.13–2.67) on musical vocal behaviors, rhythmic imitation of musical patterns, turn taking within musical contexts, instrument playing, and singing following music therapy sessions (129, 131). No statistically significant effects were demonstrated on mindful awareness and heart rate variability following CMT (151). Three studies reported positive trends in qualitative data on parent/teacher and participant satisfaction, feasibility of implementation, and social validity of CMT (116, 140, 166).

We were able to calculate a total of 66 ES from 7 studies, i.e., 9 ES from 2 out of the total 4 Level I studies, 31 ES from 1 out of the total 5 Level II studies and 26 ES from 4 out of the total 6 Level III studies. Out of these 66 calculated ES, 8 ES from 2 Level I studies (1 yoga, 1 theater) and 12 ES from 4 Level III studies (2 music, 2 theater) suggested mostly medium-to-large-sized effects on assessed outcomes (see **Tables 4A–C**, **6**). Overall, there is *preliminary evidence* from mostly within-group designs supporting the effectiveness of music therapies in enhancing children's musical skills and theater-based interventions in improving salivary cortisol levels and reducing stress in individuals with ASD.

Short- and Long-Term Effects of CMT

The efficacy and utility of any therapy depends not only on the effects assessed during and immediately following the intervention, but more importantly on the carryover of training effects into real-world settings beyond the duration of the training. Only 17 (7 Level I, 7 Level II, 3 Level III studies) out of the 72 studies assessed the short- and long-term effects of CMT through follow-up (FU) testing that was conducted between 2 weeks and 12 months post-intervention. Of the 17 papers, only 9 (2 music, 1 yoga, 3 martial arts, 3 theater) studies found sustained improvements in outcomes at FU. The music studies (116, 140) that compared rock drumming and improvisational music therapy, respectively, with standardized care found improvements in social and motor outcomes at 2 weeks and 12 months FU, respectively (see **Table 3A**). Three martial arts-based studies from a single group of authors found retention of positive improvements on behavioral and social communication outcomes at 1-month FU (see **Table 3B**) (86, 122, 153). Sustained improvements were also seen following the SENSE theater and SDARI interventions in social communication and behavioral domains (see **Table 3C**) at 1.5- and 2-months post-intervention respectively (163, 165). The only study in the review that conducted multiple FU sessions (at 3, 6, and 12 months) assessed the effects of a drama-based intervention on social communication and behavioral outcomes (170). However, the study only reported outcomes at the final FU visit and suggested sustained improvements in autism severity and emotion recognition at 12 months post-intervention compared to baseline values (170). Lastly, 1 yoga-based intervention study found sustained improvements in executive functioning at 1.5 months post intervention compared to the posttest and baseline measures (152). On the other hand, 8 studies (3 music, 1 yoga, 1, martial arts, 1 theater, 2 dance) found that the immediate beneficial effects of CMT were not sustained at FU (87, 134, 136, 137, 146, 172, 173). Overall, although 9 of the 17 papers claimed sustained beneficial effects of CMT in individuals with ASD, our calculations suggested that only 4 out of the 22 calculated ES (ES: −0.79–0.71) from a Level II yoga and a Level III theater-based intervention study (152, 170) were statistically significant (i.e., CI did not include 0). Thus, there is currently *insufficient evidence* for *short-to-long-term sustained benefits* following CMT in individuals with ASD.

DISCUSSION

Summary of Results

Creative movement therapies have been an ongoing topic of study over the past 3 decades. Within CMT approaches, the effects of music- and yoga-based therapies have been studied since the 1990s and 2000s, whereas dance, theater, and martial arts have been studied only more recently over the past decade. Given that this area of study is still in its infancy, there is presently lack of rigorous, definitive evidence supporting the use of CMT approaches within the standard-of-care clinical practice in ASD. There have been a few reviews in the past assessing the individual effectiveness of music, yoga, martial arts, theater, and dance approaches in individuals with ASD. Despite the common underlying theoretical framework and the key intervention ingredients across these different approaches, to date, there has been no umbrella review that has systematically compiled evidence across different types of CMT approaches in individuals with ASD. Our paper addresses this critical gap by providing a comprehensive review of the literature through August 2021, supplemented with a critical risk of bias assessment on different CMT approaches as applied to individuals with ASD. By conducting both a narrative literature synthesis and a quantitative review through calculation of ES estimates of treatment effects, we are able to systematically compare and contrast the efficacy of different types of CMT approaches in individuals with ASD.

Of the total 72 studies, we were able to calculate within- and/or between-group ES estimates for around 89% studies (23 music, 7 yoga, 16 martial arts, 10 theater, and 7 dance, 1 music and dance) of which around 45% studies ($N = 29$) showed statistically significant, non-zero effects of CMT on assessed outcomes across domains. Specifically, we found evidence for (1) medium- to large-sized improvements in social communication skills from over 30% of the studies (mostly Levels I and II) that assessed these outcomes, (2) medium-sized improvements in the behavioral domain from around 33% studies (mostly Levels II and III) that assessed these skills, (3) medium-to-large improvements in motor outcomes from around 33% studies (mostly Level 1) that assessed movement performance, and (4) medium-to-large improvements in cognitive skills from over 65% (all Level I) of the studies that assessed this domain. In comparison, we found limited evidence to date for the positive impact of CMT on sensory, affective, and functional participation domains. In terms of CMT types, our review suggests that there is presently strongest evidence for the beneficial effects of music-based therapies in promoting social communication skills (5 out of 7 Level I music studies), followed by limited, yet positive evidence for both martial arts and yoga in promoting motor and cognitive skills (2 Level I studies for each approach for each domain), and for martial arts in promoting social communication skills (2 out of 3 Level I studies). Below we summarize the potential mechanisms of change for individual CMT approaches.

Music Therapy Interventions

Our literature search revealed the largest number of studies for music-based interventions compared to all other CMT approaches, with around 40% studies reporting significant improvements (ES: 0.02–4.11) in measured outcomes. Specifically, 35% studies ($N = 7$) showed improvements of varying sizes in social communication skills (ES: 0.02–4.06) and around 38% ($N = 3$) studies suggested large improvements in behavioral-affective outcomes (ES: 1.28–4.11).

Previous literature in the field of music and autism suggests that children with ASD particularly enjoy musical experiences, and in fact have enhanced musical perception skills (53, 178). From a brain imaging standpoint, there is substantial evidence that musical practice promotes multimodal integration by activating long range connections that simultaneously engage the auditory, visual, somatosensory, motor, and premotor areas as well as brain networks such as the mirror neuron system that are especially dysfunctional in ASD (52, 101, 106). Given the considerable overlap between brain substrates underlying speech and music, and the overall structural similarity between music and language, it has also been argued that musical training can in fact lead to enhanced speech processing in individuals with ASD (52). Overall, there is considerable behavioral and neuroimaging evidence to support the mechanisms for beneficial effects of music-based training in ASD (179).

Our review findings of consistent improvements in social communication skills following music therapies is not surprising given that such activities are based in rhythm, melody, and harmony, and involve components of singing, listening, music making with instruments, moving to the beat of the music, and spontaneous improvisation, all of which provide abundant opportunities for practice of social communication skills such as turn taking, joint attention, imitation, and verbal communication (53). Several of the reviewed studies also provided opportunities for flexibility and child-led activities during training that probably fostered children's engagement and led to better outcomes (4, 6, 27, 118, 119, 135). Although authors also hypothesized that musical training provides a non-intimidating context that may contribute to a reduction in off-task behaviors, stereotypes, and other repetitive behaviors in participants (130, 131), there is presently a need for more rigorous, high-quality research to support the use of music-based approaches in improving behavioral impairments in ASD. Moreover, music making using different types of instruments challenges the fine motor and cognitive systems as it typically involves complex, sequential, and precise finger and hand movements that require intricate motor planning and execution (53). Although the current evidence on the effects of music-based interventions on sensorimotor and cognitive skills is scant, this is definitely an area that deserves further attention.

Taken altogether, although music therapy approaches have the strongest evidence among other CMT approaches, there is a clear need for more research to assess the multisystem effects of these interventions on primary and secondary comorbidities in ASD.

Yoga Therapy Interventions

Yoga-based interventions fall under the category of holistic mind-body therapies and are based on principles and techniques of yogic practice that date back several millennia to ancient India. Yoga and mindfulness practice has been postulated to have physical, mental, and spiritual effects (180, 181). Studies included in our review evaluated the effects of yoga practice on behavioral, social communication, and motor skills as well as on physiological parameters, with very few studies assessing effects on affective control, cognitive, and functional skills. We were able to calculate ES estimates from around 55% of all yoga studies; nevertheless, a majority of the studies indicated medium-to-large improvements (ES: 0.43–2.66) in measured outcomes. Our analyses indicated promising beneficial effects in behavioral regulation ($N = 3$, ES: 0.43–2.66), motor ($N = 2$, ES: 0.76–2.66), and cognitive skills ($N = 2$, ES: 0.91–1.42) following yoga-based interventions.

Yoga-based programs emphasize the practice of breathing control and mindful body awareness that may help individuals with ASD manage their behavioral and mood/affective symptoms (88, 145, 148, 150). Moreover, the practice of static and dynamic postures that focus on improving balance, core muscle strength, flexibility, and body awareness may impact the sensorimotor systems (150) and also have physiological effects on digestion, sleep, and HR variability (88, 145, 148); see **Table 5** for components). Yoga and mindful awareness have also been found to help with attention regulation, memory, and executive control (152, 154, 155). Additionally, the only study that provided mindfulness training to adolescents with ASD and their caregivers found improved quality of parent-child interactions as evidenced by decreased parental stress and improved behavioral regulation (146). Despite extensive evidence for the whole-body effects of yoga in healthy individuals (182–184), our review suggests that the use of yoga-based interventions in ASD is presently an under-researched topic that deserves greater systematic investigation.

Martial-Arts Interventions

Around 56% of reviewed martial arts-based studies reported significant small-to-large improvements in measured outcomes (ES: 0.29–5.34), specifically in social communication ($N = 4$, ES: 1.13–1.15), cognitive ($N = 2$, ES: 0.42–1.19), and motor ($N = 2$; ES: 3.14–5.34) domains. Moreover, improvements in the cognitive domain i.e., in executive functioning, which includes working memory, flexible thinking, and inhibitory control are supported by high-quality Level I studies [(104, 154, 161); see **Table 6**]. This is not surprising given the heavy emphasis in martial arts training on discipline, structured practice of multistep action sequences, and movement precision, all of which require focused attention, motor planning, task switching, and working memory (75, 104, 123, 154, 159).

The reviewed studies also suggested the potential for martial arts training to impact socialization, behavior, and motor skills. For instance, martial art training led to improved synthesis

TABLE 5 | Intervention guidelines for CMT interventions based on reviewed literature.

Characteristics	Suggested guidelines for clinicians
Music	
Duration	8–16 weeks
Frequency	1–2 times per week
Time	1–1.5 h per session
Type	- Improvisational music therapy - Relational therapy - Family-centered music therapy
Components	- Hello songs and whole body warm-up activities - Music making using instruments like shakers, drums, tambourines, cymbals, maracas, etc. - Music making allowing child opportunity to explore instruments and music - Gross motor movements to the beat of music. Could involve turn taking or imitation-based rhythmic synchronization games where children match up movements to tempo of music and to actions of social partners - Cool-down and farewell songs
Yoga	
Duration	8–16 weeks
Frequency	3–5 times per week
Time per	0.5–1 h per session
Type	- Relaxation - Creative yoga - Mindfulness training - Mandala yoga
Components	- Whole body warm-up activities - Individual poses with holds, focusing on upper body and lower body flexibility, core strength, and balance - Partner poses involving joint yoga poses with a social partner - Mindfulness practice and breathing exercises - Whole body relaxation
Martial arts	
Duration	12–14 weeks
Frequency	2–4 times per week
Time	1 h per session
Type	Kata, Karate, Tai Chi, Mixed Martial Arts, Judo, Taekwondo, and Mind-body exercise
Components	- Whole body warm-up activities - Practice of individual movements/postures depending on type of martial art for example, punches and kicks for Kata or Judo, gentle poses and stretches for Tai Chi, etc. - Practice of sequences/flows that involve multiple movements put together - Cool down stretches
Theater	
Duration	10–12 weeks
Frequency	3–5 times per week
Time	2–4 h per session
Type	SENSE theater, SDARI, SCIP
Components	- Warm up games and theatrical improvisational games - Dramatic activities focused on facial expressions, body language, emotions, perspective taking, group cohesion, voice modulation, verbal and non-verbal communication, and acting

(Continued)

TABLE 5 | Continued

Characteristics	Suggested guidelines for clinicians
	- Script reading, character development, script memorization - Role playing and dialogues - Rehearsals of scenes and theatrical performances - Peer-mediated theater activities - Theatrical games, role-play and rehearsals - Improvisational activities targeting imitation, modeling, etc. - Public performances on completion of training
Dance	
Duration	12 weeks
Frequency	2 times a week
Time	1 h per session
Type	DMT
Components	- Whole body warm-up activities - Individual activities focused on exploring body movement flow in space and on increasing body awareness with and without music - Interactive imitation, mirroring, and synchronization-based choreographed activities in dyads, small groups, and larger groups - Improvisational dance sequences - Verbal reflections - Cool down and relaxation
General recommendations	
Setting	- Indoor settings like the child's home, child's school, community center, etc. - Outdoor open settings that provide space for free movement
Intervention providers	- Specialized instructor (music therapist, yoga certified teacher, dance movement therapist, etc.), - Licensed professionals (PT, OT, SLT)
Assistants	- Caregivers, school staff, undergraduate students or research assistants

and metabolism of neurotransmitters oxytocin, serotonin, and dopamine (75, 122). In fact, disturbed metabolism in these very neurotransmitter systems is thought to underlie the social dysfunction and stereotypies commonly seen in individuals with ASD (75, 122, 153). Similarly, high-energy, dynamic, martial art movement routines are thought to physically resemble stereotypical movements characteristic in ASD, perhaps serving as a functional "substitute" for repetitive behaviors, while still providing the same level of sensory input and reinforcement (75, 122). Although there is presently evidence from only 2 Level I studies, it seems plausible that martial arts training may also have effects on the sensorimotor system through practice of poses and action sequences that require good postural control, balance, multi-limb coordination, strength, agility, and optimal processing in the vestibular- and tactile-proprioceptive systems (104, 158). Our review of the existing literature suggests that among all CMT approaches, martial arts-based therapies seem to have the strongest evidence at present for promoting multisystem development in social communication, behavior, motor, and cognitive domains.

Theater-Based Interventions

Although a majority of theater-based studies assessed social communication and behavioral-affective outcomes, only around 42% (i.e., 2 Level I, 1 Level 1 and 2 Level III studies) of reviewed studies reported medium-to-large improvements (ES: 0.56–2.55) across these domains as well as a reduction in cortisol levels (ES: 0.73–2.55) following theater training. In fact, 2 of these studies were conducted by the same research group (126, 165). The reviewed theater studies typically provided training in a group format emphasizing interactions with peer models, specialized instructors, teachers, and other staff (87). Such a socially embedded and interactive context may provide plenty of opportunities for individuals with ASD to practice critical social communication skills such as joint attention, turn taking, perspective taking, and dialogue delivery, while also learning to recognize and express subtle socio-emotional cues related to facial expressions, voice intonation, and body language. It is therefore surprising to see a lack of statistically significant effects in support of enhanced social communication and behavioral-affective skills following theater training. A salient difference between theater and other CMT approaches is the average session duration, with theater interventions on an average lasting for much longer, i.e., around 2.9 h/session (see **Table 5**). It remains to be seen if the long duration of intervention sessions impacted abilities of individuals with ASD to sustain engagement during the training program. Overall, despite the highly interactive nature of theater, at present, there is insufficient evidence to support the use of theater-based training to facilitate social communication and behavioral-affective skills in individuals with ASD.

Dance Therapy and Combined Interventions

Although all individual reports ($N = 8$; 2 Level I, 6 Level II) concluded positive effects of dance-based therapies, our ES calculations from data reported in 6 papers suggested that none of the ES were statistically significant. This was the singular approach where studies recruited participants across the lifespan from 14 to 65 years. The wide age-range might have added to the variability of data, undermining the effects reported in these studies. Dance is an embodied experience incorporating elements of complex coordination, motor planning, and balance that may provide individuals with ASD opportunities to express their emotions through fluid bodily movements and to engage in mirrored practice during group choreography (172, 173). Despite the potential for promising effects on multiple systems through the very embodied nature of the experience, the current evidence on dance therapy in ASD is very limited. We call for future research to fully explore the use of dance-based interventions in individuals with ASD. We specifically recommend that future studies assess the effects of dance approaches on participants within a narrower age range.

Implications for Clinical Practice

Based on the studies reviewed, we suggest intervention guidelines for clinicians working with individuals with ASD in terms of assessments and interventions pertaining to CMT approaches.

TABLE 6 | Summary of reviewed studies that assessed specific domains and number of studies that showed improvements based on ES calculations.

CMT approach	Social communication (*N* = 47)	Behavior (*N* = 21)	Affective (*N* = 20)	Sensory (*N* = 3)	Motor (*N* = 15)	Cognitive (*N* = 6)	Functional participation (*N* = 3)	Other domains (*N* = 16)
Music	20 (7)	5 (2)	5 (1)	1 (1)	5 (1)	0 (0)	1 (0)	5 (2)
Yoga	4 (1)	4 (3)	3 (0)	0 (0)	4 (2)	2 (2)	1 (0)	4 (1)
Martial arts	7 (4)	3 (1)	0 (0)	0 (0)	4 (2)	4 (2)	0 (0)	2 (0)
Theater	12 (3)	6 (1)	8 (1)	1 (0)	0 (0)	0 (0)	0 (0)	5 (3)
Dance and combined approaches	4 (0)	3 (0)	4 (0)	1 (0)	2 (0)	0 (0)	1 (0)	0 (0)

Number mentioned outside parenthesis indicates number of studies that assessed outcomes related to specific domains and number within parenthesis indicates the number of studies that showed improvements in specific outcomes based on our ES calculations.

In terms of assessment measures, we recommend that clinicians use a combination of domain-specific standardized tests, observational measures, parent report questionnaires/interviews, and video coding to assess the impact of CMT approaches on multiple systems (see **Tables 3A–C**). Ultimately, the choice of assessment tools will depend upon multiple factors including the domains assessed as well as participant characteristics such as age, autism severity, functional level, receptive and expressive communication, and intellectual abilities. From our own experience, we recommend that objective clinician-based assessment tools be supplemented with parent reports to allow assessment of the individual's skills across a variety of structured and naturalistic activities and environments. We also recommend that researchers collect video data of testing and training sessions that can be scored at a later time by unbiased coders, thereby again allowing an evaluation of multiple snapshots of target behaviors across a variety of settings such as the lab, home, school, etc.

In terms of treatment, **Table 5** provides a summary of our suggested intervention guidelines for the different CMT training approaches in terms of FITT principles (*F*requency, *I*ntensity, *T*ime, *T*ype). Note that our guidelines are based on the reviewed literature, specifically, training programs that led to appreciable improvements in assessed treatment outcomes. The choice of CMT approach should ultimately depend on the preferences of the individual with ASD/their family. Clinicians should choose the approach that their client is most excited about and that they are comfortable delivering. Moreover, based on the evidence from this review, we recommend that there is at present, most consistent evidence from high-quality studies with low risk of bias for enhancements in social communication skills following music and martial arts interventions, and in motor and cognitive skills following yoga and martial arts practice. There is need for more systematic research to support the use of theater and dance-based approaches in the plan of care of individuals with ASD.

To administer CMT interventions to their clients with ASD, allied health professionals may need to consult with certified instructors and work collaboratively with them to tailor interventions to their client/family's needs. Moreover, several studies reported using common training strategies derived from conventional ASD treatments such as ABA, PECS, TEACHH, etc. while delivering CMT approaches with individuals with ASD. While structured practice will be an integral part of every CMT-based session, we strongly recommend that clinicians reserve time during sessions for free play and improvisation that will afford individuals with ASD opportunities for creative movement exploration and self-expression. Although there is a need for more rigorous research in this field, our review certainly suggests that CMT approaches involve embodied experiences that engage multiple systems/domains, are fun and engaging, and may provide individuals with ASD a variety of activity options fostering lifelong learning and creative expression.

Implications for Research

Around 75% of the reviewed studies employed between-group designs; however, <50% of the total studies were RCTs which are considered the gold standard for intervention efficacy research. There is a need for greater methodological rigor of clinical trials to reduce risk of bias by ensuring random and concealed assignment of participants to intervention and control groups, blinding of therapists and assessors, ensuring baseline similarity between groups prior to group assignment, and employing intention-to-treat analyses when possible. Since RCTs require significant amount of financial and personnel-related resources and are not always feasible to conduct in clinical settings, several studies in our review used pre-post designs. Our risk of bias assessment for pre-post designs indicated a need for better justification of sample sizes using power analyses, administration of tests at multiple times to obtain stable estimates of the child's behavior at baseline and post-intervention, better assessment and reporting of validity and reliability of selected outcome measures, and blinding of assessors to ensure unbiased estimates of participant performance.

Overall, across all study designs, we recommend that future studies provide more information on sample characteristics within the original report including measures of autism severity, IQ levels, as well as functional skills assessed using parent questionnaires such as the VABS. This is crucial since, the effects of CMT approaches might differ across participants based on these above-mentioned characteristics. Interestingly, a very small proportion of the reviewed studies included participants with intellectual disability and similarly even fewer studies recruited youth and adults with ASD, suggesting a need for more research with these subject demographics. In terms of study quality, future studies should report on steps taken to assess and ensure treatment fidelity during intervention delivery.

Among reviewed CMT approaches, the greatest quantity of evidence is for music-based interventions; there is therefore, a need for more rigorous research on other CMT approaches as well as efforts directed toward replication of the effects of music-based therapies on multiple systems in ASD using large sample size studies. Specifically, our review suggests that yoga- and martial arts-based therapies may be promising to promote multisystem development in individuals with ASD. Although reviewed studies assessed a variety of outcomes, the most frequently assessed domains included social communication and behavioral skills. Given the embodied nature of CMT approaches and their proposed mechanism of action on multiple systems, it would be important for future studies to holistically assess other developmental domains including sensorimotor, affective, and cognitive systems that also present as significant challenges for individuals with ASD. Moreover, researchers should go beyond the impairment domain and begin assessing the impact of CMT approaches on function and participation of individuals with ASD. In order to understand the carryover effects of CMT approaches, studies will need to assess treatment effects both in terms of short-term effects i.e., immediately following intervention completion, as well as the long term maintenance of training-related gains at follow-up. Finally, we urge that authors include their data within the original reports to enable calculation of ES estimates for measured outcomes and meta-analytic analyses.

Limitations

Although we used a comprehensive search strategy (see **Appendix 1**) to identify eligible studies, it is possible that we may have missed relevant research. For the purposes of our review, we only included clinical trials and pre-post study designs with the exclusion of case studies, narrative reports, and other types of qualitative reports. We also excluded conference proceedings and unpublished theses and dissertations from this review. Finally, we limited our review to only articles published in English. Although our original intention was to restrict our review to studies that used CMT approaches in individuals with ASD, there were a few papers ($N = 5$) in our review that recruited mixed samples, thereby adding to the heterogeneity of the sample. In terms of intervention components, several studies reported using training strategies derived from conventional, evidence based ASD treatments while delivering CMT to participants. Therefore, at present, the literature does not allow us to tease apart the true effects of the key ingredients of the CMT approaches themselves vs. those of the training strategies used in conjunction with the CMT approaches. In a related vein, a majority of the studies did not report on acceptability, implementation feasibility, cost-effectiveness, etc. of interventions. The extent of the literature does not presently allow the development of clinical practice guidelines for the ASD population; instead, the suggested treatment guidelines reported in our paper are based only on the reviewed studies and the dosing parameters that led to gains in measured outcomes in the reviewed studies.

CONCLUSIONS

Our systematic review aimed at providing a comprehensive summary of the literature through August 2021 on the effects of various types of CMT approaches for individuals with ASD. Our search identified a total of 72 articles that used music, yoga, martial arts, theater, and dance-based intervention programs in 1,939 number of individuals with ASD between 3 and 65 years. Our quantitative synthesis of the published literature suggested strong and consistent evidence for small-to-large improvements in social communication skills following music and martial arts training as well as medium-to-large sized improvements in motor and cognitive skills following martial arts and yoga training. Presently, there is limited evidence in support of theater and dance-based approaches as well as the utility of all CMT approaches in improving affective, sensorimotor, and functional participation skills in individuals with ASD. Our review offers future directions for research examining the effects of CMT approaches in ASD as well as provides intervention guidelines for clinicians to incorporate CMT approaches in their plan of care for their clients with ASD.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

SS was responsible for conception of the manuscript. WCS, AB, and SS were involved in project design. NA and SS finalized and coded the articles and were responsible for data extraction and analyses. NA and SS put together the first draft of the manuscript. All authors were involved in proof reading and editing of the manuscript prior to submission.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.722874/full#supplementary-material

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Note: All citations with an "" indicate that these studies were included in our systematic review.

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Implementation of Video Feedback Within a Community Based Naturalistic Developmental Behavioral Intervention Program for Toddlers With ASD: Pilot Study

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Video feedback (VF) is an intervention delivery technique that complements naturalistic developmental behavioral interventions (NDBI) and parent-mediated interventions (PMI) by using caregiver-child interaction videos reviewed with a clinician to facilitate behavioral change in caregivers. Although VF has been implemented in PMI with young children with ASD, examinations of feasibility and acceptability, as well as the potential effectiveness of VF in community settings, have been limited. In this pilot randomized control trial (NCT03397719; https://clinicaltrials.gov/ct2/show/NCT03397719), families were randomized into a state-funded Early Intervention (EI) NDBI program or the NDBI program augmented with VF. Results demonstrated high levels of implementation and acceptability of VF augmenting the community-based EI program in caregivers and clinicians. Both groups showed significant improvements after 6 months in social communication symptoms and some areas of developmental and adaptive skills.

Clinical Trial Registration: https://clinicaltrials.gov/ct2/show/NCT03397719, identifier: NCT03397719.

Keywords: early intervention (EI), parent-mediated intervention, naturalistic developmental behavioral intervention (NDBI), video feedback, community-based services, technology, autism spectrum disorder (ASD)

INTRODUCTION

In recent years, research has explored the use of Video feedback (VF) to augment Parent Mediated Intervention (PMI) for young children with various developmental delays (1–3). VF interventions typically consist of filmed caregiver-child interactions that the caregiver watches with a clinician who facilitates guided reflection on caregiver and/or child behaviors. Common intervention targets through VF include parental sensitivity to child cues, child behavior, and parent-child attachment. Across varying clinical populations, treatment purposes, and theoretical orientations, the use of VF with caregivers to deliver some or all intervention has been found to enhance caregiver-child interactions and improve caregiver and child behavior (2, 3).

PMI, or intervention delivery by a parent or caregiver, serves as a core component of many comprehensive treatment models for children with autism spectrum disorders (ASD) (4). In

PMIs a clinician guides the caregiver (also referred to as "parent coaching") to use specific skills during interactions with their child to increase their child's developmental skills and improve the caregiver-child relationship. The inclusion of caregivers in treatment through PMI focuses on the generalization of child skills outside of the clinic setting, with goals to increase caregiver skills or competence and enhance engagement in the caregiver-child dyad (5). PMI has strong empirical support (6), classifying it as an evidence-based practice (5). In fact, many research review panels recommend PMI as an essential feature of early intervention and treatment for individuals with ASD [Autism Intervention Research—Behavioral Network [AIR-B] (7); National Standards Project [NSP] (8)]. In particular, studies suggest that PMI holds the potential for generalization and maintenance of treatment gains that surpass those of intervention delivered directly to the child by a clinician, allowing the caregiver to support the child's development across a wide range of settings (9, 10). Additionally, coaching caregivers based on collaboratively chosen goals can reduce caregiver stress and improve family functioning as a whole (11).

The inclusion of caregivers in treatment is a part of a broader shift toward Naturalistic Developmental Behavioral Interventions (NDBI) for young children with ASD (12). NDBIs are evidence-based treatment approaches for young children with ASD founded in developmental and behavioral learning principles (12). Given the strong support for the use of PMI in treatment for ASD, clinicians have used *in-vivo* coaching to train caregivers to utilize various NDBI strategies, such as providing natural learning opportunities, following the child's lead during interactions, and balancing their role as a social partner (12). In a recent meta-analysis of different types of early intervention, NDBIs stood out as effective (13). NDBIs incorporating PMI have led to gains in social communication, receptive language, joint engagement, play skills, adaptive skills, and cognitive levels (14–19).

VF can be integrated into PMI to maximize the caregiver engagement and learning of various NDBI strategies in the treatment process [see Aldred et al. (1)]. VF used with caregivers of children with ASD to enhance the intervention delivery has been found to improve child language outcomes (20), increase parental self-efficacy (21), increase parental synchrony (22), lead to a long-term reduction in autism symptoms (9), and reduce parental intrusiveness (21). VF is not only clinically useful, but has been well-received by families. Specifically, caregivers have reported strong positive feelings toward VF, indicating that it has allowed them to reflect on their own behavior, learn about their child's behavior, and understand how to implement intervention techniques (23).

Community-based EI services for toddlers with ASD or developmental delays are mandated by the Individuals with Disabilities Education Act (24) and are suggested to be delivered in naturalistic settings. However, not all EI programs provide home-based services, but services may be more center- or classroom-based (25). Thus, interventions such as VF that can be incorporated into everyday activities and routines have been identified as preferable to families of young children with ASD (26). However, despite promising results from past studies on the use of VF in PMI for children with ASD, investigations on the feasibility, acceptability, and potential effectiveness of VF implemented in community-based early intervention (EI) settings have been extremely limited. A handful of studies show the feasibility of VF integrated into community-based interventions, mainly for preschool and school-age children with ASD (27, 28). Studies have also yet to examine the effectiveness of VF in toddlers with ASD, an especially critical developmental period given the downward trend in the age of diagnosis for ASD and the importance of early intervention (29).

In the present study, we conducted a preliminary RCT to examine how VF can augment PMI as a part of a community-based NDBI EI program. Stakeholder input (e.g., clinicians and caregivers) was continuously monitored and incorporated, following participatory research guidelines for adapting evidence-based practice for young children with ASD to community settings (30, 31). Engagement of stakeholders is also critical to maximize program sustainability to maintain fidelity of the intervention when moving from controlled research settings to more natural applications where fidelity may be variable (2, 32). Specifically, we aimed to (1) demonstrate the feasibility of integrating VF within PMI sessions; (2) explore the acceptability of VF from caregivers and clinicians; and (3) compare preliminary treatment effects between the NDBI treatment with and without augmented VF.

METHODS

Participants

Participants included individuals at the consumer level (i.e., children and caregivers) and service level (i.e., clinicians). Fifteen toddlers with ASD and their caregivers were drawn from a 6-month, community-based, state-funded NDBI EI program which enrolls up to 12 children per year. All children enrolled in the EI program were invited to participate in the study and were randomized into the NDBI vs. NDBI+VF group (see section Procedure). For the NDBI+VF group, the usual caregiver coaching sessions were augmented by VF. There were no significant differences between treatment groups at baseline regarding child and caregiver demographic characteristics as well as hours services received outside of the CADB EI program (**Table 1**).

Clinicians ($n = 4$) were assigned to a family upon entry to the program, prior to randomization. Clinicians included individuals with extensive training in NDBIs including a Psychologist, a Psychologist and Board-Certified Behavior Analyst (BCBA), a Post-Doctoral Fellow in Psychology, and a Speech-Language Pathologist. Two of these clinicians provided care to participants randomized to the NDBI+VF group.

Procedure

This study was reviewed and approved by Weill Cornell Medicine Institutional Review Board. After families were assigned a clinician (based on availability), provided their written informed consent to participate in the study, and completed a baseline evaluation, they were randomized into one of two groups,

TABLE 1 | Baseline demographics and tests of group differences (Kruskal–Wallis or Fisher's exact test).

	NDBI+VF group ($n = 8$) M (SD) or n (%)	NDBI group ($n = 7$) M (SD) or n (%)	Whole group ($n = 15$) M (SD) or n (%)	Kruskal–Wallis or Fisher's exact test* H or p
Child measures ($n = 15$)				
Age (months)	25.63 (5.11)	28.23 (5.29)	26.84 (5.18)	0.97
Sex (males)	5 (62.5%)	5 (71.43%)	10 (66.67%)	1.00
Race				0.65
White	6 (75%)	3 (42.86%)	9 (60%)	
Asian	1 (12.5%)	2 (28.57%)	3 (20%)	
Other	1 (12.5%)	2 (28.57%)	3 (20%)	
Autism symptom severity				
ADOS-2 CSS				
CSS SA	6.63 (1.77)	7.86 (1.07)	7.20 (1.57)	3.21
CSS RRB	7.25 (3.11)	7.71 (1.5)	7.47 (2.42)	0.01
BOSCC-clinician				
SC	26.00 (9.27)	24.93 (5.81)	25.46 (7.46)	0.07
RRB	9.00 (2.58)	8.36 (4.04)	8.68 (3.27)	0.15
BOSCC-caregiver				
SC	26.86 (7.56)	21.64 (5.67)	24.25 (6.97)	2.16
RRB	11.00 (3.55)	7.79 (3.25)	9.39 (3.67)	2.77
Developmental Levels				
MSEL or DAS (n = 14; 1)				
Non-verbal ratio IQ	86.78 (16.92)	80.83 (21.81)	84.00 (18.88)	0.48
Verbal ratio IQ	65.57 (25.41)	65.40 (28.31)	65.49 (25.81)	0.12
MSEL (n = 14)				
Visual reception AE	22.50 (7.54)	19.50 (4.59)	21.21 (6.41)	0.71
Fine motor AE	19.38 (3.02)	20.17 (1.94)	19.71 (2.56)	0.02
Receptive language AE	15.50 (7.48)	15.50 (5.75)	15.50 (6.55)	0.01
Expressive language AE	15.38 (5.26)	14.00 (3.74)	14.79 (4.56)	0.04
Adaptive skills: VABS				
Communication AE	16.06 (10.75)	17.14 (4.19)	16.57 (8.1)	0.86
Daily living AE	19.00 (8.02)	16.00 (3.65)	17.60 (6.34)	0.41
Motor skills AE	22.75 (7.88)	20.93 (4.31)	21.90 (6.32)	0.03
Socialization AE	13.75 (12.75)	11.29 (4.39)	12.60 (9.55)	0.12
Hours of services per week ($n = 14$)	16.07 (7.18)	10.24 (8.07)	13.16 (7.94)	1.80
Caregiver measures ($n = 15$)				
Age (Years)	41.52 (5.56)	37.04 (4.09)	39.43 (5.29)	1.93
Sex (females)	7 (87.5%)	7 (100%)	14 (93.33%)	1.00
Race				0.15
White	7 (87.5%)	3 (42.86%)	10 (66.67%)	
Asian	1 (12.5%)	3 (42.86%)	4 (26.67%)	
Other	0 (0%)	1 (14.29%)	1 (6.67%)	
Education				0.67
BA/BS or above	7 (87.5%)	6 (85.71%)	13 (86.67%)	
Below BA/BS	1 (12.5%)	1 (14.29%)	2 (13.33%)	
Income				1.00
Below $35,000	1 (12.5%)	0 (0%)	1 (6.67%)	
$81,000–$100,000	2 (25%)	1 (14.29%)	3 (20%)	
$101,000–$130,000	1 (12.5%)	2 (28.57%)	3 (20%)	
Over $161,000	4 (50%)	4 (57.14%)	8 (53.33%)	
Relationship to child				1.00
Mother	7 (87.5%)	7 (100%)	14 (93.33%)	
Father	1 (12.5%)	0 (0%)	1 (6.67%)	

(Continued)

TABLE 1 | Continued

	NDBI+VF group ($n = 8$) M (SD) or n (%)	NDBI group ($n = 7$) M (SD) or n (%)	Whole group ($n = 15$) M (SD) or n (%)	Kruskal–Wallis or Fisher's exact test* H or p
MONSI-CC (n = 14)				
Environmental set-up	7.43 (2.35)	9.00 (1.61)	8.21 (2.1)	2.38
Child guided interactions	17.00 (1.87)	18.79 (1.6)	17.89 (1.91)	3.51
Active teaching and learning	25.14 (5.03)	27.21 (2.98)	26.18 (4.12)	0.26
Opportunities for engagement	2.57 (0.98)	3.50 (1.56)	3.04 (1.34)	2.07
Natural reinforcement and scaffolding	13.07 (2.37)	13.71 (1.38)	13.39 (1.89)	0.02
Total score	65.21 (11.26)	72.21 (8.02)	68.71 (10.07)	1.05

[*] All values did not reach statistical significance. CSS SA, Comparison score social communication; CSS RRB, Comparison score restricted and repetitive behaviors; BOSCC, Brief Observation of Social Communication Change; MSEL, Mullen Scales of Early Learning; DAS, Differential Ability Scales; AE, age equivalent, VABS, Vineland Adaptive Behavior Scales; MONSI-CC, Measure of NDBI Strategy Implementation—Caregiver Change.

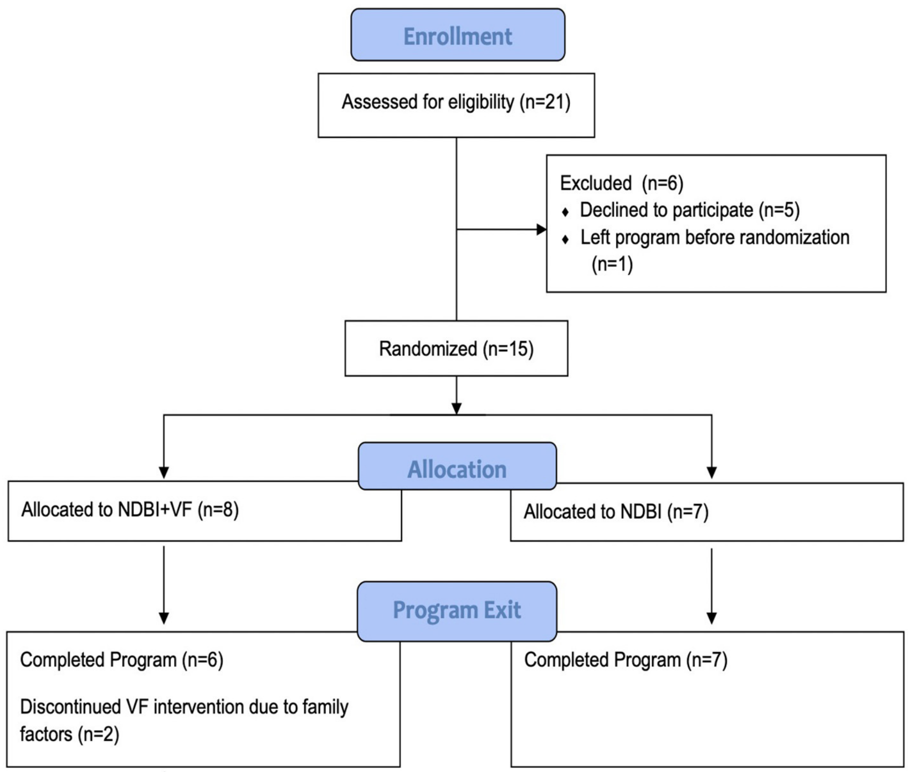

FIGURE 1 | CONSORT diagram.

"NDBI" ($n = 7$) vs. "NDBI+VF" ($n = 8$) groups. Randomization was completed by study staff using a concealed allocation sequence (i.e., online random number generator) based on age, gender, and IQ using a matched random assignment process (see CONSORT diagram in **Figure 1**).

NDBI Group

All families received NDBI (standard care), which consisted of group-based (i.e., classroom) clinician-mediated intervention (6 h/week) and individual parent-coaching sessions (3 h/week); see Swain et al. (33) for additional programmatic details. Parent coaching sessions occurred in the center (1 h/week) and also at home (2 h/week) when families lived within 30 min of the center. In addition, children and families received Speech Therapy, Occupational Therapy, and Social Work sessions depending on their Individualized Family Service Plan (IFSP). All caregivers were also invited to participate in weekly 60-min psychoeducation and support groups (2 h/week total). NDBI strategies included but were not limited to: following the child's lead with toy choices; imitating play; sitting face-to-face;

providing developmentally appropriate cues; and modeling and prompting for social communication and play (12).

NDBI+VF Group

In addition to the NDBI, the NDBI+VF group participated in weekly video-based feedback during the first 10–15 min of one parent coaching session per week. Caregivers and clinicians leveraged novel technological tools (e.g., 360-degree camera and tablet) to prepare for and execute VF sessions. VF centered around the use of NDBI strategies (mentioned above) learned from previous sessions in the recorded home interactions with their child. Clinicians and caregivers collaboratively identified three, 10-min activities and routines that caregivers could carry out with their child at home the week prior to review (30 min total). Caregivers used an LG 360-degree camera to record videos at home without a videographer to ensure naturalistic interactions, allowing the caregiver and child to move freely while remaining in the 360-degree frame. The LG 360-degree cameras did not require the use of the tripod, allowing the camera to be placed on bookshelves, dressers, counters, etc. to capture interactions in the home, or held by hand in the community. These raw videos were then transferred to an iPad by research staff and reviewed by the clinician to prepare for the caregiver coaching sessions. Recordings shorter than 10-min were also included for review by the clinician.

Before each session, clinicians selected two short segments from the caregivers' recordings that week to watch with the caregiver on the iPad, one highlighting an acquired skill for the caregiver (strengths) and one highlighting developing skills (areas for improvement). The length of the segment varied depending on the skill to be highlighted, but was typically around 1–2 min long. To begin the session, clinicians set up preferred toys to keep the child occupied, and began the VF with a video which highlighted a positive attempt from the caregiver or attainment of skill. Next, the clinician asked the caregiver to reflect on the recorded interactions prior to making observations. Then, clinicians noted an antecedent (caregiver action), behavior (child's behavior), and/or consequence (outcome) to highlight as it related to the goals of the family. After providing reinforcement for caregivers' desired behaviors (by pointing out the positive consequences of their behavior), a second video was used to show a future opportunity to utilize new parenting skills. Again, the clinician obtained the caregiver's comments and reflections prior to the clinician making observations. Next, the clinician discussed the skill or technique that would have been helpful during the recorded interaction and supported the caregiver in learning the skills during the current parent coaching session (e.g., modeling, providing handouts, and using examples from the previous or current sessions). Clinicians also allowed the caregiver to ask questions and inquire about the skill. To close the VF component of the session, the clinicians and caregivers worked collaboratively to identify future activities for the caregiver to record in-home.

Measures

Implementation Measures

In order to examine caregiver implementation of VF, the duration of recordings and the number of videos brought in each week were documented. Videos were categorized by type (i.e., play with toys, play without toys, and activities around personal independence and daily living skills). The total dosage of video recording was calculated by dividing the total number of minutes recorded by the number of weeks in the intervention for each caregiver.

Fidelity ratings were assessed regarding clinician treatment implementation of NDBI and VF approaches. Clinicians for both groups were required to meet modified criteria on the ESDM fidelity rating at the beginning of the data collection (34). Clinicians were considered to have met fidelity if they reached no scores under 3 (out of a 1–5 scale) and a mean score of 80% on two consecutively coded joint activity routines. ESDM fidelity was coded by the lead psychologist in the program, an ESDM trainer and an experienced ESDM interventionist (author JW). Fidelity for VF was collected quarterly or when a clinician was assigned to a new child randomized to the VF group. VF fidelity included ratings of pre-planning activities (e.g., the clinician watched the caregiver/child interaction videos prior to the session and noted at least two segments to show the caregiver) and VF session guidelines (e.g., the clinician obtained the caregiver's comments and reflections prior to the clinician making observations). A score of 12 out of 14 (85%) across activities was required to meet fidelity. VF fidelity was completed by raters who achieved inter-rater reliability (85%) across three videos.

Acceptability Measures

Caregiver acceptability was measured by attrition rates, service utilization (hours of treatment accessed by each participant), and a Caregiver VF survey. Service utilization was calculated using billing records from classroom and parent coaching sessions. The study-specific Caregiver VF survey was completed anonymously by caregivers in the NDBI+VF group to assess caregiver acceptability after the completion of the program. Survey questions targeted intervention acceptability, practicality, and implementation based on feasibility research guidelines (30).

Clinician acceptability was measured by a VF worksheet used before, during, and after each VF session and a Clinician VF survey given after the completion of treatment for all children in the study. The VF worksheet was used to record notes while preparing videos to review with the caregiver, record caregiver reflections, and included questions such as "How helpful was the video in teaching parent concepts?" and "Did you use the video to inform or direct your coaching during the most recent home session?" (on a 1–10 scale). The Clinician VF survey, completed by two clinicians who provided VF for the study, included open-ended questions to obtain qualitative information regarding programmatic strengths and challenges.

Child and Caregiver Outcome Measures

All measures assessing autism symptoms, developmental levels, adaptive functioning, and caregiver strategy use were completed at intervention entry and exit (6 months after entry) by evaluators blind to treatment condition. All the treatment outcome measures used in the study were dimensional which allowed the quantification of changes over time.

Autism Symptom Severity

The Brief Observation of Social Communication Change (BOSCC) (35) is a new treatment outcome measure used to quantify changes in social communication skills (SC) and restricted and repetitive behaviors (RRB) in minimally-verbal children based on a 12-min play-based interaction between an adult (e.g., caregiver, clinician) and child. Studies have shown that the BOSCC is more sensitive to changes in core ASD symptoms as compared to the Autism Diagnostic Observation Schedule (ADOS) (35, 36). BOSCC sessions were collected with both caregivers (BOSCC-Caregiver) and clinicians (BOSCC-Clinician) in the clinic to assess improvements in child symptoms across interactants. BOSCC sessions were rated by coders who were blind to treatment condition, time points, and other treatment-related information, and had established reliability. At baseline only, autism symptom severity was measured by the ADOS-2 (37), a semi-structured, standardized, naturalistic assessment. Severity was measured using calibrated severity scores (CSS) for Social Affect (SA) and Restricted and Repetitive Behaviors (RRB) domains (38).

Developmental Levels

The Mullen Scales of Early Learning (MSEL) (39) or Differential Abilities Schedule (DAS-II) (40) were used to measure child verbal and non-verbal abilities at entry ($n_{MSEL} = 14$, $n_{DAS} = 1$) and exit ($n_{MSEL} = 11$, $n_{DAS} = 1$). The MSEL and DAS-II have shown high convergent validity in previous studies of children with ASD (41, 42). Nonverbal and verbal mental ages (NVMA and VMA) were calculated from both measures to examine changes. NVMA was calculated by averaging the age equivalents (AEs) on the Visual Reception and Fine Motor subscales on the MSEL and the Picture Similarities and Pattern Construction subtests on the DAS-Early Years. VMA was calculated by averaging the AEs on the Receptive Language and Expressive Language subscales of the MSEL and the Verbal Comprehension and Naming Vocabulary subtests on the DAS-Early Years. Ratio IQs were derived by dividing nonverbal (NVRIQ) or verbal (VRIQ) mental age by the chronological age in months. NVRIQ and VRIQ were used to quantify baseline IQ scores, while MSEL domain age equivalents (AEs) were used to capture developmental changes over time for consistency (only one child was given the DAS).

Adaptive Skills

The Vineland Adaptive Behavior Scales, 2nd and 3rd editions (VABS) (43), a parent interview, was used to measure adaptive functioning. AEs were used to capture changes over time for the Communication, Daily Living Skills, Socialization, and Motor Skills domains.

Caregiver NDBI Implementation

The Measure of NDBI Strategy Implementation–Caregiver Change (MONSI-CC) (44) was used to examine changes in caregivers' NDBI strategy use. BOSCC-Caregiver and MONSI-CC ratings were based on the same segments of 12-min caregiver-child interaction videos. The MONSI-CC yields scores in five domains (Environmental Set-up, Child-Guided Interactions, Active Teaching and Learning, Opportunities for Engagement, and Natural Reinforcement and Scaffolding) and a Total Score. Total scores may range from 20 to 100, with higher scores indicating effective and appropriate use of strategies taught in NDBI. The MONSI-CC was rated by coders who had established reliability on the measure and were blind to treatment condition, time points, and other treatment-related information.

Data Analysis

Analyses were conducted for the 13 children who had completed 6 months ($M_{NDBI+VF} = 5.16$, $SD = 0.98$; $M_{NDBI} = 4.74$, $SD = 0.54$) of intervention. Caregiver implementation of VF was evaluated using the total dosage of video recordings and video categorization, while clinician implementation of VF was evaluated by VF fidelity ratings. To evaluate the acceptability of NDBI+VF by caregivers, attrition rates were compared between the two groups using Fisher's exact test, an independent samples *t*-test was used to compare mean group differences regarding parent coaching and classroom intervention service utilization, means and SDs were obtained from the Caregiver VF survey. To examine the acceptability of NDBI+VF in clinicians, we also obtained means and SDs from VF worksheets. Additionally, an independent samples *t*-test was used to compare mean differences between families receiving home and clinic sessions vs. clinic sessions only on the VF worksheets.

Given the small sample size in NDBI+VF and NDBI groups, non-parametric statistics were used for analyses to compare the treatment effects between the groups. First, the Kruskal–Wallis test was used to test differences in all outcome measures between the NDBI+VF and NDBI groups at intervention entry. Next, the Wilcoxon signed-rank test was used to examine significant change within each treatment group as well as across both groups for BOSCC-Clinician and Caregiver SC and RRB domain totals, MSEL domain age equivalents, Vineland domain age equivalents, and MONSI-CC domain and total scores. Effect size was calculated using [$r = Z/\text{sqrt}(N)$], with the interpretation of r values as follows: .5 = large effect, .3 = medium effect, .1 = small effect (45, 46). For variables that showed significant change from these analyses in one or both groups, Reliable Change Index (RCI) (47, 48) scores were calculated to examine percentages of participants showing statistically significant change for each treatment group. RCIs were calculated using the formula: $SE_{Diff} = SD_1 \times \sqrt{2 \times \sqrt{1 - r}}$ based on the SD of our sample at intervention entry and test–retest reliability from instrument manuals or literature. RCIs were followed up with Fisher's exact tests between the NDBI+VF and NDBI groups to confirm whether there is a significant difference in the proportion of children positive change, no change, or negative change. Spearman's rho non-parametric r correlations were used to examine the association between caregiver (MONSI-CC) and child (BOSCC-Clinician and Caregiver) changes.

RESULTS

Caregiver Feasibility

Caregiver Implementation

Caregivers in the NDBI+VF group recorded an average of 8.05 total hours of caregiver-child interaction videos (SD = 5.92, Range = 2.46–18.73) across an average of 39.5 videos (SD = 28.53, Range = 14–94) over the course of the 6-month intervention. Each week, caregivers recorded an average of 20.33 min (SD = 14.55, Range = 13.40–46.83) of interactions. Caregivers recorded interactions on average for 60% of weeks during the 6 months of intervention (SD = 16%, Range=33–75%). For each VF session that occurred, the clinician reviewed an average of 33.15 minutes (SD = 15.46) prior to each session.

Across all videos recorded by the caregivers, 63% of videos captured play activity with toys (e.g., play at a table, reading books), 9% captured play without toys (e.g., singing, dancing, playing on a playground), 27% captured activities around personal independence and daily living skills (e.g., feeding, dressing, bath time, and outdoor safety), and 3% were not viewable (e.g., a video was blurry or a file was corrupt).

Caregiver Acceptability

Both groups demonstrated acceptable attrition rates ($M_{NDBI+VF} = 25\%$ [$n = 2$]; $M_{NDBI} = 0\%$). Results from Fisher's exact test showed that there was no statistically significant association between group and attrition rate ($p = 0.27$).

No group differences in service utilization (hours of treatment by each participant) were found between the NDBI+VF and NDBI groups. Weekly service utilization hours were $M = 2.16$ (SD = 0.58) h for individual parent coaching and M=5.08 (SD=0.46) hours of classroom intervention. Results from an independent samples t-test showed that there were no differences between the NDBI+VF and the NDBI groups in the hours of parent coaching [$M_{NDBI+VF} = 2.07$, SD = 0.53, $M_{NDBI} = 2.15$, SD = 0.65; $t_{(11)} = 0.21$, $p = 0.84$] or classroom intervention [$M_{NDBI+VF} = 5.18$, SD = 0.27, $M_{NDBI} = 4.97$, SD = 0.60; $t_{(11)} = -0.80$, $p = 0.44$].

Results from the Caregiver VF Survey for families in the NDBI+VF group (on a scale of 1–7, 7 being the highest) were available for 4 caregivers (66%). Questions regarding practicality found that caregivers easily operated the camera (M = 7.00, SD = 0.43), understood how to record videos (M = 7.00, SD = 0.00), found time to carry out recordings (M = 5.25, SD = 1.30), incorporated VF into daily routines (M = 5.25, SD = 1.30), and felt that they had enough time with their clinician for VF sessions (M = 6.75, SD = 0.43). Regarding ratings of implementation, caregivers reported that they worked with the clinician to decide what to record (M = 6.75, SD = 0.43) and followed through with the recordings (M = 6.25, SD = 0.83). In regard to acceptability and satisfaction, caregivers reported that watching video in session helped their learning (M = 7.00, SD = 0.00) and they felt that they benefited from parent coaching sessions (M = 6.75, SD = 1.25). Caregivers also rated that the recordings benefited their child (M = 5.00, SD = 1.73), and all caregivers said they would recommend VF to other families (M = 7.00, SD = 0.00). Caregivers reported that they had no recommended changes about the VF component of the intervention. However, difficulties reported by caregivers included constraints on time, concerns about being recorded, having their homes recorded, and distracting the child during the VF session. Caregivers most enjoyed capturing and receiving feedback on their interactions in naturalistic settings. Caregivers also reported that VF helped them to understand themselves and their children better. Caregiver feedback was incorporated through requested modifications to the protocol (e.g., some families requested a text reminder over the weekend to remember to record videos for NDBI+VF; some families requested that they record videos on their own devices when the camera was not readily accessible although this was rare; families requested an individualized approach to homework allowing for the flexibility to choose routines based on their needs).

Clinician Feasibility

Clinician Implementation

The mean fidelity score for VF was 12.5 for 10 sessions (12 of 14 needed to meet fidelity) across the two clinicians that implemented the VF intervention.

Clinician Acceptability

Clinician VF worksheet data were obtained from 70 VF sessions across the six children in the NDBI+VF group. Responses to "How helpful was the video in teaching parent concepts" (on a scale of 1–10 with 10 being the highest) had a mean of 7.71 (SD = 1.76). When families were split by those with home sessions ($n = 4$) and those with no home sessions ($n = 2$), clinicians working with families whose sessions were limited to the clinic (parent coaching was *not* delivered in the home) reported VF significantly more helpful (M = 9.09, SD = 0.71) than those working with families whose sessions were held both in the home and in the clinic [M = 6.10, SD = 1.15; $t_{(61)} = 12.62$, $p < 0.001$]. Clinicians reported that 64% of the time, the video informed or directed their most recent parent coaching session. Clinicians also reported that they worked collaboratively with caregivers to select home recording activities for 83% of the sessions.

Of the four clinicians who participated in the study, two clinicians were assigned to children who were randomized to the NDBI+VF group. In response to open-ended questions about what they liked most about VF, clinicians reported that it gave insight into the child's behavior in the home for families without home sessions, and into caregiver-child interactions without the presence of clinicians for families with and without home sessions. Clinicians reported that barriers to VF included the amount of time needed to prepare the session and that it sometimes feels cumbersome for some caregivers to record the recommended amount. One clinician reported that VF sessions often sparked important questions about caregiver techniques that there is not always time to address in the child-focused session, and it may be helpful to have a separate time for the feedback.

TABLE 2 | Wilcoxon signed-ranks test for change from Intervention Entry to Exit.

	NDBI Group				NDBI+VF Group				Whole group			
	n	*Z*	*p*	*Effect size r*	*n*	*Z*	*p*	*Effect size r*	*n*	*Z*	*p*	*Effect size r*
Child measures												
Autism symptom severity BOSCC-Clinician	6				6				12			
SC		**−1.997**	**0.05**	**−0.82**		**−2.023**	**0.04**	**−0.83**		**−2.758**	**0.01**	**−0.80**
RRB		−0.405	0.69	−0.17		−1.153	0.25	−0.47		−1.068	0.29	−0.31
BOSCC-Caregiver	6				6				12			
SC		**−2.201**	**0.03**	**−0.90**		**−1.992**	**0.05**	**−0.81**		**−2.943**	**0.00**	**−0.85**
RRB		−1.261	0.21	−0.51		**−2.207**	**0.03**	**−0.90**		**−2.559**	**0.01**	**−0.74**
Developmental Levels: MSEL	5				6				11			
Visual Reception AE		**−2.032**	**0.04**	**−0.91**		**−2.207**	**0.03**	**−0.90**		**−2.941**	**0.00**	**−0.89**
Fine Motor AE		−1.483	0.14	−0.66		**−1.997**	**0.05**	**−0.82**		**−2.493**	**0.01**	**−0.75**
Receptive Language AE		**−2.023**	**0.04**	**−0.90**		−1.782	0.08	−0.73		**−2.669**	**0.01**	**−0.80**
Expressive Language AE		**−2.023**	**0.04**	**−0.90**		**−1.992**	**0.05**	**−0.81**		**−2.756**	**0.01**	**−0.83**
Adaptive Skills: VABS	7				6				13			
Communication AE		**−2.371**	**0.02**	**−0.90**		**−2.201**	**0.03**	**−0.90**		**−3.183**	**0.00**	**−0.88**
Daily Living AE		−1.609	0.11	−0.61		**−2.207**	**0.03**	**−0.90**		**−2.765**	**0.01**	**−0.77**
Motor Skills AE		**−2.197**	**0.03**	**−0.83**		**−2.032**	**0.04**	**−0.83**		**−2.982**	**0.00**	**−0.83**
Socialization AE		**−2.201**	**0.03**	**−0.83**		**−1.997**	**0.05**	**−0.82**		**−2.904**	**0.00**	**−0.81**
Caregiver measures												
MONSI-CC	6				6				12			
Environmental Set-Up		−1.782	0.08	−0.73		−1.156	0.25	−0.47		**−1.965**	**0.05**	**−0.57**
Child Guided Interactions		−1.577	0.12	−0.64		−1.472	0.14	−0.60		**−2.161**	**0.03**	**−0.62**
Active Teaching and Learning		−1.472	0.14	−0.60		−0.315	0.75	−0.13		−1.337	0.18	−0.39
Opportunities for Engagement		−1.490	0.14	−0.61		−1.761	0.08	−0.72		**−2.197**	**0.03**	**−0.63**
Natural Reinforcement and Scaffolding		−0.213	0.83	−0.09		−1.841	0.07	−0.75		−1.132	0.26	−0.33
Total Score		−1.787	0.07	−0.73		−1.261	0.21	−0.51		**−2.159**	**0.03**	**−0.62**

BOSCC, Brief Observation of Social Communication Change; MSEL, Mullen Scales of Early Learning; AE, age equivalent, VABS, Vineland Adaptive Behavior Scales, MONSI-CC, Measure of NDBI Strategy Implementation—Caregiver Change. Bolded numbers indicate statistical significance $p \leq 0.05$.

Child and Caregiver Behavior Change

Results from the Kruskal–Wallis test of initial differences showed that there were no significant differences between the NDBI+VF and NDBI groups at intervention entry for all baseline and outcome measures (all $p > 0.05$; **Table 1**).

Autism Symptom Severity

Using Wilcoxon signed-rank tests, the NDBI+VF group showed significant change in SC on the BOSCC-Clinician and Caregiver as well as significant change in BOSCC-Caregiver RRB (**Table 2**). The NDBI group showed significant change in the BOSCC-Clinician and Caregiver in SC. BOSCC-Clinician SC effect sizes were large for both groups. RCIs revealed that impairments in SC and RRBs measured by the BOSCC scores in the NDBI+VF group decreased in 2 out of 6 (33%) cases for BOSCC-Clinician SC and BOSCC-Caregiver SC and RRB. In the NDBI group, reliable decreases were shown in 2 out of 6 (33%) cases for BOSCC-Clinician SC and BOSCC-Caregiver RRB and no cases for BOSCC-Caregiver SC (**Table 3**). Based on the Fisher's exact test, the proportion of subjects showing reliable change did not differ by group.

Developmental Levels

Based on the Wilcoxon signed-rank test, developmental levels measured by the MSEL AE showed significant change in the NDBI+VF group in visual reception, fine motor, and expressive language (**Table 2**). The NDBI group showed significant change in visual reception, receptive language, and expressive language. Effect sizes were large for all domains for both groups. RCI revealed that there was a reliable increase in 4 out of 6 (67%) of cases across all domains in the NDBI+VF group. The NDBI group showed a reliable increase in 2–4 out of 5 (40–80%) cases across the domains (**Table 3**). Results from the Fisher's exact test found no significant differences in reliable change between the two groups across all subscales.

Adaptive Skills

On the VABS, the Wilcoxon signed-rank test revealed that the NDBI+VF group showed significant change across all domain

TABLE 3 | Reliable Change Indices from Intervention Entry to Exit.

Measure	Difference score for RCI	NDBI+VF group				NDBI group			
		n	% RC+	% RC0	% RC–	n	% RC+	% RC0	% RC–
BOSCC-clinician									
SC	8.55	6	0%	67%	33%	6	0%	67%	33%
BOSCC-caregiver									
SC	7.30	6	0%	67%	33%	6	0%	100%	0%
RRB	3.75	6	0%	67%	33%	6	0%	67%	33%
MSEL AE									
Visual reception	7.95	6	67%	33%	0%	5	40%	60%	0%
Fine motor	3.10	6	67%	33%	0%	5	40%	60%	0%
Receptive language	8.23	6	67%	17%	17%	5	80%	20%	0%
Expressive language	5.93	6	67%	33%	0%	5	60%	40%	0%
VABS AE									
Communication	6.36	6	83%	17%	0%	7	43%	57%	0%
Daily living	5.83	6	67%	33%	0%	7	57%	43%	0%
Socialization	7.01	6	67%	33%	0%	7	71%	29%	0%
Motor skills	5.54	6	67%	33%	0%	7	43%	57%	0%

Difference Score for RCI was the amount of change needed between entry and exit to reach statistical significance using the SDs of the sample at intervention entry. BOSCC, Brief Observation of Social Communication Change; MSEL, Mullen Scales of Early Learning; AE, age equivalent; VABS, Vineland Adaptive Behavior Scales.

AEs; the NDBI group showed significant change on all but one domain AEs (i.e., daily living; **Table 2**). Effect sizes were large for both groups. Based on RCI, 5 out of 6 (83%) cases in the NDBI+VF group showed a reliable increase in communication. Additionally, 4 out of 6 (67%) cases in the NDBI+VF group showed a reliable increase in daily living, socialization, and motor skills. In the NDBI group, 3–5 out of 7 (43–71%) cases showed a reliable increase across domains (**Table 3**). Based on the Fisher's exact test, there were no significant differences in reliable change between the two groups across all subscales.

Caregiver NDBI Implementation

Based on Wilcoxon signed-rank test, the MONSI-CC showed no significant changes in the NDBI+VF or NDBI groups. Effect sizes ranged from small to moderate levels for both groups across different domains. When both groups were combined, significant improvements in NDBI strategies were noted in Environmental Set-Up, Child Guided Interactions, and Opportunities for Engagement (**Table 2**).

Association Between Caregiver and Child Changes

Spearman's rho non-parametric correlations between changes in child BOSCC-Clinician and Caregiver scores and MONSI-CC total score showed that improvement in child social communication symptoms over time measured by the BOSCC-Clinician was significantly correlated with improvement in caregiver implementation of NDBI strategies over time measured by the MONSI-CC Total Score for the NDBI+VF group ($r = -0.83$, $p = 0.04$) but not for the NDBI group ($r = -0.37$, $p = 0.47$).

DISCUSSION

This pilot RCT examined the implementation, acceptability, and feasibility of VF as an augmentation to PMI NDBI within a community-based EI program for children with ASD. VF was successfully integrated into parent coaching sessions, with clinicians reporting that the intervention was helpful in coaching caregivers. Additionally, caregiver implementation and acceptability measures found caregivers in the NDBI+VF group recorded a sufficient amount of video to facilitate the intervention and no differences in attrition rates or service utilization between the groups. Caregivers reported that VF was beneficial for themselves and their children and helped them to learn NDBI strategies. Preliminary treatment effects between the NDBI+VF and NDBI groups showed comparable amounts of change in social communication symptoms between the groups with varying treatment effects in some developmental and adaptive skills.

Implementation, Acceptability, and Feasibility of NDBI+VF

This study demonstrated the feasibility of integrating VF into a community-based EI program, from both caregiver and clinician perspectives. Caregiver implementation of VF was acceptable, with most families recording home interactions close to the clinician-recommended dosage of 30-min weekly. All but one caregiver who completed the program agreed that they had time to complete recordings and were able to incorporate the recordings into daily routines. One family reported that they felt limited by the busy schedule due to other commitments such as work and other educational and treatment services. Attrition rate and service utilization were not affected by adding VF to the existing, comprehensive EI (NDBI), suggesting that VF did not add any extra burden to the families and can be successfully integrated into community-based EI. Informal feedback from families who refused to participate in or dropped out of the study revealed a busy schedule and a lack of support system as possible barriers. Caregivers expressed high satisfaction with VF and believed that the VF was beneficial for their children. For caregiver behavioral change to occur in VF, it is important that families buy into the utility of the video recording and review (1), as they did in the present study. Our VF intervention allowed for the inclusion of caregivers not just as passive recipients of intervention, but also in the roles of intervention collaborator and agent of the intervention (49), promoting caregiver buy-in to the intervention. In addition, caregivers in the NDBI+VF group reported increased insight into their own interactive strategy implementation because they reported that VF helped "to understand how we can play with our kids," and "to find my shortcomings," consistent with reflections of caregivers who received VF in past studies (23, 27, 50).

Clinician insight regarding the implementation of VF revealed that VF may be especially useful for families without access to home sessions. EI services are sometimes limited to center-based interventions in the U.S., which limits generalizability to naturalistic settings (25). Clinicians reported that VF gave insight into home routines and behavior occurring in the home setting outside of their presence, even for families who could not receive home sessions. In fact, the recording of home interactions also allowed for caregivers to record and clinicians to review the routines that were not always feasible for clinicians to be present for, such as early morning or bedtime routines. Additionally, receiving feedback on behavior in naturalistic settings is believed to aid in the generalization of caregivers' skills learned in the clinic to the home setting (19) and contribute to the utility of the VF intervention (1, 22, 51). While we did not collect data systematically on the reasons why sometimes the videos did not directly inform the coaching session, clinicians anecdotally reported that the focus of the particular session did not always align with the feedback given to the homework videos reviewed that day, although in general, the videos were helpful to inform the overall intervention goals and monitor progress over time.

The incorporation of technology (i.e., 360-degree cameras and tablets) may have also bolstered caregiver and clinician adherence to intervention implementation due to its portable nature and ease of execution. Interventions for children with ASD have increasingly leveraged technological resources, including clinician-mediated parent coaching and behavioral assessment (52). In the current intervention, the availability of small, portable, high-quality cameras allowed for the extension of technological tools into the home environment, without the need for resources such as an additional videographer and with minimal loss of data. This also reduced the efforts of research staff who did not have to make home visits and minimized the effect of an observer on the dyadic interaction. Furthermore, the cameras were provided to families at a relatively low cost to the program. As such, the opportunity to engage families in VF was not dependent upon the family having specific technology in the home, or even internet connection, underscoring the possibility of VF implemented across families with various socioeconomic backgrounds.

Caregiver and clinician surveys revealed barriers to community-based implementation of VF. Feedback from clinicians included the notable amount of time needed to devote to preparing the VF session, highlighting the importance of administrative support as well as the importance of clinician buy-in to see the benefit of the model. As mentioned above, caregiver surveys revealed that the largest barrier may be finding time for recordings in daily routines given other commitments and busy schedules. For some families, it may also be more appropriate to deliver additional VF sessions without the presence of a child, as occupying the child during feedback has been identified as a challenge in previous research as well (50). In this adult-only setting, the session may be devoted to providing feedback with minimal distractions and sufficient time for discussion. However, integrating VF within the *in-vivo* coaching sessions with caregivers and the children, as in the current intervention, provides opportunities to apply the feedback right away during the session. Therefore, the utility of providing a separate VF session may depend on the specific needs of the family. In addition, many of these barriers identified may be even more pronounced in under-resourced families. This highlights the need for future studies with more diverse samples to examine additional barriers to the implementation of VF in various community settings.

Analyses of Child and Caregiver Changes

The interpretation of the results from the child and caregiver analyses warrants caution given the preliminary nature of the study with a small sample size. In the current pilot RCT, child and caregiver gains were noted across *both conditions*. Children from both groups showed significant improvements in social communication impairments, visual reception, expressive language, as well as adaptive communication, motor, and socialization skills. Caregivers also demonstrated improved use of NDBI strategies. Children in the NDBI+VF group showed significant improvement in fine motor and only marginal improvement in receptive language, whereas receptive language improvement in the NDBI group reached statistical significance. The results may suggest that VF embedded in a comprehensive, community-based NDBI program may not have yielded additional social communication symptom reduction, improvements in developmental levels in young children with ASD, or increased NDBI strategy use for caregivers beyond the gains from the NDBI program alone, although further replications are needed. However, children in the NDBI+VF group demonstrated additional areas of improvement in comparison to those in the NDBI group, including gains in adaptive daily living skills and RRB symptom reduction. This may be reflective of caregivers who received VF having increased opportunities to receive coaching in this area given that nearly a third of videos recorded focused on these skills (e.g., dressing, bath time, and feeding). The improvement in the RRB domain (which includes behaviors such as repetitive play acts, fixated interests) may be explained partly because children's play routines and themes have broadened and become less rigid while interacting with caregivers, which was one of the major targets of VF based on home play interactions. This effect on RRBs following PMI focused on social communication and play has also been found in other NDBI (53). Given the small sample size, future studies with more diverse samples should explore the benefits of VF on daily living and play skills in young children with ASD, in addition to *in-vivo* parent coaching, especially when home-based intervention is not feasible. Finally, for children in the NDBI+VF group, decreases in social communication symptoms with clinicians were significantly associated with improvements in caregivers' use of NDBI strategies. This positive relationship in the NDBI+VF group aligns with previous VF findings that showed increases in caregiver created opportunities (21) and caregiver synchrony as a mediator of child communication outcomes (9).

Limitations and Future Directions

Caregiver VF surveys were collected from 66% of the NDBI+VF group, and because the surveys were completed anonymously, we could not statistically compare the characteristics of the 4 families that completed the Caregiver VF Survey and those that did not. Therefore, it is important to note that the survey data may not represent the experiences of all families involved, and replications are needed before the results on the acceptability of the VF are generalized. Although the preliminary findings on treatment effects are promising, they should be considered within the context of limitations. For example, because of missing data for certain measures, the direct comparison of results among different instruments is not feasible. In addition, the lack of group differences noted in developmental and adaptive skills may be a result of several factors. Primarily, our intervention was a pilot RCT and featured a small sample size with low power. Furthermore, although measures like the MSEL and VABS are standardized to allow for direct comparison of participants to similarly aged peers, their focus on relatively broad areas of development may preclude their ability to capture hypothesized finer grain change in families receiving the VF component. For example, changes in children's feeding behaviors after using VF sessions to focus on food tolerance may only be captured by a few items in the VABS daily living skills domain, and thus would not be reflected in significant changes in overall scores.

An additional limitation warranting consideration is that the VF dosage recommended in the current study may have been cumbersome for some caregivers, as has been reported in previous VF interventions (28). While many families in the current study recorded the recommended amount of interactions or more, there was variability across families. However, measurement of the factors surrounding caregiver motivation to engage with the intervention to maximize the effectiveness of VF (1) has been difficult to implement (2) and was outside of the scope of the study. Furthermore, there were a few families in the broader EI program who did not want to participate in the study. Although, we were not able to gather information on the reasons why they declined to participate in the study and why some families discontinued the intervention, future research may explore ways to adapt recommendations for dosage of recording based on the family's needs and to identify factors contributing to caregiver motivation to engage in VF and barriers to incorporating VF in daily routines. Additionally, more research is required to fully understand the utility of VF not only in conjunction with *in-vivo* sessions with the children, but also in replacement of them. If VF can be used to provide the appropriate amount of support for some families who have limited access to services, future studies should also examine the validity of VF incorporated into remote, telehealth-based interventions. The cost of the 360-degree cameras and transferring of videos to another device may also be a barrier to the incorporation of VF in community settings or remote interventions, thus future research may consider VF leveraging more readily available technology (i.e., smartphone videos).

Conclusion

Results from the current preliminary study demonstrate the initial feasibility of VF in a community-based EI program. Caregivers successfully implemented the VF intervention in their daily routines and reported high acceptability toward the intervention. Clinicians delivered VF to fidelity within their intervention sessions and believed VF was an effective tool to teach caregivers NDBI strategies. Findings showed comparable gains in child and caregiver skills, with some additional areas of improvement in children with ASD participating in the NDBI+VF intervention, although the results should be replicated with larger, more diverse samples before they can be generalized into other contexts.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors upon request while following the institutional regulations.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Weill Cornell Medicine Institutional Review Board. Written informed consent to participate in this study was provided by the participants' legal guardian.

AUTHOR CONTRIBUTIONS

CK participated in the design, statistical analysis, interpretation of data, performed measurement, and drafted the manuscript. DS, BV, AL, JG, and JW participated in the data collection and helped to draft the manuscript, and interpretation of the data. EC-W helped to analyze the data and draft the manuscript and performed the measurement. SK conceptualized the study, participated in its design, coordination, interpretation of data, statistical analysis, and drafted the manuscript. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

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Examining US Public Early Intervention for Toddlers With Autism: Characterizing Services and Readiness for Evidence-Based Practice Implementation

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As the rates of Autism Spectrum Disorder (ASD) increase and early screening efforts intensify, more toddlers with high likelihood of ASD are entering the United States' (US') publicly funded early intervention system. Early intervention service delivery for toddlers with ASD varies greatly based on state resources and regulations. Research recommends beginning ASD-specific evidence-based practices (EBP), especially caregiver-implemented intervention, as early as possible to facilitate the development of social-communication skills and general learning. Translating EBP into practice has been challenging, especially in low-resourced areas. The main goal of this study was to obtain a more comprehensive understanding of public early intervention system structure, service delivery practices, and factors influencing EBP use for children with ASD in the US. Participants ($N = 133$) included 8 early intervention state coordinators in 7 states, 29 agency administrators in those states, 57 early intervention providers from those agencies, and 39 caregivers of children with ASD receiving services from those providers. Online surveys gathered stakeholder and caregiver perspectives on early intervention services as well as organizational factors related to EBP implementation climate and culture. Stakeholders identified key intervention needs for young children with ASD. In general, both agency administrators and direct providers reported feeling *somewhat effective* or *very effective* in addressing most needs of children with ASD. They reported the most difficulty addressing eating, sleeping, family stress, and stereotyped behaviors. Data indicate that children from families with higher income received significantly higher service intensity. While administrators and providers reported high rates of high-quality caregiver coaching (>60%), caregivers reported low rates (23%). Direct providers with more favorable attitudes toward EBP had greater EBP use. In turn, provider attitudes toward EBP were significantly associated with implementation leadership and culture at their agency. Results suggest that publicly funded early intervention programs in the US require additional resources and training for providers and leaders to support improved implementation climate and attitudes toward ASD EBPs. Results also suggest that more state system support is needed to increase use of ASD-specific EBP use, including high-quality caregiver coaching, to better serve toddlers with ASD. Recommendations for implementation strategies are addressed.

Keywords: ASD, autism, early intervention, community-based research, implementation science, health services

INTRODUCTION

Autism Spectrum Disorder (ASD) is one of the most common forms of neurodevelopmental disabilities, with a rate of 1 in every 54 children born in United States (US) (1). Increases in awareness and screening have led to a higher demand for autism-specific early intervention services. This has led to a need to better understand how public service systems address early intervention for toddlers with ASD who have delays across multiple areas of development (2).

Research demonstrates that specific early intervention models can lead to significant gains in social communication, language development, and adaptative behavior in young children with ASD (3–6). Several groups have published recommendations and quality indicators for best practices in early intervention for ASD (7) that include using evidence-based approaches, beginning intervention as early as possible, active involvement of caregivers as part of the intervention, individualizing treatment based on child, family, cultural, and contextual needs, using curriculum content with a focus on child's social communication, play skills, cognitive, self-help, and behavioral needs, and providing high levels of staff education and training. Recent studies strongly support the role of caregivers' active involvement in early intervention for achieving optimal short and long-term outcomes (8). Toddlers with ASD may also require a higher intensity of service provision to optimize outcomes (9), although the specific number of hours per week needed is not clear (10, 11).

Despite broad agreement on most of these recommendations, in practice meeting these standards within the available publicly funded early intervention community service system remains very challenging. A recent meta-analysis (12) found less favorable outcomes when children with ASD received community intervention compared to hospital/University-based intervention demonstrating significant differences between the types of services being tested and recommended by researchers, and the community services most families receive. Challenges in community implementation may be related to many variables: the complexity of ASD-specific evidence-based practices (EBP), limited opportunities for and variability in staff training, lack of autism-specific support, large caseloads and high overall work demands, low-intensity of service delivery, high diversity both clinically and culturally among clients and areas served, and low funding rates, among others. However, we have limited information about the specific barriers that limited implementation of EBPs in community early intervention services. To bridge the gap between research and practice, researchers must first understand the implementation context.

In the US, children under the age of 3 with an ASD diagnosis or early signs of ASD are typically eligible for public early intervention services provided by Part C of the Individuals with Disabilities Education Act (13). Few states have clear policies or practices in place regarding the type or intensity of Part C early intervention services for young children with ASD, and only a quarter of states have specific intervention guidelines (14). Services may range from simple surveillance, such as a monthly visit from a social worker to intensive interventions, such as 20 h a week of intervention involving delivery of EBPs and parent education. The average service intensity in Part C is 90 min per week (15). As a result of these variables high-quality ASD-specific practices are especially difficult to access in low-resource areas of the US (16). For example, although Part C requirements prioritize and mandate family involvement in early intervention, existing data indicate that most community providers have caregivers playing a passive rather than an active, collaborative and participatory role in their child's intervention (17–21). This lack of active capacity building for primary caregivers allows for little carryover of intervention strategies into daily routines and does not accomplish the Part C goal of building early intervention competence in the child's family (22).

To better understand how to improve translation of EBP, such as parent coaching, into publicly funded early intervention services, we must identify the current service landscape at multiple levels and from varied perspectives (23). Factors related to organizational leader, direct service provider, and consumer characteristics, as well as the organizational climate for innovation, are all related to the quality and use of EBP. The recent field of implementation science provides guidance for identifying determinants of high-quality use of EBP to guide training, adaptation, and implementation of innovative EBP.

For example, direct service providers report that intervention practices developed in research settings are too rigid and do not serve the diversity and complexity of day-to-day practices (24, 25). This is concerning as data indicate that providers' perceptions toward EBPs are linked to uptake and delivery (26). Thus, practitioner attitudes toward EBPs have been considered a target mechanism to improve EBP implementation (27, 28). Data from one early study indicated early intervention providers working with children with ASD had more favorable attitudes toward EBPs than mental health professionals generally and perceived less divergence between their current practice and EBP (29). However, to the best of our knowledge no recent studies have specifically examined provider attitudes toward the use evidence-based early intervention strategies for ASD, including caregiver involvement in intervention, or whether direct providers are considering the evidence-base of their practices when intervening with their clients (14, 30).

So far, a majority of implementation work has focused primarily on direct service providers as the end-users of EBPs, and less on other individuals involved in community implementation (31). However, implementation science has identified leadership as a key component of successful EBP adoption, implementation, and sustainment in community services (32). Leadership can drive EBP implementation through fostering an organizational context in favor of EBP use, for example, by prioritizing provider access to EBP training. Leaders can be instrumental in institutionalizing EBPs, allocating resources strategically to ensure continuity of implementation, or by serving as EBP champions (32). Therefore, leaders can have a profound influence on both the organizational climate (i.e., staff perception of their work environment) and culture (i.e., normative beliefs and shared behavioral expectations in an organizational unit), which in turn can shape the perceptions, attitudes, and implementation by direct service providers (33).

Overall, there are limited data regarding implementation of EBP in community-based early intervention settings, particularly for families in low-resource areas and from historically marginalized backgrounds. Preliminary data indicate that providers report implementing broader elements of EBP strategies rather than the specific techniques that underlie each EBP, adapting them in various ways to meet child and family needs as they deem appropriate (34). Thus, there is a need to describe the early intervention services taking place for toddlers with an elevated likelihood of ASD, and to examine the organizational context that could support use of EBP in low-resourced community settings.

The current study adds to the small body of the literature in this area by studying the structure and practices involved in community Part C delivery in the US public early intervention system focusing on services for children with or at high likelihood of having ASD living in low-resourced areas. Specifically, we aimed to: (1) characterize early intervention services for ASD across seven states serving families in low-resource areas in the US; (2) examine intervention practices and strategies and use of EBP in these systems; and (3) examine organizational and contextual factors influencing system readiness for EBP implementation.

MATERIALS AND METHODS

The survey described in this study was conducted as part of a larger community-partnered project designed to adapt an evidence-based early intervention for use in low-resourced service systems. The study used a community-based participatory research methodology (35) with partners in seven states. Partner groups included a mix of representatives including researchers, early intervention agency administrators and direct service providers, and caregivers of children with ASD participating in the early intervention system in their state. The teams met to identify methods for supporting services in rural and low-resource communities within their state and to collaborate on survey development, recruitment, and data interpretation. This specific study involved surveying early intervention stakeholders at multiple levels of the Part C delivery structure.

Recruitment and Distribution

Participants included individuals involved in one of four distinct tiers of the federally funded (Part C of the IDEA) early intervention delivery structure in the US, specifically providing services for children with or at high likelihood of having ASD. Inclusion criteria were as follows: (a) State Part C Coordinators (coordinator) serving as the designated state early intervention system leader for each participating state. (b) Agency administrator (administrator) participants had to have at least 1 year of experience leading an agency serving children with ASD under age 3 in a low-income region of the state, at an agency funded through the Part C system, and have at least one qualifying direct service provider also working at that agency. (c) Direct Service Providers (provider) met the following inclusion criteria: (1) having served at least 2 toddlers with high likelihood of ASD in the past year in a participating agency, and (2) having at least 1 year of experience with the population. (d) Primary Caregivers (caregiver) had the following inclusion criteria: (1) legal guardians of a child with or at high likelihood of having ASD participating in Part C services and (2) receiving services from a participating provider.

To facilitate a high response rate and obtain a broad view of publicly funded early intervention services for young children with ASD and their families in the US, participants were recruited from two primary sources. First, participants were recruited from the larger project's partners in 7 US states (i.e., Pennsylvania, New Mexico, Montana, Maine, Colorado, California, and Alabama). Participants originating from referrals through state partners consisted of approximately 27.4% of all survey participants. All other participants were recruited through a nomination system starting with state coordinators and ending with caregivers. State coordinators nominated at least two administrators in agencies providing early intervention services to low-resource and/or low-income families within their state. Participating administrators nominated at least three providers in their agency that directly serve young children with autism or high likelihood of autism. Finally, participating providers nominated at least one family on their caseload with a young child in this population. This method provided 72.5% of our total participant pool. If we did not get a response from at least one provider or one family, the study coordinator contacted the referral source to request an additional nomination.

The study team distributed online surveys via REDCap between November 2015 and April 2016 through email. To accommodate any technical or language barriers, arrangements

TABLE 1 | Participants and agency demographics.

Variable	Coordinators *M* (SD)	Administrators *M* (SD)	Providers *M* (SD)	Caregivers *M* (SD)	Total
Number of participants	*n = 8* (6%)	*n = 29* (22%)	*n = 57* (43%)	*n = 39* (29%)	*n = 133* (100%)
Child age (in month)	–	–	–	40.2 (21.2)	–
Participant's age (in years)	55.9 (4.5)	51.8 (10)	44.6 (12.5)	–	–
% Of children with ASD in agency	6.3 (4.7)	9.7 (9.3)	29.5 (31)	–	–
Years of experience with ASD	–	18.2 (11)	13.9 (9.3)	–	–
Gender					
Female	100%	90%	95%	100%	95%
Ethnicity					
Non-hispanic*	88%	86%	86%	79%	85%
Hispanic	12%	14%	12%	21%	15%
Race					
White	75%	90%	86%	77%	85%
Hawaiian/Pacific Islander	12%	3%	5%	8%	6%
Black/African American	12%	7%	5%	13%	8%
Asian	0%	0%	2%	0%	<1%
Amer Indian/Alaskan	0%	0%	2%	3%	1%
Highest education					
Some high school/HS/GED	0%	0%	0%	24%	7%
Some college	0%	0%	2%	29%	9%
College degree	25%	28%	32%	24%	28%
Master's degree	62%	62%	60%	16%	48%
Doctorate	12%	7%	0%	0%	2%
Other	0%	7%	3%	3%	5%
Primary discipline					
Psychologist	–	14%	14%	–	–
Marriage/family therapist	–	4%	2%	–	–
Social worker	25%	11%	7%	–	–
Speech therapist	–	4%	22%	–	–
Physical therapist	–	4%	–	–	–
Educator	63%	50%	31%	–	–
Behavior specialist	–	–	5%	–	–
Others	10%	14%	14%	–	–
Marital status					
Married	–	–	–	59%	–
Divorced	–	–	–	6%	–
Cohabiting, no marriage	–	–	–	13%	–
Single and unmarried	–	–	–	22%	–
Family annual income					
Under $25,000	–	–	–	26%	–
$25,000–$49,000	–	–	–	21%	–
$50,000–$74,999	–	–	–	15%	–
$75,000–$99,999	–	–	–	26%	–
$100,000 and above	–	–	–	13%	–

The percentages not reaching 100% are due to minor-missing data.
**The terms Hispanic, Non-hispanic were used in the survey at the time. We use the more appropriate term Latinx in the manuscript.*

were made to collect surveys from Spanish-speaking families over the phone. One survey was collected via postal service. Each participant received a survey-package specific to their role (coordinator, administrator, provider, caregiver). Participants were contacted by both phone and email with reminders to complete the survey and to answer any questions. Upon completion of the survey, participants were offered a $20 gift card for their participation.

Respondents

One hundred and eighty one participants across 7 states were contacted, and 133 participated (73%). Participants included 8 state coordinators (88% response rate; two states had two coordinators complete the survey and one state did not complete the survey); 29 administrators (76% response rate), 57 providers (73% response rate), and 39 caregivers of children with autism (81% response rate). Seventy-three percent of all participants completed the survey, 29% remained unopened or unfinished, and 3% formally declined. See **Table 1** for respondents' demographics.

Surveys

Surveys were chosen to characterize the early intervention service system context including service setting, funding, service intensity, parent/caregiver involvement and child needs, use and perspectives of EBP, and readiness for EBP implementation. Surveys asked about the types of intervention practices being used, including providers' perceived confidence using the interventions, and use of caregiver training method (e.g., psychoeducation/training, caregiver practice with feedback/coaching, etc.). Surveys included demographic questions, components of the ACT SMART Agency Assessment Battery (described below), and questions about implementation of new practices. **Table 2** lists the surveys completed at each participant level.

Participant Demographics Survey

Participants at each level responded to questions describing their agency, experience and/or family. All participants provided information about their age, gender, race/ethnicity, and education. Caregivers responded to questions about marital status, income, and primary language spoken (one family completed the survey in Spanish) in the home. State coordinators, administrators and providers responded to questions about their primary discipline and years at the agency. Administrators and providers also indicated their years of experience working with youth with ASD and responded to questions about their training.

TABLE 2 | Participant survey completion.

Participant Type	Survey components
State Part C coordinators	Participant demographics Agency demographics ASD—Needs, Strategies and Context Survey (ASD-SIS)
Agency administrators	Participant demographics Agency demographics ASD—Needs, Strategies and Context Survey (ASD-SIS) Modified Practice Attitudes Scale (MPAS)—adapted
Direct providers	Participant demographics Agency demographics ASD—Needs, Strategies and Context Survey (ASD-SIS) Organizational Readiness to Change Assessment (ORCA) Texas Christian University Organizational Readiness for Change 4-Domain Assessment (TCU ORC-D4) Modified Practice Attitudes Scale (MPAS)—adapted
Caregivers	Participant demographics ASD-needs, strategies and context survey (ASD-SIS) Caregiver/client survey

Agency Demographics Survey

Coordinators, administrators, and providers responded to questions regarding the percentage of children served in their agency/state had ASD, the service setting(s) and funding sources.

ACT SMART Agency Assessment Battery

This assessment battery, developed by Drahota et al. (36) specifically to provide a comprehensive, multi-level assessment of agencies providing services to children with ASD, compiles adapted versions of the ASD-Needs, Strategies and Context Survey (37), the Modified Practice Attitudes Scale [MPAS; (38)], the Organizational Context subscale of the Organizational Readiness for Change Assessment [ORCA; (39)], and TCU Organizational Readiness for Change-D4 [ORC-D4; (40)]. Measures were selected to evaluate the type and quality of intervention strategies and services being delivered within participating agencies and the extent to which services were perceived to be meeting client needs as well as organizational factors hypothesized to impact the quality and delivery of ASD services (e.g., communication within agencies; readiness for change; staff attributes, and attitudes) (41). A caregiver component was included to obtain perspectives on child and family needs, service provision and acceptability. Subscales from the following assessments were used in this study.

ASD-Needs, Strategies, and Context Survey

Participants across levels reported on areas of intervention need for children with ASD and how well a variety of needs were being addressed by the current system/agency, service intensity, and caregiver education and training methods. Administrators, providers, and caregivers were asked about the typical presenting problems of children with ASD or high likelihood of ASD. The specific need areas assessed included: *communication, social interaction, play, learning, sleep, eating, sensory, behavior challenges, stereotyped behaviors, repetitive and/or restrictive behaviors, parent-child engagement, and family stress around the child*. Administrators and providers also reported on the perceived effectiveness in addressing these needs on a Likert scale from: *not being addressed, not effective, somewhat effective, or very effective (37).*

Additionally, participants across levels (including caregivers) indicated service intensity (number of hours per week), service location (home, school, community, childcare, clinic) and caregiver involvement (e.g., participation in goal development, observation of providers, practice using strategies, feedback on use, etc.). To better understand parent/caregiver involvement, we defined *caregiver training* as observation of providers working with the child, reading materials/resources and/or discussing the intervention with caregivers and *caregiver coaching* as providing the parents opportunities to practice a specific strategy with feedback and specified at-home practices between visits.

The measure also assessed which, if any, autism-specific practices were being used within the agency as perceived by administrators and providers. The listed items included evidence and non-evidence-based practices including 26 therapeutic strategies or interventions specific to ASD services for early intervention. Strategies were adapted slightly to include only those strategies appropriate for early intervention settings (e.g., intervention packages such as cognitive behavioral therapy and social skills training and treatment strategies such as cognitive restructuring were removed). Strategies and packages were listed by name in alphabetical order with no definition or information about their evidence base. Direct providers were further asked to rate their level of confidence in delivering any treatment strategies they said they reported utilizing on a Likert Scale ("I feel confident in my delivery of this practice": *1–Disagree Strongly; 5–Agree Strongly)*.

Organizational Readiness to Change Assessment (ORCA)–Organizational Context

The ORCA-Organizational Context Scale (39) assessed organizational culture, defined as "normative beliefs and shared behavioral expectations in an organizational unit" (43 p. 770). Specifically, the ORCA measures staff perceptions of the quality of the organizational context to support practice change and innovation. The scale is comprised of six subscales: *leadership culture* (i.e., norms and expectations regarding how leaders behave and how things are done at the agency), *staff culture* (i.e., norms and expectations regarding how staff behave and how things are done at the agency), *leadership practices* (i.e., staff perception of leadership behaviors), *measurement* (i.e., staff perception of supervisor feedback), *readiness to change among opinion leaders* (i.e., performance measures and procedures for feedback and accountability), and *resources to support practice change*. Subscales consists of three to six items and all items are scored on a 5-point Likert scale from 1 (strongly disagree) to 5 (strongly agree). Scale and subscale scores are calculated by dividing the total score by the number of items on the scale resulting in scale score values of 1–5. Average scores below 3.8 are considered areas in need growth, while scores between 4 and 5 are considered areas of strength (i.e., 3.8–3.9 indicate an average score). Reliability tests indicate that the ORCA context subscale tool meets standard requirements of 0.80. Cronbach's alpha for reliability at 0.85.

Texas Christian University Organizational Readiness for Change 4-Domain Assessment

The ORC-D4 (40, 42) measures organizational climate, defined as the "way people perceive their work environment" across four major domains comprised of 21 scales and 125 items and [(43). p. 769]. Specifically, this measure assessed staff perceptions of their role in the organization. This project used the Staff Attributes (Growth, Efficacy, Influence, Adaptability, Satisfaction) Scale. For Staff Attributes, *growth* measures the extent to which staff value and perceive opportunities for professional growth; *efficacy* measures staff confidence in their own intervention skills; *influence* is the willingness and ability of staff to influence coworkers (be an opinion leader); *adaptability* is the ability for staff to adapt to a changing environment, and *satisfaction* examine overall job satisfaction. ORC-D4 scores have been associated with *higher satisfaction with training, greater openness to innovations* (44, 45), and better client functioning (42, 46). Response categories for the items on the ORC-D4 are on a 5-point Likert scale from 1 (strongly disagree) to 5 (strongly agree). Scale scores are computed by averaging scale items and multiplying by 10 to obtain a range of 10–50. A score of 30 indicates the scale's mid-point (neither agreeing nor disagreeing). Thus, scale scores above 30 indicate greater agreement and scale scores below 30 indicate greater disagreement with the construct. For Staff Attributes, scores above 40 are in the 75th %tile and considered a strength, excepting the *efficacy* scale which requires a score of 44.

Modified Practice Attitudes Scale

Adapted from the longer Evidence-Based Practices Attitude Scale (EBPAS) measure, the MPAS assessed attitudes toward treatment manuals specifically (47). The 8-item MPAS assessed both direct provider (consistent with original measure) and administrators (e.g., items were modified to reflect administrator attitudes toward providers use of EBP) attitudes toward EBP. A sample item includes: "[I am willing to OR I am willing to have clinical staff] use new and different types of interventions if they have evidence of it being effective." Participants indicated their agreement with each item from 0 (*not at all*) to 5 (*to a very great extent*). The total score ranges from 0 to 40, and higher scores reflect more favorable attitudes toward use of EBP with scores above 32 indicating this as an area of strength. Scores below 22.5 indicate an area for growth in an organization. The cronbach's alpha for the MPAS was 0.80 in the original measure development study (27). For the current survey responses, the MPAS alpha coefficient maintained an 0.80 (38).

Data Analysis

Data analyses were conducted using the SPSS 23.0 statistical software program. The characterization of early intervention services in the US was examined using descriptive statistics and mean difference analyses (i.e., Chi-square tests and independent samples *t*-test). Concretely, Chi-square tests (through contingency tables based on Bonferroni *post-hoc* method) were conducted to identify the discrepancies across the participant groups (i.e., administrators, providers, and caregivers) on intervention intensity, type of parent/caregiver training, coaching given and received, and the presenting needs of children with ASD. Two-tailed independent sample *t*-tests were used to detect discrepancies between administrators and providers on the perceived effectiveness of their team at addressing child's needs. To examine intervention practices and strategies used, and organizational variables associated with readiness to implement evidence-based practices, we conducted descriptive statistics, *Pearson* correlational analyses, and multiple

TABLE 3 | Intervention intensity reported by each participant.

Intensity per month	Administrator % (n = 28)	Provider % (n = 48)	Caregiver % (n = 35)
Fewer than 6 h	50	50	43
From 6 to 15 h	32	25	14
More than 15 h	18	25	43

TABLE 4 | Intervention intensity by income (caregivers).

Intensity per month	Lower income % (n = 18)	Higher income % (n = 17)
Fewer than 6 h	56	29
From 6 to 15 h	17	12
More than 15 h	28	59

Under $50,000 is referred to as low income, while $50,000 and above is referred to as high income based on median income in the US in 2016 being $59,039 (48).

linear regression analysis (i.e., using a backward elimination method to determine best model fit).

RESULTS

Early Intervention Services in the US: Characterizing Services for ASD

Service Setting

The most frequent early intervention setting was the home (over 85% of all participants). The second most common setting was the community (coordinator = 37.5%, administrator = 67.9%, provider = 58.6%). Very few children received services in a clinic (<15%), and ∼25% received services in school or daycare settings. We did not collect information about specific type of school or daycare setting or opportunities to interact with typically developing peers.

Methods Used for Therapeutic Goals

The most frequent method to establish intervention goals was through collaboration with caregivers. Respondents across levels similarly reported that early intervention goals were based on child and family needs (72.3%). Other methods included observing the child's behaviors and skills (53.6%) and using a specific assessment (44.1%).

Private vs. Public Funding Source

Based on agency report, 96.4% of the interventions provided to children with ASD were publicly funded (Part C), with a smaller percentage of interventions paid for privately (i.e., insurance, private pay, employer supported).

Intensity

All groups of participants agreed that about half of the children received fewer than 6 h of intervention per month. Administrators reported that only 18% of children received more than fifteen hours a month, while direct providers reported 25%, and caregivers reported that 43% received more intensive services (see **Table 3**). Because most services were provided in home (85%) it is likely these were provided using a one-to-one provider/child ratio. Surveys did not ask about caseloads. Although caregivers descriptively reported higher-intensity services, a Chi-square test showed that the differences reported by the three groups (i.e., administrators, providers, and caregivers) were not significant [$\chi^2_{(4)} = 6.27$, $p = 0.180$].

When stratifying caregivers' report by family income, children from lower income families (< $50,000/year) were most likely to receive fewer than 6 h of intervention per month (n = 10, 56%). Children from families with higher income (> $50,000/year), were more likely to receive more than fifteen hours per month of intervention (n = 10, 59%). For more detailed information see **Table 4**. A Chi-square test analysis stratifying intensity of intervention by those families getting fifteen or less hours per month and those getting more than fifteen hours per month [$\chi^2_{(1)} = 3.44$, $p = 0.064$] revealed marginally significant differences.

Caregiver Training and Coaching

We asked participants about the use of caregiver training and caregiver coaching in early intervention. All participants reported high rates of caregiver training (68–97%; see **Figure 1**) while reported rates of coaching varied (23–75%). Chi-square test showed significant differences [$\chi^2_{(3)} = 20.95$, $p < 0.001$] between groups of participants with regards to the reported frequency of caregiver training and caregiver coaching usage. While coordinators, administrators, and providers reported a high use of caregiver coaching strategies (over 60%), caregivers reported very low rates (23%). Providers indicate high rates of caregiver education and lower rates of caregiver coaching. However, caregivers did not report receiving training and coaching as often as the program staff reported (see **Figure 1**).

Presenting Needs of Children With ASD in Early Intervention

Administrators, providers, and caregivers were asked about the typical presenting problems for children with or at high likelihood of having ASD. All participant groups agreed the most frequently identified needs were addressing the development of communication, social interaction, play skills, concerns related to sensory differences, and behavioral challenges. All these areas were reported as key areas of need by over 80% of participants, regardless of participant role.

Chi-square tests were conducted to examine differences between the three groups (i.e., administrators, providers, and caregivers) in the reported areas of need. Results showed an overall agreement among the three participant groups in the reported areas of needs for young children with ASD. However, significant differences were found [$\chi^2_{(2)} = 11.97$, $p = 0.003$] between the caregivers and both administrators and providers. Caregivers reported

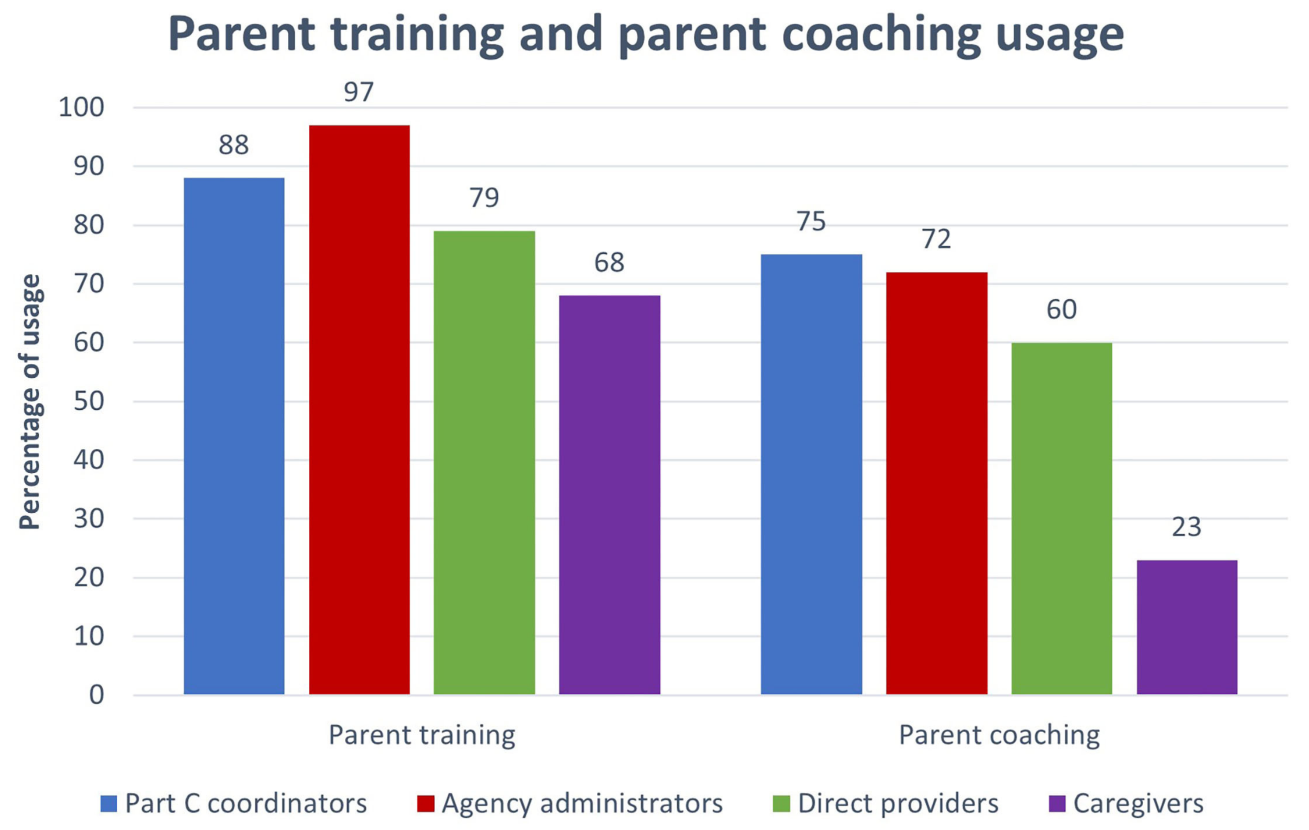

FIGURE 1 | Parent coaching and parent training usages reported by all participants. Parents coaching refers to at-home practice together with feedback on parents use of strategies.

significantly higher levels of concern about *learning differences* (91%) compared to both professional groups (i.e., 50% administrators and 70% direct providers). See **Table 5** for more details.

Perceived Effectiveness of the Interventions Addressing Client Needs

Overall, descriptive analyses showed that administrators and direct providers reported feeling *somewhat effective* or *very effective* in addressing the needs of children with ASD. Communication skills were the only area where both administrators and direct providers reported the highest effectiveness (i.e., over 50% of both groups reported feeling *very effective*). There were four areas in which both groups felt less effective. More concretely, <25% reported feeling *very effective*, addressing *sleeping, eating, stereotyped/repetitive behaviors, or family stress.*

TABLE 5 | Presenting client needs: children with ASD in early intervention.

Needs	Respondents		
	Administrators % (*n* = 28)	**Providers** % (*n* = 54)	**Caregiver** % (*n* = 32)
Communication skills	100	90	100
Social interaction skills	100	90	100
Play skills	93	92	100
Learning differences	50_a	70_a	$91_{a,b}$
Parent-child engagement	75	52	47
Sleep challenges	68	60	66
Eating differences	71	75	94
Sensory differences	89	83	88
Behavior challenges	86	80	84
Stereotyped behavior	75	65	69
Family stress	75	72	84

Variable in italics had significant differences across groups.
The different subscripts (a,b) refer to significant differences across those specific groups.

Comparing Agency Administrators' and Direct Providers' Perceptions of Early Intervention Effectiveness

A Student *T* test was conducted to identify differences between administrator and provider perceptions of effectiveness in addressing the developmental needs of children with ASD. Results indicated significant differences between administrators and direct providers in two areas: *social interaction* [$t_{(78)} = 2.21$, $p = 0.03$] and *stereotyped behaviors* [$t_{(67)} = -2.27$,

TABLE 6 | Percentage of leaders and providers who report using practices/strategies in early intervention and provider's reported competence.

Practice/strategy	Administrator strategy use % (n = 28)	Provider strategy use % (n = 65)	Provider reported high competence % (n = 65)
Evidence-based practice			
Reinforcement/rewards	75	75.4	95.9
Modeling	89.3	73.8	89.6
Visual supports (schedules)	82.1	69.2	86.6
Prompting	67.9	63.1	92.7
Alternative communication systems (e.g., PECS, sign, devices)	89.3	63.1	70.7
Parent-implemented intervention	60.7	53.8	73.5
Responsive teaching DIR/Floortime	35.7	46.2	96.5
Functional behavior assessment	39.3	46.2	65.5
Pivotal response training—naturalistic	53.6	44.6	82.8
Differential reinforcement	17.9	41.5	74.1
Positive behavior support (PBS)	35.7	41.5	92.6
Task analysis	14.3	41.5	76
Discrete trial teaching	28.6	40.0	73.1
Antecedent-based Intervention	25.0	40.0	84.6
Extinction	14.3	35.4	65.2
Social-communication intervention (e.g., SCERTS, Project ImPACT)—parent implemented	21.4	33.8	63.6
Early start denver model	35.7	32.3	33.3
Emerging evidence			
Sensory diet*	46.4	49.2	65.7
Expressive language-based therapy (e.g., HANEN)	32.1	47.7	87.1
Sensory integration*	75.0	47.7	48.4
Imitation-based intervention/reciprocal imitation training	28.6	41.5	74.1
Joint-attention intervention/instruction (e.g., JASPER)—naturalistic*	25.0	35.4	56.5
Music therapy	17.9	21.5	57.1
No evidence to support			
Play therapy	35.7	49.2	83.9
Dietary changes	28.6	33.8	54.5
Massage/touch therapy	35.7	24.6	56.3

**Considered emerging evidence at the time of the survey by the NAEYC report.*
Competence's columns indicate percentage of providers indicating feeling competent on this particular practice/strategy.

p = 0.04]. More specifically, providers reported better skills in addressing social skills than was perceived by administrators. The opposite views were reported regarding stereotyped behaviors. That is, administrators perceived higher effectiveness of early intervention for addressing stereotyped behavior than providers.

Association Between Client Needs and Effectiveness Addressing Those Needs

When we combine these two sources of information, the presenting needs, and the effectiveness of the interventions addressing those specific needs, results showed that most administrators and direct providers reported feeling *somewhat effective* or *very effective* addressing client's highest needs (i.e., communication skills, social interaction, play skills, sensory differences, and behavior challenges). Administrators and direct providers disagreed about the effectiveness of intervention for *social interaction*. While over 50% of direct providers reported feeling *very effective* in supporting development of social interaction, only 28% of the administrators felt that way.

Intervention Practices and Strategies for ASD utilized in Early Intervention

Administrators and providers reported on the practices used in their programs. **Table 6** shows the proportion of participants reporting the use of a particular practice or strategy. Determination of the level of evidence for each strategy was based on the *Evidence Based Practices for Children, Youth, and Young Adults with Autism Spectrum Disorders Report* (2014) and the group's review of comprehensive treatment models (49). The 2014 review was used, rather than the 2020 update, to examine provider use of EBP identified at the time of the survey.

Most administrators and providers endorsed many different practices. A similar proportion of providers reported using evidence-based practices, practices with emerging evidence, and those with no/limited evidence (i.e., EBP = 58.1%, emerging evidence = 55.4% and no evidence = 48.1% based on the 2014 report). All providers endorsed using at least 3 (out of seventeen) EBP. Providers tended to endorse strategies that addressed specific behaviors rather than comprehensive interventions addressing multiple areas of development.

Provider Competencies

Over 75% of providers *agreed* or *strongly agreed* that they felt competent delivering the following evidence-based practices and strategies: reinforcement/rewards (95.9%), modeling (89.6%), visual supports like schedules (86.6%), prompting (92.7%), responsive teaching DIR/Floortime (96.5%), pivotal response training—naturalistic (82.8%), positive behavior support (92.6%), task analyses (76%) and antecedent-based intervention (84.6%), see more details in **Table 6**.

Provider Training

The majority (76.3%) of providers indicated they received training through their school and/or educational coursework. However, over 50% of providers reported a need for more training in the following areas of competency: (a) ASD-related training (70.1%); (b) improving behavioral management of clients (59.7%); (c) improving engagement of caregivers during the session (56.1%); (d) increasing participation in interventions by clients with ASD or their families (54.4%); and (e) caregiver coaching strategies or methods (50.9%).

Provider Readiness to Implement EBP in Early Intervention Programs

Attitudes Toward EBPs

MPAS scores did not differ by respondent type. Administrators, overall, had an MPAS mean score of 31.53 (SD = 4.90) and providers had a mean score of 30.79 (SD = 5.08) indicating this is an area that could benefit from additional growth and training across administrator and provider levels.

Organizational Context

Providers indicated that their early intervention agencies had average leadership culture (as indicated by ORCA scores; **Table 7**) for innovation implementation. They considered leadership practices, staff culture, and opinion leaders (at the staff level) as strengths in their organizations in terms of readiness to support the use of new practices. Measurement (i.e., leadership feedback on the use of intervention practices) and having resources to support practice change were both areas of need in early intervention agencies.

TABLE 7 | Organization readiness to change (ORCA)—context scale.

Subscale (n = 52 providers)	Mean (SD)	Rating
Leadership culture	3.96 (0.79)	Average
Staff culture	4.27 (0.59)	Strength
Leadership practices	4.00 (0.82)	Strength
Measurement (leadership feedback)	3.75 (0.79)	Growth/Need
Readiness to change (opinion leaders)	4.42 (0.63)	Strength
Resources to support practice change	3.64 (0.86)	Growth/Need

Provider Attributes

Providers in early intervention agencies considered the attributes of staff in their agencies as strengths on two ORC-D4 staff attribute subscales (see **Table 8**): influence (i.e., staff interaction based on sharing and mutual support) and satisfaction (i.e., general satisfaction with one's job and work environment). They rated staff as average in the areas of growth, efficacy, and adaptability which may indicate that staff do not highly value or make use of opportunities to advance their own professional growth, may have poor confidence in their ability to deliver interventions or conduct their work well, and feel they have limited ability to effectively integrate new innovations at their agency.

Organizational Factors Associated With Attitudes Toward EBPs by Providers

Results showed a moderate positive association between provider attitudes toward EBPs and EBP usage ($r = 0.39$, $p = 0.01$). However, there was no association between attitudes toward EBPs and the provider's perceived competence using the EBP ($r = 0.07$, $p = 0.61$).

Regarding organizational factors, correlation analyses showed that provider attitudes toward EBPs were significantly associated with three of the organizational scales, leadership culture ($r = 0.38$, $p = 0.01$), staff culture ($r = 0.28$, $p = 0.04$), and growth ($r = 0.39$, $p = 0.01$), with low-to-moderate positive associations. That is, higher leadership culture, staff culture, and growth were related to more favorable attitudes toward EBP practices and strategies.

A linear regression analysis (i.e., backward elimination method) was conducted to assess whether organizational factors were related to the attitudes toward EBPs. Results of the linear regression model were significant, showing that ∼31% of the variance in attitudes toward EBP was explainable by *readiness to change*, *leadership culture*, *resources to support practice change*, and *growth*, [$F_{(4,47)} = 5.40$, $p = 0.001$, $R^2 = 0.31$]. *Leadership culture* was significantly associated with attitudes toward EBPs, $B = 2.70$, $t_{(47)} = 3.17$, $p = 0.003$. This indicates that on average, a one-unit increase of *leadership culture* (as measured by the ORCA) was associated with increased attitude toward EBPs (MPAS) by 2.70 units. *Growth* (measured by the ORC-D4) was significantly associated with attitudes toward EBPs, $B = 0.43$, $t_{(47)} = 3.29$, $p = 0.002$. This indicates that on average, a one-unit increase of *growth* was associated with an increased attitude toward EBPs (MPAS) of 0.43 units. **Table 9** summarizes the results of the regression model with the best model fit.

DISCUSSION

This study examined three aspects of current early intervention practices for ASD to identify routes to improve translation and implementation of EBP in US publicly funded community early intervention settings. First, we sought to characterize the services delivered across seven states serving families in low-resource areas of the US. We found high levels of agreement across stakeholders in terms of the service setting, intensity, and needs of children entering the community early intervention system. Agency stakeholders and caregivers reported contrasting information about the extent of caregiver coaching delivery, with few caregivers reporting receipt of high-quality in-person coaching with their child. Interestingly, caregiver report of psychoeducation closely aligned with providers' rates of reported caregiver coaching. Over 50% of participating providers reported the need for more training in caregiver coaching strategies. Second, we specifically examined the current use of EBP in the system. The vast majority of providers reported using multiple strategies, about half of which could be considered evidence-based. While many providers felt competent in their delivery of several EBPs, endorsed strategies were specific rather than comprehensive, and 70% indicated the need for additional training in specific EBPs for ASD. Third, we examined organizational and contextual factors influencing system readiness for EBP implementation. Our data support a positive link between attitudes toward EBPs and EBP usage. Leadership culture and staff attribute growth were positively associated with providers' attitudes toward EBPs, pointing to contextual factors as potential leverage points to intervene upon to increase EBP use in community early intervention settings.

The US regulations for Individuals with Disabilities Education Improvement Act of 2004 (13) include several guidelines for Part C that support a "natural environment" for intervention, often interpreted as being the child's home for very young children, the use of scientifically-based interventions, and building early intervention competence within the child's family, including family involvement in goal setting and intervention delivery. No specific recommendations are provided for service intensity.

Our data indicate that a vast majority of children receive Part C services in the home or another community setting and very few are going to a clinic for services. This is very consistent with Part C regulations. Although no clear data exist to determine the specific intensity needed for early ASD services (11), general consensus in the field recommends at least ten hours of comprehensive treatment per week (10). Our data indicate that most children with ASD residing in low-resourced areas of the US receive ∼6 h of intervention per month (i.e., fewer than 2 h per week) through publicly funded early intervention services. Providers responses indicated these services were predominantly a mix of individual strategies, rather than comprehensive, integrated programs. Moreover, low-income families reported receiving fewer service hours per month overall than higher-income families and the number of hours reported by low-income families aligned with Part C providers' overall report of service intensity. This suggests that higher-income families may be supplementing public early intervention services with additional intervention hours funded through insurance or self-pay methods. Higher-income families may also be able to use advocacy to garner more hours from the public system. To improve equity in provision of care, identifying equity-focused implementation strategies and allocation of services will be key to prevent widening disparities in access to needed services. However, ensuring the use of high-quality intervention in community programs may be even more critical given that poorly implemented interventions are not likely to improve child outcomes regardless of intensity.

Understanding the use of EBP in early intervention may provide some information regarding quality. Although to date, no specific intervention model or method has been established as the general standard for early intervention for ASD, many EBPs leading to gains in social communication, language, adaptative behavior, and learning have been identified (3–6, 49, 50). Some EBPs focus on specific skills and behaviors while others are applied across a range of skills and behaviors (50, 51). Both targeted and comprehensive strategies may need to be adapted to work within various public early intervention delivery systems (e.g., increased feasibility).

According to our results, most administrators and providers endorsed delivering multiple practices to youth with ASD, some with evidence and some with no/limited evidence. These results are consistent with prior studies in which providers report using an eclectic approach, combining different practices and strategies according to their personal criteria, typically in an

TABLE 8 | TCU Organization Readiness for Change (ORC-D4)—staff attributes scale (*n* = 52 providers).

Subscale	*M* (*SD*)	Rating
Growth	39.90 (0.50)	Average
Efficacy	41.79 (0.44)	Average
Influence	40.12 (0.59)	Strength
Adaptability	39.13 (0.48)	Average
Satisfaction	44.82 (0.57)	Strength

TABLE 9 | Results for linear regression for attitudes toward EBPs.

Variable	*B*	*SE*	95% CI	β	*t*	*p*
(Intercept)	14.95	6.13	[2.61, 27.29]	0.00	2.44	0.019
Readiness to change	−1.86	1.09	[−4.05, 0.33]	−0.23	−1.71	0.094
Leadership culture	2.70	0.85	[0.98, 4.41]	0.42	3.17	0.003
Resources to support practice change	−1.09	0.76	[−2.61, 0.44]	−0.18	−1.44	0.158
Staff attributes growth	0.43	0.13	[0.17, 0.70]	0.43	3.29	0.002

Results: $F_{(4,47)} = 5.40$, $p = 0.001$, $R^2 = 0.31$.

unsystematic manner (25, 34). Providers reported competence in delivering several focused EBPs such as using rewards, modeling, prompting, and using visual supports. While they reported some confidence using a few complex EBPs (e.g., pivotal response training), fewer providers reported skills to deliver comprehensive interventions. This is consistent with observational studies indicating more accurate use of more structured, less complex interventions (52). However, comprehensive interventions may result in stronger outcomes (10, 52). Additionally, consistent with reports of limited coaching by caregivers, fewer providers reported confidence in their ability to effectively use caregiver coaching strategies or caregiver-implemented interventions, indicating a need for additional training or EBP adaptation to fit the system of care.

This lack of confidence in caregiver coaching may be a primary reason most caregivers in our sample reported receiving psycho-education rather than active, direct coaching with feedback, even though providers reported providing coaching. This discrepancy in reported use of caregiver coaching and training between administrators, providers, and caregivers is a common finding in publicly funded service provisions. For example, Straiton et al. (53) found a similar discrepancy between early intervention providers and caregivers in Michigan; providers who reported utilizing caregiver training were not typically endorsing EBP that aligned with caregiver training but rather psychoeducation and parental check-in strategies. Several factors could explain the discrepancy between caregivers and providers, including pre-service exposure to child and family-guided interventions (30). Some providers may use these terms and approaches synonymously. There may also be discipline-specific differences among coaching techniques where some may be more educational/structural than family-centered (54). Finally, caregiver expectations of intervention structure could also play a role in how they perceived coaching within the early intervention system.

Interestingly, another area of agreement among stakeholders included providers and administrators reporting challenges related to addressing eating, sleeping, family stress, and stereotyped behaviors presented by children with ASD in the early intervention setting. Other than stereotypy, these challenges involve associated but not ASD-specific behaviors, linked to higher levels of parenting stress, suggesting the need for targeted trainings in these areas. However, consistent with other studies, administrators and providers differed in reports of client needs, practice use and effectiveness of practices (34, 55). These discrepancies may imply a mismatch between provider training needs and training opportunities provided by administrators. Further, since providers are unlikely to communicate directly with state autism coordinators, it may be that individuals who can facilitate policy or funding for training are not aware of the support needed for providers to be able to meet the needs of their clients.

Organizational readiness to adopt and utilize new practices is critical for successful implementation of EBPs within an organization (56). Organizational readiness consists of motivation to try new practices, general capacity within an organization to support new practices, and necessary innovation-specific capacities, such as knowledge, skills, and resources. Both individual perspectives on the organizational climate as well as perspectives about the organizational norms are necessary to evaluate the capacity of an organization to deliver a new EBP at both the leader and provider levels (42). Organizational culture is a complex and dynamic set of constructs that coalesce to form an overall culture of readiness to implement an EBP (33).

Consistent with our finding that leadership characteristics relate to provider attitudes toward EBP, the implementation literature has established *leadership* as a key component for the successful adoption, implementation, and sustainment of EBP (57). Rather than considering only how we can provide adequate professional development to providers, we must also consider how to train leaders who support and recognize providers in their pursuit of improving high quality services (58).

In general, our data suggest that early intervention agencies could benefit from improved leadership climate and culture for innovation. While providers indicated some organizational strengths, such as the influence of opinion leaders, satisfaction with their work environment and culture for innovation at the provider level, they also reported challenges with consistent measurement of practice use, obtaining resources and feelings of efficacy and adaptability. Additionally, both administrators or providers reported relatively average or neutral attitudes toward EBP in general. The fact that attitudes toward EBP were associated with greater use of EBP highlights the importance of a focus on agency and provider buy-in to improve research-based early intervention services. Organizational context, in turn, explained much of the variance in EBP attitudes, indicating that a multi-level intervention addressing implementation readiness at the system, agency, and provider levels may be key to improving the quality of public early intervention programs (28, 58).

Limitations

Our study has several limitations that should be noted when interpreting the results. First, although we sought diverse, representative stakeholders by focusing recruitment in states serving low-resourced areas (e.g., rural) which resulted in our caregiver sample having a range of incomes represented and 21% of caregivers identified as Latinx, a majority of our sample identified as white and non-Latinx. Additionally, most of the caregivers were married, with little representation of unmarried and single parents (i.e., 22%). Further, the administrator and provider samples are reflective of the limited diversity of the population. For instance, the American Speech-Language-Hearing Association (ASHA), the major professional organization for speech-language pathologists, reported that in 2020 96.3% of SLP members were female and 81.0% were white (59). Second, although we used a nomination system to connect the different participating layers to allow us greater consistency in understanding agreements and disagreements between participants, this complex recruitment method resulted in a small total sample size, limiting our statistical power and resulting in a less diverse sample overall.

Recommendations for Practice

Our findings describe the early intervention features in low-resourced areas of the US, which could help future research translating EBPs into community programs to improve access to effective intervention for toddlers with ASD and their families. Given the limited resources of the system and low intensity of services, ensuring high-quality and model-adherent EBPs is especially important for families who cannot afford to pay for hours over and above what the public system provides.

The early intervention system itself and the agencies that provide early intervention services funded through the US Part C system would benefit from leadership training that supports implementation and sustainment of EBP, including caregiver coaching. Scientists have developed leadership training specific to supporting high-quality use of EBP (28, 58); testing these training programs in early intervention settings has the potential to increase access to quality care. Understanding how to create an organizational context and culture that values, supports, and rewards EBP use could drive low-resourced community services toward a general and effective use of EBPs, even in low-intensity services. Changing organizational culture is likely to influence provider attitudes toward EBPs, which in turn may additionally promote use of these EBPs and increase access to scientifically-supported interventions for more children and families.

Attitudes and practice can also improve through professional training. Professional training facilitates the use of caregiver training and coaching (53). Our results clearly suggest a majority of providers would welcome training in caregiver coaching as well as other specific EBP for autism symptoms and related concerns (e.g., sleep, feeding).

The best treatment response for young children occurs when early intervention combines both clinician- and caregiver-implemented components (60). Therefore, training in EBP and caregiver coaching designed to fit the early intervention context could boost providers' general capacity to implement best practices, including increased use of collaborative interventions involving primary caregivers. Long-term outcomes are stronger when there is an active participation of caregivers in the early intervention program (8). In low-resourced environments where low-intensity treatment hours are more likely to be delivered, a child's day-to-day learning opportunities rely more on caregiver use of EBP than children receiving high-intensity treatment. Thus, caregiver active involvement in intervention delivery is crucial to optimize learning opportunities and facilitate positive child outcomes (61). To meet this goal, providers need specific training in how to engage and coach caregivers successfully, how to support caregivers in integrating EBP into daily routines and activities, and how to adapt strategies to meet the individual needs of the family and child with ASD (62).

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board (IRB) for the University of California, Davis, project ID: 780328-22. The patients/participants provided their electronic informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AA: contributed to study conceptualization, methodology, fieldwork, and leading statistical analyses and interpretations of results, writing the original text, and contributing my own postdoctoral funding. AS: contributed to conceptualization, methodology, project multisite administration and supervision, obtaining project funding, and completing original writing. MT: contributed to the field work management, project administration, supervision, and significant review and editing of the manuscript. MM: contributed to project administration and fieldwork as well as manuscript editing. AD: provided study measures, contributed to results interpretation, provided original text, and edited manuscript content. MP: facilitated recruitment and project administration at one site, provided original text, and contributed to reviewing and editing the manuscript. AB: contributed to recruitment and project administration at one site, reviewed and edited the manuscript. EG: contributed by overseeing the fieldwork, local recruitment and administration of the project at one, and grant/manuscript editing. EM: contributed to recruitment at one site, survey development, and manuscript editing. SR: contributed to the study conceptualization, methodology, obtaining project funding, administering and supervising the project, and editing the document. All authors contributed to the article and approved the submitted version.

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Combining a Being Imitated Strategy With IBT Improves Basic Joint Attention Behaviors in Young Children With ASD

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In the present study, we examined how an initial being imitated (BIm) strategy affected the development of initiating joint attention (IJA) among a group of children newly diagnosed with autism spectrum disorder (ASD). One group received 3 months of BIm followed by 12 months of intensive behavior treatment (IBT) which equaled treatment as usual whereas a second group received IBT for the entire 15-month study period. We utilized two measures of IJA: an eye gaze and a gesture score (point and show). IJA did not change during the first 3 months of treatment, nor were any significant between-group differences noted. However, at the end of the 15-month-long intervention period, the BIm group used eye gaze significantly more often to initiate joint attention. No significant change was noted for the gesture score. These results suggest that an early implementation of a being imitated strategy might be useful as less resource intensive but beneficial "start-up" intervention when combined with IBT treatment as a follow-up.

Keywords: autism spectrum disorder, early intervention, being imitated, joint attention, intensive behavior treatment

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INTRODUCTION

Autism is a neurodevelopmental disorder characterized by impairments in communication and social interaction, along with a restricted repertoire of activities and interests (1). One example of an early developing communication and social interaction skill found to be problematic for autistic children is joint attention, an ability that signifies that a child has developed a capacity to coordinate attention between a social partner and a proximal object or is able to use eye gaze or gestures to establish a moment of triadic attention between him/herself, another person (e.g., a parent), and an object or event (2). A child's ability to follow gaze and to respond to bids for joint attention from others are important both for language and early social-cognitive development [e.g., (3, 4)]. In typical development the first steps to master joint attention are usually observed toward the end of the first year and joint attention is often described as an important developmental milestone [e.g., (3, 5–7)]. Thus, it is of much relevance that several studies have shown that a delayed or altered developmental trajectory of joint attention is one of the earliest problems reported for children with autism [e.g., (8, 9)].

Although joint attention is comprised by both the ability to respond to joint attention bids (RJA) and the ability to initiate joint attention bids (IJA) we focus here only on the latter since IJA has been found to be especially delayed or protracted in children with autism [e.g., (10, 11)]. Joint attention is commonly first observed by a child's eye gaze responses or through gestures such as pointing or showing, abilities that are known to promote learning and communication in incidental situations (12). Difficulties to develop the ability to initiate joint attention will thus have a negative effect on autistic children's daily learning opportunities which makes it critical to target IJA in interventions for young autistic children (3, 4).

In a relatively recent meta-analysis, Murza et al. (13), present support for joint attention interventions in young children with autism spectrum disorder (ASD). A joint attention intervention implies a training of any aspect of sharing attention with a partner about an object, event, or mutual interest. Two different intervention approaches were identified, a general developmental approach that include social interactive strategies [e.g., (14, 15)] and a more focused developmental approach [e.g., (16, 17)]. Murza et al. (13) reported that all 15 reviewed randomized experimental studies demonstrated a statistically significant treatment effect size despite differences in treatment administration, e.g., dosage and design. However, this meta-analysis also revealed that there is limited evidence supporting long-term effects of interventions aiming to develop joint attention.

Imitation has been highlighted as a promising way to promote social behaviors that build up joint attention skills. Of special interest are reports showing that children with autism increase their social motivation as a consequence of being imitated (18–22). Imitation recognition increases children's awareness of being the object of other's social attention, a first step on the road to develop joint attention skills [see (23)]. As an example, Escalona et al. (18) reported that children with autism specifically increased their tendency to initiate social behaviors after only a brief being- imitated intervention. A recent review by Contaldo et al. (24) concludes that a "being-imitated strategy" seems to be generally successful in increasing the social competence and play skills of autistic children. Not only in experimental paradigms but also as part of clinical treatment programs. Thus, this strategy has become more and more accepted since Nadel's first studies and is today included in many intervention programs aimed at children with autism and their parents [e.g., (16, 17, 25–27)].

In the study, we use a being imitated (BIm) strategy in conjunction with a comprehensive program that represented the preferred method (treatment as usual, TAU) at the participating Habilitation clinical center for children with ASD. A comprehensive program is a manualized and broader treatment program that aims to target all or almost all areas deemed important for children with ASD (28). In the literature those programs are often categorized as either Applied Behavior Analysis (ABA) (29) or Intensive Behavior Treatment (IBT) (30). Meta-analyses have revealed that IBT programs generally are effective in promoting medium-effect-size gains in intellectual function, language development, acquisition of daily living skills, and social functioning (31, 32). Of special interest here is that imitation on demand for a long time has been included in programs built on behavioral theory as an ability that needs to be trained in order to improve a child's learning skills [e.g., (33)] but imitation *per se* is not usually the focus since the programs have a much broader scope. IBT is the dominating intervention strategy in Sweden (34, 35) and it usually entails that parents and preschool teachers jointly carry out the training of targeted areas (e.g., imitation, communication, or verbal skills).

The present study examined the effects of two treatment programs. The first one is a novel program that combines an initial 3-month long BIm intervention with 1-year of IBT treatment (Novel = BIm+IBT). The second program used only IBT during the whole 15 months period (TAU = IBT only). Thus, all children received treatment over the same treatment period, they were also allocated randomly to one of the two treatment programs, and were all newly diagnosed with autism according to DSM-IV-TR (36).

The main hypothesis of the study was that the novel program (BIm+IBT) would promote a faster development of behaviors important for initiating joint attention over time than TAU (IBT). Measure of joint attention behaviors were the children's looking pattern (eye gaze) and gestures (pointing and/or showing).

METHOD

Participants

All children referred to the Child and Adolescent Habilitation Services in Gothenburg, Sweden, between March 2011 and December 2012, who had a chronological age (CA) of between 24–48 months, and who were recently diagnosed with ASD according to DSM-IV-TR (36) were offered to participate in a randomized control study testing treatment. However, children with severe epilepsy judged to hinder therapy were excluded. After initial testing at T1, the experimenter picked an envelope (prepared by the administrator for blinded randomization) that contained the group assignment, either a novel treatment program with BIm for 3 months followed by IBT for 12 months, or a comparison group that received treatment as usual (TAU = IBT) for the whole 15-month intervention period (see **Figure 1**).

The current study is a follow-up of a previous study that examined the development of language and social domains from T1 to T2 (**Figure 1**) (37). The current sample consists of thirty children (see **Table 1**) that (1) fulfilled the basic inclusion criteria, (2) followed through with training phases 1 (either BIm or IBT) and 2 (IBT for 12 months), and (3) completed our assessment of joint attention, the Early Social Communication Scale (ESCS; 37) both before the treatment commenced (T1) and after the first training phase (T2). Here, we add data for a long-term follow-up (T3) with a specific focus on initiating joint attention. Of the 30 children that qualified for the follow-up study 25 were boys, with an average chronological age of 40.9 months (SD = 6.2, range: 26 – 49 months). A majority of the children (n = 26) lived with both parents, while four children lived in single-parent households. Parental education was as follows, primary education (i.e., 9 years in school) n = 11 mothers and 14 fathers, secondary education (12 years in school) n = 8 mothers and 4 fathers, tertiary education (bachelor or master's degree) n = 11 mothers and 12 fathers.

All participants diagnosis were based on a thorough neuropsychiatric work-up using the following clinically validated instruments: The Diagnostic Interview for Social and

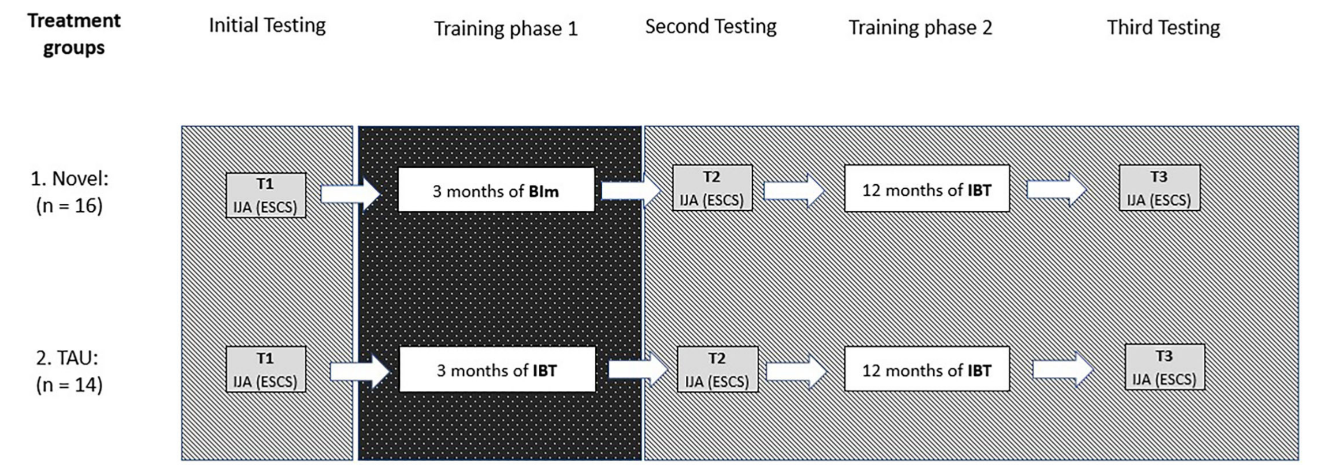

FIGURE 1 | Study design for the participating children ($n = 30$) in the current study. Differences in procedure between the two treatment groups, Novel and TAU, are only found within the dark dotted column. The rest of the procedure was identical (light gray lined area). Attrition in Novel group: $n = 3$, Attrition in TAU group: $n = 5$. Testers for ESCS did not know the group allocation of the child they tested. BIm, Being Imitated; TAU, Intensive Behavior Treatment (IBT); IJA, Initiating Joint Attention; ESCS, Early Social Communication Scale.

TABLE 1 | Baseline characteristics of the participating children at start, comparing data for T1 for all children in the sample ($n = 30$) and comparing data for T1 excluding data for children who did not participate at T3 (attrition: $n = 8$) between the two treatment programs: Novel (BIm + IBT) and TAU (IBT only).

	Sample Group[b]				**Included in final analysis Group[b]**			
	Novel $n = 16$		**TAU $n = 14$**		**Novel $n = 13$**		**TAU $n = 9$**	
	M	**SD**	**M**	**SD**	**M**	**SD**	**M**	**SD**
Age (months)	42.6	6.1	39.0	5.9	41.8	6.5	36.9	6.1
Mental age[a]	20.6	6.7	20.8	9.0	20.6	6.7	19.0	10.0
Expressive language (PEP-R)	5.1	5.0	10.6	10.3	4.2	3.1	8.2	8.9
Expressive language (VABS-II)	14.8	9.2	16.6	9.2	12.9	7.4	14.1	8.5
Receptive language (PEP-R)	7.8	8.4	10.9	10.8	6.4	6.8	8.1	9.9
Receptive language (VABS-II)	15.4	14.6	19.21	12.1	11.4	6.0	14.9	7.3
Gender (F/M)	2/14		3/11		2/11		1/8	
Two-parent families	12		14		10		9	

[a] *Estimated with Bayley;* [b] *All comparisons between groups are non-significant.*

Communication Disorders (38), Autism Diagnostic Review-Revised (39), Autism Diagnostic Observation Schedule (40), and the Social Communication Questionnaire (41). All clinical staff had extensive time as professionals with both typical and autistic children and were certified in each assessment procedure.

Treatment Allocation

As already stated, the children were randomized to either a novel program that combined BIm and TAU or to TAU for the whole intervention period (**Figure 1**). The novel program meant that the children received an imitation-based intervention (BIm) for the first 3 months (from T1 to T2) followed by IBT for the remaining 12 months (from T2 to T3). Our second program, TAU, entailed IBT for the whole 15-month period (from T1 to T3). Both groups had a brief pause of 2–4 weeks after T2 and before continuing with IBT for one year. On average, T2 was conducted 4.9 months (SD = 1.1 months) after T1, and T3 was conducted 12.5 months (SD = 1.3 months) after T2. The actual length of the intervention and of the follow-up period did not differ between the two treatment programs (all $p > 0.4$).

Background Measures

At T1, before randomization and before treatment commenced the children's language levels were evaluated through two subscales from the Psychoeducational Profile, third edition [PEP-R; (42)] and from an interview with the preschool teachers using two subscales from the Vineland Adaptive Behavior Scales, second edition [VABS-II; (43)]. For the sake of clarity these instruments were also used at T2 representing data that has been published elsewhere (37). Mental age was estimated with the Swedish version of the Bayley Scales of Infant and Toddler Development, third edition (44).

Measure of Initiating Joint Attention (IJA)

To measure initiating of joint attention (IJA) at T1, T2, and T3, we used the Early Social Communication Scale (ESCS, 37), a structured assessment in which the experimenter presents toys. The toys used in the procedure were strictly selected due to manual descriptions and were exclusively used in the test situation. The experimenter and the child were both seated opposite to each other on either side of a table in a room specially prepared to for the test procedure. The assessment took ∼12–14 mins and was videotaped. For our present study, we used only the ESCS tasks that measure IJA (45): eye contact and alternating eye gaze constitutes our eye gaze measure while point and show constitutes our measure of gestures relevant for initiating joint attention bids. Eye contact was noted if the child held an inactive toy and looked at the tester while alternating gaze was coded whenever the child looked back and forth between the tester and an active object.

During the ESCS, the experimenter presented one toy at a time. All children were assessed three times, before the intervention commenced (T1), after three months (T2) and finally 1 year later when the intervention ended (T3). The ESCS was coded from video tapes recorded during the test sessions independently by one research assistant and two master's students in psychology. All three coders were first trained using reference material from typically developing children and proceeded to coding the current material once they were proficient with the infant material (inter-rater reliability ≥ 0.90). The intra-class coefficients between the three coders for the present study material indicated a strong agreement (range, 0.88–0.97). The coders were blind to the aim of the current study, to the children's study treatment group, and to the test phase (T1, T2 or T3) in which the recording was made.

Novel Treatment (Being Imitated)

The Being Imitated (BIm) intervention was new and unknown to the participating preschool teacher who carried out the intervention. BIm is based on theories and therapeutic strategies mainly formulated by Nadel et al. (20, 46) and Nadel (47) but for the present study, a Swedish manual was developed [Spjut Jansson, (48)]. Adhering to the manual meant that the trainer (a) followed the child's attentional cues, (b) allowed the child to choose the course of the interaction and use of materials, and (c) provided intensified opportunities for the children to engage in activities that are like those in which typically developing peers engage. The imitation procedure was implemented by trained preschool teachers (see below for details on preschool teachers' training), who held training sessions with the children for 30 mins each day over 12 weeks. During these sessions, the adult imitated all behaviors exhibited by the child (except those judged to be harmful or to cause self-injury to the child). The purpose of this procedure is to establish reciprocity by providing the child with an opportunity to show his or her own communication skills and to learn about the social world (49).

All sessions were conducted in a room of the child's preschools, with only the child and the preschool teacher present. Following the procedure of Nadel et al. (50), two sets of identical toys were used to provide opportunities for synchronic imitation. Toys were selected with consideration of each individual child's developmental level and fine motor repertoire, following selection principles to standardize the object variation. One-third of the toys were new to the child (novelty was expected to increase the child's interest), one-third were familiar (e.g., flashlight and a doll), and one-third were selected with the aim to promote object manipulation (e.g., balls, cars, and blocks). The use of familiar toys aimed to reduce any initial resistance and/or anxiety in the child (51), while the offer of commonly used toys was intended to accelerate interest in and skills at using similar toys as other children. For each child a room at the preschool was chosen that was secluded and used in a restricted and limited manner. The selected room enabled the teacher to exclusively attend to the child without any delays or disturbances or interferences from other children or colleagues. Prior to the study, seven experienced clinicians were trained in the method by two of the authors (BSJ and MH) and one experienced colleague in order to be able to support and supervise the preschool teachers. The preschool teachers were similarly trained by the supervisors from the Habilitation Services. They were also filmed for 10–15 mins at the start of the intervention and were thereafter regularly evaluated by two experts (BS and an experienced colleague). Daily protocols and diaries were also used to check treatment fidelity.

All sessions were conducted by the child's preschool teacher, except for one session each week that was conducted in cooperation with a trained supervisor. This supervised session was intended to check treatment fidelity through online supervision and thus increase the preschool teacher's compliance with the BIm manual. The supervised sessions also provided an opportunity to discuss issues that occurred during the treatment sessions with the children.

Treatment as Usual

Intensive Behavior Treatment (IBT) constitutes the treatment of choice at the participating Habilitation Services and is seen as TAU in the context of this study. This is a manualized comprehensive program, with a curriculum mainly built on insights from ABA (52, 53). IBT uses discrete trial training plus strategies, such as reinforcement, prompt, and prompt fading, with the aim of errorless learning. The manual instructed the preschool teacher and parents to move over time from discrete trials to naturalistic training as the children develop the desired skills. The implemented training was evaluated after each session. Thirteen skills were targeted with specific exercises, with at least six skills covered each day. The training was expected to take 20–25 h each week, with the parents responsible for 10 h and the preschool teachers for 15 h. The parents and preschool teachers participated in supervised sessions lasting 1–1.5 h twice a month. At the beginning, workshops were provided with the aim of teaching the parents and preschool teachers the necessary theoretical knowledge and strategies.

Both parents and preschool teachers completed written reports describing their daily use of exercises and time spent training in order to assess treatment fidelity to the planned program. Parents and preschool teachers also underwent supervised training and treatment fidelity checks by clinicians or special educators who were experienced with the method, on average twice a month.

Planned and Executed Training

For the Novel group, the plan called for each child to spend 2.5 h per week training with the "being-imitated strategy" during the first 3 months. The mean training time reported by the preschool teachers was 2.2 h per week (SD = 1.0 h) during the first 12 weeks. Over the following 12 months, these children received IBT, that is treatment as usual. They received 20–25 h a week of training provided by parents or preschool teachers, which was in accordance with the planned amount of training for each child. For the TAU group, during the first 12 weeks, the plan called for the children to undergo 15 h per week of training, and the children actually received an average of 14.4 h a week (SD = 2.5 h). During the last 12 months of IBT, both parents and preschool teachers reported 20–25 h of weekly training, also in accordance with the planned time.

Statistical Analysis

First, treatment effects in the eye gaze score were examined with a mixed-design analysis of variance (ANOVA) with repeated measures across time-points with three levels (T1 to T3) and between group measure interventions (Novel vs. TAU). Then effects on gestures are examined with the same model that was used with eye gaze. We report h^2_p for the ES of the factors included in the model. These models were run using IBM SPSS, version 26.0.0.0. To enable comparisons with other studies, the ES for between-group differences were calculated using Hedge's *g* (54). Following the method of Hedges and Olkin [see also (55)], Hedge's g was corrected for small sample size, reducing the effect size by about 4%. Durlak (55) further suggests taking account for pre-test effect sizes when calculating effect size for post-treatment effects. Hence, the effect sizes for post-tests (at T2 and T3) were adjusted for the difference at the previous testing time-point (e.g., adjusted $ES_{T2} = ES_{T2} – ES_{T1}$).

Ethics

This study was conducted according to guidelines laid down in the Declaration of Helsinki, with written informed consent obtained from a parent or guardian for each child before any assessment or data collection. All procedures involving human subjects in this study were approved by the Regional Ethical Review Board of Gothenburg (418-10, 2010).

RESULTS

The initial study sample of the current study was $n = 30$ children with the aim of analyzing longitudinal changes in initiating joint attention behavior over the time points. However, there is attrition of $n = 8$ children (3 in the Novel Treatment group and 5 in the TAU group, see Attrition section below for details). Thus, the following analyzes are based on $n = 22$ children, with $n = 13$ in the Novel treatment group and $n = 9$ in the TAU group.

Eye gaze (eye contact and alternating eye contact) and gestures (pointing and showing) were the dependent variables of interest. Eye gaze was more common than gestures (**Table 2**) at all three time points. Changes in behavior were analyzed with a 3 (time-points T1, T2, and T3, as the within-participant factor) by 2 (Novel vs. TAU as the between-participant factor) repeated measures ANOVA.

Changes in Eye Gaze Score

For the eye gaze score (**Figure 2**), we detected a significant effect of time [$F_{2, 40} = 6.78$; $p = 0.003$; $h^2_p = 0.25$] as well as an interaction between time and treatment [$F_{2, 40} = 3.58$; $p = 0.037$; $h^2_p = 0.15$], but no between-group differences [$F_{1, 20} = 0.05$; $p = 0.83$; $h^2_p = 0.002$]. Tests of within-participant contrast indicated that the eye gaze did not significantly differ between T1 and T2 [$F_{1, 20} = 0.16$; $p = 0.69$; $h^2_p = 0.008$] but significantly increased from T2 to T3 [$F_{1, 20} = 12.03$; $p = 0.002$; $h^2_p = 0.38$]. The interaction between time and treatment was non-significant for T1 to T2 [$F_{1, 20} = 1.71$; $p = 0.21$; $h^2_p = 0.08$] but was significant from T2 to T3 [$F_{1, 20} = 5.07$; $p = 0.036$; $h^2_p = 0.20$]. The eye gaze increased from T2 to T3, an effect that was carried by the observed increase in the novel group. The adjusted effect sizes (Hedge's g) were-−0.53 for T2 and 1.10 for T3, however, only the second effect size was significant.

Changes in Gesture Score

For the gestures score, we detected no significant effect (**Figure 3**) in the analyzes over time-points, the interaction between time-point and treatment, or for the observed between-group difference (F values < 2.25; $p > 0.16$). Adjusted effect sizes (Hedges *g*) were 0.13 for T2 and 0.11 for T3, but none were significant.

Attrition

As pointed out above, data for eight children could not be included in the final analyses. Due to technical issues for 2 children (one in each group) during the testing of ESCS at T2 no material was available for analysis. Further, 6 children (2 in

TABLE 2 | Mean frequencies for the basic building blocks—eye gaze and gestures—measuring Initiation of Joint Attention (IJA) at start (T1), after 3 months (T2) and when the intervention ended (T3) after 15 months.

	Novel *n* = 13		TAU *n* = 9	
	M	**SD**	**M**	**SD**
Eye gaze (Eye contact and alternating eye contact)				
T1	11.23	15.25	10.56	15.18
T2	8.77	9.40	15.22	15.42
T3	25.15	13.16	16.11	14.13
Gestures (Pointing and showing)				
T1	2.38	3.64	1.33	2.60
T2	2.15	4.71	0.44	0.73
T3	2.08	3.20	0.56	1.33

Two Treatment Groups: (1) Novel = Being imitated (BIm) combined with Intensive Behavior Treatment (IBT), and (2) TAU = Intensive Behavior Treatment (IBT).

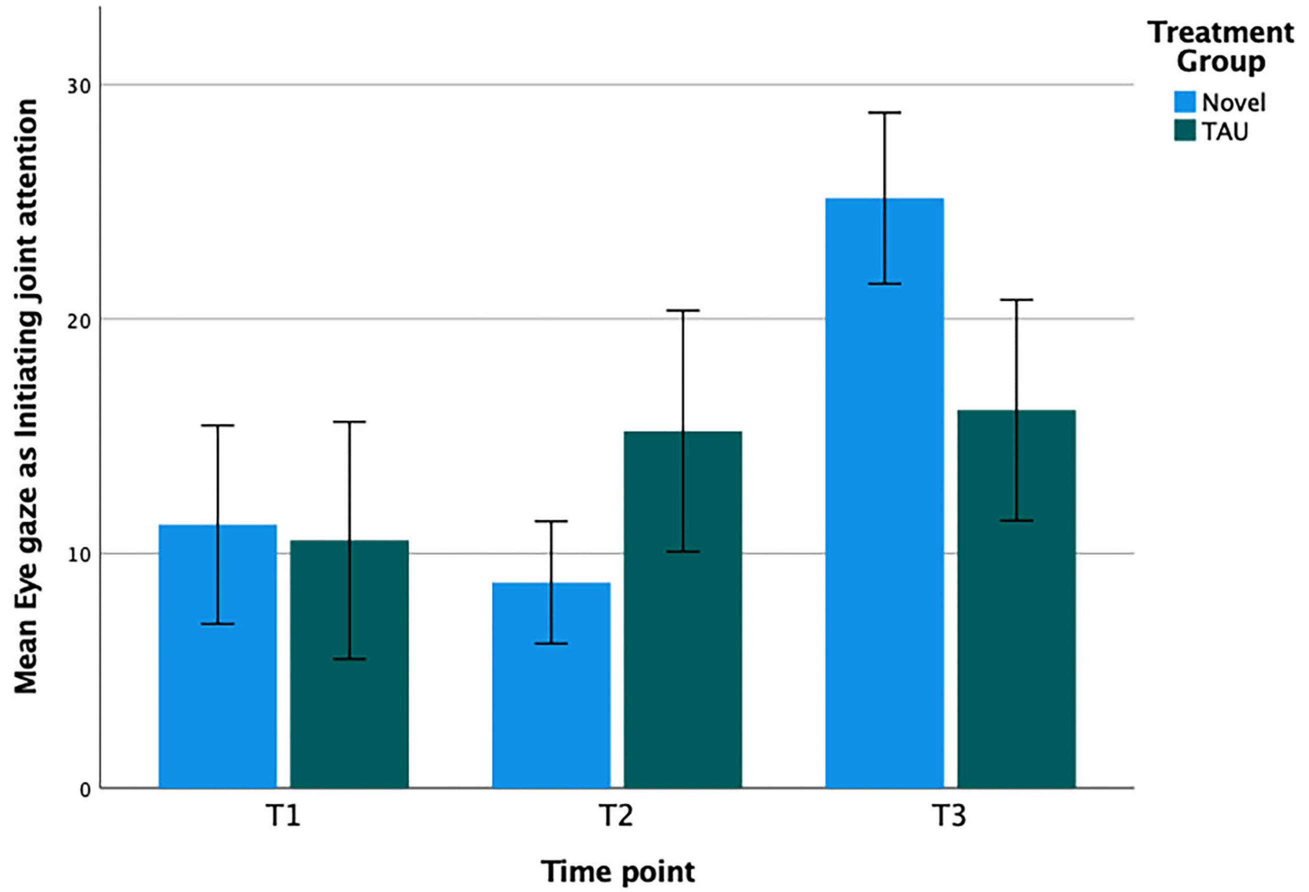

FIGURE 2 | Mean number of observed eye gaze scores with error bars displaying standard error of the mean from T1 to T3 for the Novel group and the TAU group, respectively.

the Novel group and 4 in the TAU group) declined to participate in the testing of ESCS at T3.

As the attrition rate in our study was 26 %, we examined possible effects due to attrition closer. No differences in eye gaze and gesture behaviors were found when comparing T1 and T2 scores between children that could be included in the final analysis ($n = 22$) and children that could not ($n = 8$), all p's > 0.60. However, the chronological age of the attrition group ($M = 43.9$ months, $SD = 3.2$) was significantly higher than the chronological age of the included children ($M = 39.8$ months, $SD = 6.7$), $t_{(25.34)} = 2.22$, $p = 0.035$, equal variances not assumed. Overall, the two final intervention groups were not statistical different from each other at T1 on chronological age (see **Table 1**), language measures (see **Table 1**), or IJA measures (independent t-test for eye gaze: $p = 0.92$, gestures: $p = 0.46$, see also repeated-measure analyses above).

DISCUSSION

Here we describe a randomized controlled intervention study performed in a group of young children who were newly diagnosed with autism. The results showed that children who received a Novel package that included a focused being imitated (BIm) intervention (2.2 h weekly during training phase 1) followed by Intensive Behavior Treatment (IBT) equaling treatment as usual (TAU) (20–25 h weekly during training phase 2) showed increased ability to use eye gaze to initiate joint attention compared to the children who received TAU only (15–25 h weekly) over the complete 15-month study period. Initiating joint attention (IJA) was measured on three occasions: before initiation of training, shortly after the end of the first training phase and finally after the second training phase (i.e., after 15 months of treatment). Group comparisons revealed no significant between-group differences before the intervention started or after the first training phase. However, testing after the second training phase demonstrated a significant improvement in eye gaze measures (eye contact and alternating gaze) but not for gestures (point and show) for the Novel intervention (BIm+IBT) compared to TAU (IBT only). This finding suggests that an intervention that builds on a being imitated strategy promotes the development of some of the behaviors needed for young children with autism to initiate joint attention bids.

It is interesting that the intervention found effects over a 1-year period (between T2 and T3) but not any short-term effects

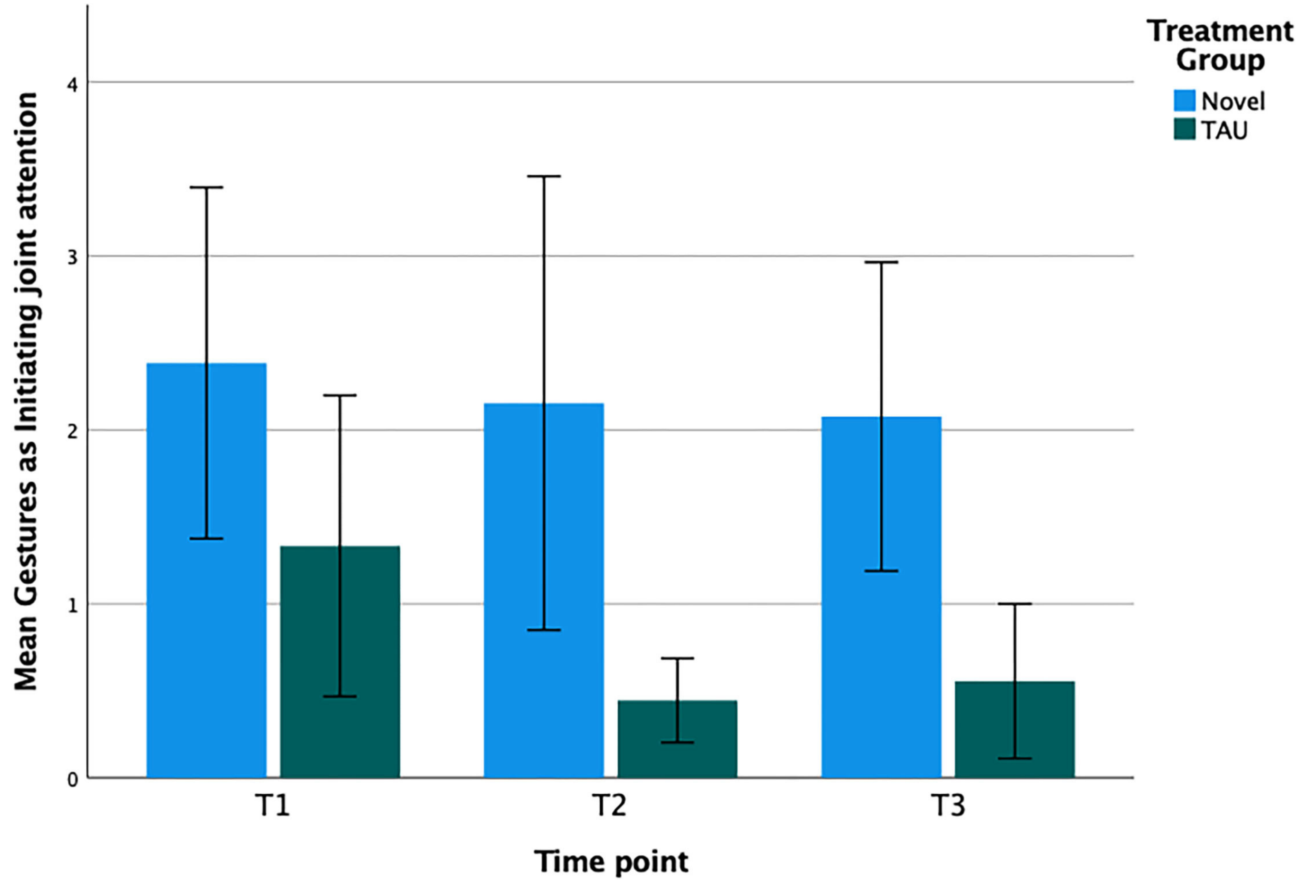

FIGURE 3 | Mean number of observed gestures scores with error bars displaying standard error of the mean from T1 to T3 for the Novel group and the TAU group, respectively.

from (T1 to T2). This was a bit unexpected since positive short-term effects have been reported in the literature [e.g., (56)]. On the other hand, similar findings to ours have also been reported. For instance, Kaale et al. (57) found a similar pattern following an intervention conducted by non-specialist trainers (preschool teachers). It is worth noting that studies relying on specialist-mediated interventions seems to be more effective in promoting joint attention skills as measured with ESCS [e.g., (16, 58)].

The significant effect emerged when comparing the intervention groups between 3 months (T2) and 15 months (T3), which is the period during which both groups received IBT, the TAU program. Compared to TAU only, the Novel intervention showed higher gains in one of our joint attention measures, with a large effect size. Specifically, the eye gaze score significantly increased for the children in the Novel group, meaning that they displayed an increase of behaviors, such as simultaneously holding an inactive toy and looking at the tester or alternating their gaze between the tester and an active object. On the other hand, gesture, our second measure of initiating joint attention—a summary score of pointing and showing—did not increase for either group. The Novel intervention group did improve in some aspects of IJA (i.e., eye gaze) but not what Mundy considered high level IJA (12), pointing and showing. It is hard to know why but one possibility is that high level behaviors take longer time to develop. They might also need more extensive experience of social interactions.

Both groups received the same treatment during the second training phase, but nevertheless showed different increases in eye gaze after this time-period. It is possible that initiating joint attention skills requires a type of scaffolding other than what is usually provided by ordinary IBT strategies. Contaldo et al. (24) suggest that the being-imitated strategy might be more salient to children with ASD, since the offered contingencies (objects and task) are more predictable and familiar, and thus require less anticipatory skills. Moreover, Nadel (21) concluded that for children with autism, responding to the experience of being-imitated indicates an altered level of recognition of time and structures.

With regards to the eye gaze score, the Novel group showed a large effect size. In a recent meta-analysis, moderate effect sizes were reported from studies that aimed to increase joint attention skills among children with autism (13). They reported an overall Hedges *g* effect of 0.35, which is lower than the presently determined effect size noted for the Novel group at T3 in our study (ES = 1.10). Our present finding of increased initiating joint attention with a large effect size is in line with the suggestion by Mundy et al. (59) that many children with ASD have the capacity to develop joint attention. More recently, Contaldo et al. (24) have highlighted the possibility that focused being-imitated training could influence the neural networks involved in social cognition. Thus, the difference between BIm and IBT (which also uses imitation exercises) may be based on the neural social reward system that is activated by a being imitated interaction [e.g., (60–62); but see (63) for a different view]. In IBT (64, 65), behaviors are concretely rewarded to increase children's willingness to repeat their behavior. On the other hand, in the being imitated intervention, the social reward arises from the sharing of the same emotional state or bodily movement (24).

The main finding of the present long-term evaluation confirmed our hypothesis that BIm, provided with a mean weekly intervention duration of only 2.2 h, promotes the development of eye gaze behaviors that constitute early initial building blocks for IJA. It must be emphasized that this effect was based on a combination of two interventions, a combined treatment program in which an initial 3-month BIm phase was followed by 12 months of IBT/TAU with a training intensity of 20–25 h per week. One possible explanation for the improved effect of the combined treatments might be that the initial implementation of a focused intervention such as BIm increase "the precursors of joint attention skill" in children with ASD. It has been suggested that BIm complements or scaffolds the benefits that a child can gain from a comprehensive IBT program (24, 37). The results from the present study indicate that combing two different programs, one focused (BIm) and one comprehensive (IBT) might be beneficial for developing generalized joint attention skills among young children with ASD.

Strengths and Limitations

Eight children in our study could not continue their treatment after T2. This attrition seriously affected the power of the study. This is especially relevant to the TAU group, in which one third the children did not participate or had incomplete data sets at T3, compared to one-fifth of the children in the Novel group.

The present study needs to be replicated in a larger group of children to explore moderators of the treatment effect, and in order to better understand possible predictors of children's development of joint attention skills. As the group of children diagnosed with ASD is rather heterogenous a considerable variation between children might be expected, even in joint intention skills such as eye gaze. Despite the small sample size and expected variation a significant result for the being imitated intervention was found. Future studies should validate the current finding and might be able to identify the optimal intervention length, e.g., the number of weeks and the number of sessions per week.

Strengths of this study include the long-term design that includes evaluation of a group of young children recently diagnosed with ASD. The validity of the results is increased by our use of an established operationalized assessment procedure. Another strength is the control of leakage—none of the children had previously received a being imitated intervention or any other behaviorally based treatment prior to the study.

CONCLUSIONS

The present results show significant improvements of eye gaze behaviors that constitute early initial building blocks for IJA in a group of children who received 3 months of being imitated treatment followed by a year of IBT, compared to a group of children who received 15 months of TAU alone. These findings indicate that a combination of interventions, including a being imitated strategy, can facilitate joint attention development among children with ASD. BIm was performed by preschool teachers with a 30-min daily training session (averaging 2.2 h a week), while in the first training phase the TAU training averaged 14.4 h a week and included training both at the children's preschools and at home with their parents. Even though the being imitated group received training of a lower intensity during the first training phase, this group showed greater improvement at the end of the 15-month study period.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Regional Ethical Review Board of Gothenburg, Sweden (418-10, 2010). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

The study was conceived by BS and MH. Data was collected by BS and analyzed by F-SK. The manuscript was written by BS, MH, and F-SK. All authors approved the final version.

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SYSTEMATIC REVIEW
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Neural Effects of Physical Activity and Movement Interventions in Individuals With Developmental Disabilities–A Systematic Review

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Individuals with developmental disabilities present with perceptuo-motor, social communication, and cognitive impairments that often relate to underlying atypical brain structure and functioning. Physical activity/movement interventions improve behavioral performance of individuals with and without developmental disabilities. Majority of the evidence on potential neural mechanisms explaining the impact of physical activity/movement interventions is based on studies in individuals with typical development; there is a dearth of systematic reviews synthesizing the neural effects of physical activity/movement interventions in individuals with developmental disabilities. In this systematic review, we have gathered evidence on the neural effects of physical activity/movement interventions from 32 papers reporting substantial neural effects and behavioral improvements in individuals with developmental disabilities. Chronic intervention effects (multiple sessions) were greater than acute intervention effects (single session). Specifically, using electroencephalogram, functional magnetic resonance imaging, diffusion tensor imaging, and functional near-infrared spectroscopy, studies found physical activity/movement intervention-related changes in neural activity, indicating normalization of cortical arousal in individuals with attention-deficit /hyperactivity disorder (ADHD), increased social brain connectivity in individuals with autism spectrum disorder (ASD), and more efficient executive functioning processes in individuals with a wide range of other developmental disabilities. Despite promising results, more research is clearly needed in this area with larger sample sizes, using standardized neuroimaging tools/variables, and across multiple diagnoses to further explore the neural mechanisms underlying physical activity/movement interventions and to replicate findings from the present review.

Keywords: developmental disabilities, autism spectrum disorder, attention-deficit/hyperactivity disorder, movement interventions, exercise, physical activity, neuroimaging, neural effects

INTRODUCTION

Individuals with developmental disabilities, including Autism Spectrum Disorder (ASD), Attention Deficit/Hyperactivity Disorder (ADHD), Developmental Coordination Disorder (DCD), Learning Disabilities (LD), and Intellectual Disabilities (ID), present with multisystem impairments in perceptuo-motor, social communication, and cognitive-behavioral performance, that in turn affects their psychosocial health/well-being and daily functioning (1). In terms of perceptuo-motor impairments, individuals with developmental disabilities present with sensory processing issues as well as motor incoordination/developmental dyspraxia, poor imitation, poor balance, and problems in functional movements such as reaching, walking, and joint actions (2–10). These difficulties could begin early on in life, affect a child's movement exploration of the environment (i.e., through interactions with objects and caregivers), and will have cascading negative effects on other developmental domains (social communication and cognitive) as well as brain structure/functioning (11–23). Individuals with developmental disabilities may also present with difficulties in social communication skills which affects their well-being, daily functioning, and their ability to establish/maintain relationships with peers and caregivers (1, 5, 24–29). They may also have cognitive impairments, such as impaired executive functioning, including poor motor planning, working memory, inhibitory control, and mental flexibility, all of which affect their daily functioning and academic performance (30, 31). Besides the difficulties in different developmental domains, these populations also have lower physical activity levels and are at greater risk of developing obesity (32–35). Physical activity/motor performance is known to have cascading effects on psychosocial well-being and cognitive performance, with low physical activity levels hindering further social and cognitive development in individuals with and without developmental disabilities (36–39). While there are some papers describing potential neural mechanisms of physical activity/movement interventions in healthy populations (40–42), there is a lack of synthesis of neural effects of such interventions in individuals with developmental disabilities. Therefore, this systematic review will focus on identifying the different neuroimaging tools and related biomarkers that objectively assess neural effects of physical activity/movement interventions in individuals with developmental disabilities.

Multiple studies using a single bout of physical activity and/or a longer period of movement interventions reported positive acute (after a single session) and chronic (following multiple sessions) effects on aerobic capacity, gross motor, psychosocial, and cognitive performance in individuals with developmental disabilities (43–45). For example, a meta-analysis of randomized control trials (RCT) conducted in children with ADHD found that physical activity reduced ADHD symptoms (i.e., attention, hyperactivity, impulsivity), anxiety, as well as improved executive functioning and social performance (43). Similarly, a meta-analysis involving children with ID found that acute and chronic physical activity/movement interventions help improve physical (health i.e., cardiovascular health, motor skill, muscular strength, etc.), psychological health (i.e., self-esteem, well-being, social-emotional skills, etc.), and cognitive performance (45). Multiple studies in children with ASD have used whole-body, creative movement therapies, such as music, dance, yoga, theater, and martial arts, in addressing their multisystem impairments (35, 46–56). Our own research group recently conducted a comprehensive review of the effects of creative movement interventions on multisystem performance in children with ASD and found medium-to-large-sized improvements in social communication skills following music and martial arts training, and in motor and cognitive skills following yoga and martial arts training (57). Taken together, physical activity and movement interventions led to positive effects on physical/psychosocial health and cognitive performance in individuals with developmental disabilities.

Besides the behavioral outcomes, neuroimaging assessments, such as structural Magnetic Resonance Imaging (MRI) including Diffusion Tensor Imaging (DTI), functional Magnetic Resonance Imaging (fMRI), Electroencephalogram (EEG), and functional Near-Infrared Spectroscopy (fNIRS), have been used to develop objective measures of abnormalities in brain structure and function associated with the aforementioned developmental disabilities (58). A meta-analytic review of MRI/fMRI studies reported shared as well as distinct structural and functional brain abnormalities in individuals with ASD and ADHD (59). Specifically, gray matter volumes were atypical in the fronto-temporal cortices of individuals with ASD, whereas the orbito-frontal cortices were abnormal for individuals with ADHD (59–61). During cognitive control tasks, atypical prefrontal/precuneus activation was reported in individuals with ASD, whereas fronto-striatal activation abnormalities were reported in individuals with ADHD (59, 62, 63). EEG abnormalities associated with arousal/motivation, inhibitory control, and mental flexibility tasks have also been reported in individuals with ASD, ADHD, and/or LD (64–66). Using fNIRS, atypical fronto-parieto-temporal activation has been reported in infants at risk for and children with ASD during naturalistic, socially embedded actions compared to age-matched controls (67–72). It would be reasonable to expect that physical activity/movement interventions that are known to have cascading effects on psychosocial and cognitive performance may also lead to associated changes in neural activity in the aforementioned neural correlates/biomarkers. Interestingly, while there is some evidence in healthy populations, there is a lack of synthesis of literature for the neural effects of the physical activity/movement interventions in individuals with developmental disabilities. Research studies conducted in healthy subjects have reported associations between neural activity and physical activity levels as well as changes in neural biomarkers post-movement interventions (73–75). Children with higher fitness levels exhibited better inhibitory control and memory, and their structural MRI revealed greater volume in basal ganglia and hippocampus, respectively (76, 77). EEG studies also showed fitness-related differences in functional activity during executive function tasks, with higher fitness levels associated with faster and larger event-related potentials (ERPs, including P3b, N2) and better executive functioning performance (74, 75, 78). Apart from correlational studies, intervention studies have used different neuroimaging tools as objective outcome measures to study the effects of physical activity. A systematic review of endurance-enhancing physical activity interventions found changes in resting-state fMRI and task-related activation in brain regions that are important for attentional control (middle frontal gyrus, superior frontal gyrus, superior parietal lobes, and anterior cingulate cortex) (73). Similarly, a systematic review of resting-state EEG studies also suggested inconsistent, but generally positive training-related changes after exercise interventions, including changes in slow (delta and theta) and fast (alpha and beta) wave activity, indicating normalized cortical-subcortical crosstalk (79). Although more research will need to be conducted, the studies in healthy subjects support the use of neuroimaging tools as objective measures for tracking intervention effects and to understand the neural mechanisms underlying training-related improvements following physical activity/movement interventions.

Compared to healthy populations, fewer studies have investigated the neural mechanisms of physical activity/movement interventions on cognitive and psychosocial functions in individuals with developmental disabilities. To our knowledge, there is no systematic review that provides a broad synthesis of neural effects after physical activity/movement interventions in individuals with developmental disabilities. Therefore, the current systematic review aims to summarize the current neuroimaging findings on chronic and acute effects of physical activity/ movement interventions and quantify effect size estimates for the neural outcome measures. We will assess the utility of neuroimaging tools as objective measures of intervention effects and explain the potential neural mechanisms by which movement interventions promote psychosocial health and cognitive performance in individuals with developmental disabilities.

MATERIALS AND METHODS

Search Strategies

We reviewed literature from four allied health, psychology, physical therapy/kinesiology, and education-related databases, including PubMed (1950–2021), PsycINFO (1969–2021), CINAHL (1937–2021), and Scopus (1966–2021). The search terms included keywords in three areas: (a) Diagnostic terms: Related to neurodevelopmental disorders, including "Autism spectrum disorder," "Attention-deficit/hyperactivity disorder," "Developmental coordination disorder", "Learning disorder," "Intellectual disorder" …etc.; (b) Intervention terms: Related to motor interventions, including "Sport," "Exercise," "Physical activity," "Intervention," "Therapy" … etc.; (c) Neuroimaging terms: Related to neuroimaging modalities including "Electroencephalography," "Magnetic resonance imaging," "Near infrared spectroscopy," etc. (detailed search terms in **Supplementary Table 1**).

Eligibility Criteria

Studies were included in the review if they fulfilled the following inclusion criteria: (a) Included individuals with developmental disorders (e.g., ASD, ADHD, DCD, LD, ID, developmental delay, etc.), (b) Tested the effects of movement interventions (e.g., physical activity, exercise, yoga, martial arts, etc.), and (c) Used neuroimaging techniques (e.g., fMRI, fNIRS, EEG, etc.) to measure intervention effects. Studies were excluded if the experimental group (a) Only involved sedentary interventions (e.g., applied behavior analysis, speech therapy, education); (b) Were review papers, case reports, and protocol papers; (c) Were in languages other than English; or (d) Were gray literature including theses and dissertations.

There is limited evidence on neural effects of movement interventions, hence, we decided to include individuals across all age ranges (including children, adolescents, adults) and abilities (with or without intellectual disabilities). We included studies on various movement interventions utilizing perceptuomotor skills (i.e., multisystem, creative movement as well as targeted physical activity interventions) with wide-ranging training lengths (i.e., one or more sessions), and that used various structural and functional neuroimaging tools to monitor the training-related neural effects. In terms of study design, we included RCT, controlled clinical trials, and cross-over studies, but not case studies to ensure study quality. Overall, we did not set additional exclusion criteria based on age, ability, or nature/content of the control group interventions.

Data Extraction and Evaluation

We conducted our latest database search on Sept 16th, 2021, with a result of 2,653 articles in total (1,036 from PubMed, 453 from PsycINFO, 1,029 from Scopus, and 135 from CINHAL). After removing duplicates and screening through our eligibility criteria, 32 articles qualified for further review (see detailed search process in **Figure 1**). All authors agreed on the eligibility of 95% of the studies. Disagreements between coders for study inclusion were resolved through consensus meetings.

Risk of Bias and Level of Evidence Assessments

The current review paper focused on the methodological rigor and quality of study designs used for assessing physical activity/motor intervention effects. Specifically, the Physiotherapy Evidence Database (PEDro) scale was used to assess the risk of bias for RCT, CCT, and cross-over design studies, while the NIH risk of bias assessment (NIH-ROB) was employed for pre-posttest studies with no control group (80, 81). The PEDro scale includes a total of 11 items which are scored on a nominal scale (No = N, Yes = Y) of which 10 items are scored for each study (maximum score 10, the first item on the PEDro is not included in the total score calculations; detailed descriptions in **Supplementary Table 2**) (80). Note that the PEDro scale criterion #2 requires a study to specifically state that allocation to the intervention was randomized. Allocation procedures using quasi-randomization or counterbalancing did not receive full scores for the criterion of allocation. A PEDro score of more than 6 is classified as high quality, while a score between 4 and 5 is classified as fair, and a score <3 is classified as a low quality study (80). The NIH assessment tool includes 12 items that are also scored on a nominal scale and

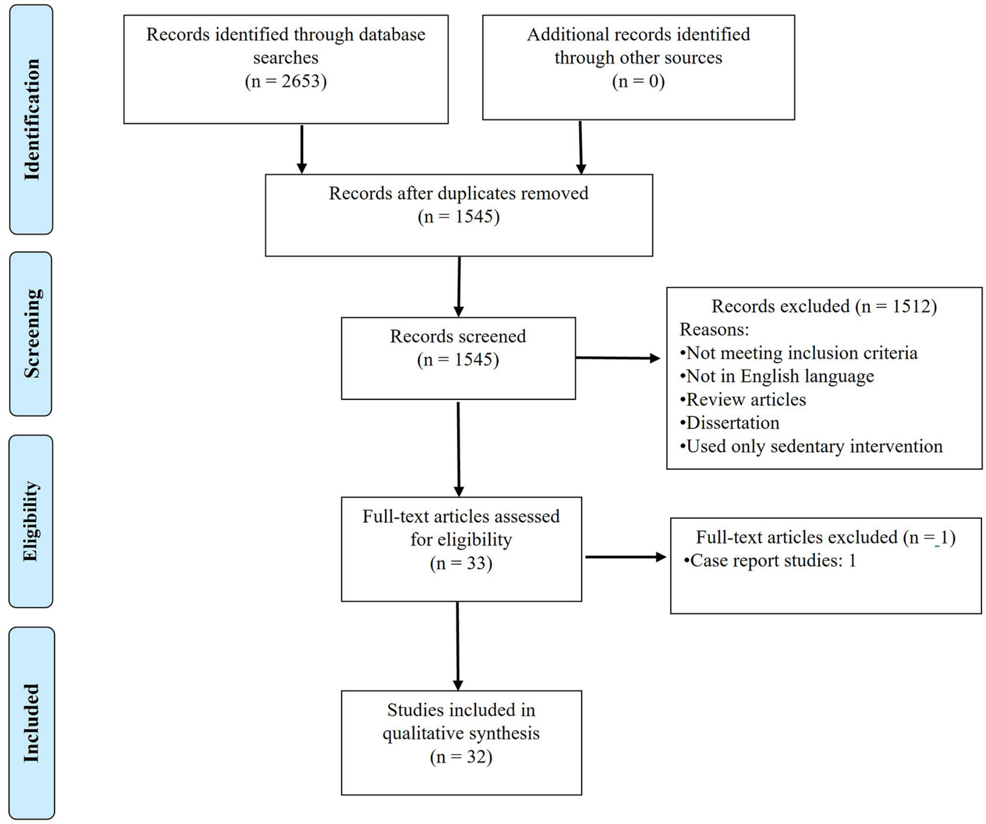

FIGURE 1 | PRISMA diagram for search process.

later summed to give a maximum possible score of 12 (detailed descriptions in **Supplementary Table 2**) (81). All authors coded 20% of the included articles (6 to 7 articles), and we established inter-and intra-rater reliability of >90%. In addition to the risk of bias assessment tools, we also assessed the levels of evidence of the reviewed papers using the tool designed by Sackett and colleagues (82). Based on the study design, the studies are classified into 5 levels: Level I: RCT or cross-over designs with "high" quality (PEDro Scale score ≥6); Level II: RCT or cross-over designs with "Fair" quality (PEDro Scale score = 4–5) and all CCT designs; Level III: Pre-posttest designs; Level IV: Conflicting evidence of two or more equally designed studies; Level V: RCTs with "Poor quality" (PEDro score ≤3) and case studies or cohort studies/single subject series with no multiple baseline assessments (82).

Data Extraction and Coding Procedures

For each of the reviewed studies, we extracted information on sample and study characteristics, methodological quality, intervention characteristics (FITT: Frequency, Intensity, Time, Type), neural and behavioral assessments used, dependent variables, and treatment effects using a standard coding template (**Supplementary Table 3**). Besides narrative descriptions, wherever data was provided in the original reports, we also calculated effect size estimates with their confidence intervals for each outcome measure in reviewed studies to estimate the magnitudes of the treatment effects. Specifically, sample size, means, and standard deviations (and/or standard errors) of the dependent variables were used to calculate the effect sizes using the Hedges' method, a method that is more valid when dealing with smaller sample sizes ($n < 20$) (83). To avoid inaccuracy and allow for fair comparisons between studies, we only calculated the effect sizes if the means and standard deviations (and/or standard errors) for the outcome variables were provided in the reviewed articles.

RESULTS

Study Characteristics and Quality Assessments

Of the 32 included articles, 13 were RCTs, 4 were CCTs, 10 were cross-over, and 5 were pre-post test designs (84–115). Seventeen studies examined chronic effects of physical activity/movement intervention, 14 studies examined acute effects only, and 1 study examined both. The PEDro scores of the studies using RCT, CCT, and cross-over designs ranged from 4 to 8 points (Average = 5.56; SD = 1.12), indicating fair to good study quality (**Table 1**). On the other hand, the NIH risk of bias scores of the studies using pre-post test designs ranged from 6 to 9 points (Average = 7.40; SD = 1.52; **Table 2**). Because of the nature of movement intervention studies, all CCT, RCT, and cross-over studies did not have the subjects blinded to grouping and the type of intervention they received (PEDro scale item #5, NIH ROB item # 8). Additionally, pre-post test design studies had small samples and a lack of assessment across multiple timepoints before and after interventions (ROB item #s 5 and 11). Although many cross-over design studies used a counterbalancing approach to account for intervention order effects, they did not specify whether their allocation to a certain intervention order was randomized or not, and hence, they did not meet PEDro scale criterion #2 (95, 100–102, 104). In terms of the level of evidence, 12 studies were Level I, 15 were Level II, and 5 were classified as Level III. No included paper was classified as Level IV or V.

Sample Characteristics

Of the 32 included papers, 16 included individuals with ADHD, 9 included individuals with ASD, 2 included individuals with DCD, 1 included individuals with LD, 3 included individuals with ID, and 1 included individuals with ID and developmental disabilities. The sample size ranged from 4 to 45 per group (Average sample size = 18.01; SD = 7.66). Due to the sex differences in the prevalence of developmental disabilities, most studies included more males than females, with an average male-to-female ratio of about 4.5:1. The majority of the studies included school-age children between 6 and 18 years (25 of the 32 studies), 2 studies included preschoolers (3–5 years), and 5 included adults with developmental disabilities (>18 years). Twenty out of the 32 studies reported the mean IQ of their participants (76.3–121.3 across studies) with only 6 studies including children with ID (**Tables 3–6**).

Frequency, Intensity, Time, and Type of Movement Interventions

Of the 32 included papers, 17 assessed the chronic effects of multiple intervention sessions, 14 assessed the acute effects after a single bout of exercise, and 1 assessed both the acute and the chronic effects of movement interventions. In the following paragraphs, we describe the Frequency, Intensity, Time, and Type (FITT) of interventions provided in the included studies (**Tables 3–6**).

Frequency

For the studies that assessed the chronic effect of exercise, the intervention frequency ranged from 1 to 5 sessions per week (average: 2.69; SD: 1.35), and intervention duration ranged between 3 and 20 weeks in total (average: 9.50; SD: 4.90). Therefore, the total training volume ranged from 9 to 60 sessions (average: 26.30; SD: 18.78; **Tables 3**, **4**). For the studies that assessed the acute effects of movement intervention, only one 1 session was conducted (**Tables 5**, **6**).

Intensity

Most studies reported training intensity using target heart rate which was expressed as a percentage of the maximum heart rate of the individual. Of the studies that assessed the chronic effects of the interventions, 7 reported the target heart rate of their movement interventions ranging from 45 to 100% of the suggested maximum heart rate (**Tables 3**, **4**). Specifically, 1 study used intervention with light to moderate intensity (<70% maximum heart rate), 3 studies used moderate intensity activities (50–70% maximum heart rate), and 3 studies provided moderate to vigorous intensity activities (>50% maximum heart rate). One study additionally reported an average heart rate of 135.97 bpm (85). For the studies that assessed the acute effects of interventions, 7 reported the target heart rate of their movement intervention, ranging from 50 to 80% of the suggested maximum heart rate (moderate to vigorous intensity activity; **Tables 5**, **6**). One study included three experimental groups with the target exercise heart rate of 30% (Light), 50–60% (Moderate), and 70–80% (Vigorous) of the suggested maximum heart rate, respectively (104). Two other studies reported average heart rate during/right after movement intervention (Vogt et al. (115): 154.50 bpm ± 10.06; Vogt et al. (110): 143.09 bpm ± 14.40; **Table 6**).

Time

The training time for the studies that assessed the chronic effects of exercise varied widely from 35 to 240 min, with an average of session time 69.44 min (SD = 48.69). The Social Emotional NeuroScience Endocrinology (SENSE-theater) treatment had the longest training time (240 min/session) (88), while the music therapy and physical activity interventions had the shortest training time (35 min/session; **Tables 3**, **4**) (96, 97, 112). For studies that assessed the acute effects of exercise, the training time ranged from 10 to 60 min, with an average training time of 27.53 min/session (SD = 11.33; **Tables 5**, **6**).

Type

For the studies that assessed chronic effects, 6 involved sustained aerobic exercises (i.e., running, cycling, stepping, jump rope activities), 2 involved circuit-based exercises with short resting bouts, 7 involved ball-related exercises (i.e., throw and catch, basketball, soccer, badminton), 3 involved martial art training (i.e., Nei-Yang Gong), 3 specifically targeted motor skills (including balance, coordination, and strength), 2 involved the use of musical instruments, 1 involved dancing, 1 involved cognitive games, and 1 used theatrical settings (**Tables 3**, **4**). The majority of the studies (12 of 14) that assessed acute effects of exercise used aerobic exercises including cycling and treadmill walking/running (**Tables 5**, **6**). In addition, 1 study used circuit training with short resting bouts, 2 targeted motor skills (i.e., balance and coordination), and 1 specifically focused on dynamic stretching exercises.

Comparison Group Interventions

For the studies that assessed chronic effects, 9 did not provide intervention to the comparison group, 1 provided applied behavior analysis training, 2 used muscle relaxation techniques, 1 used a play-based intervention, 2 provided behavioral education, 2 provided medications, and 1 used a waitlist control design (**Tables 3**, **4**). For studies that assessed acute effects, 1 did not include a comparison group, 4 did not provide intervention to the comparison group, 8 asked participants to watch a video, 1 had them listen to music, and 1 had the children involved in seated reading activities (**Tables 5**, **6**).

TABLE 1 | PEDro scores for the CCT, RCT, and cross-over design studies.

References	1	2	3	4	5	6	7	8	9	10	11	Total
Bremer et al. (84)	Y	Y	N	Y	N	N	N	Y	Y	Y	Y	6
Cai et al. (85)	Y	N	N	Y	N	N	N	N	Y	Y	Y	4
Chan et al. (86)	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8
Chan et al. (87)	Y	Y	N	Y	N	N	Y	N	Y	Y	Y	6
Corbett et al. (88)	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8
Sharda et al. (89)	Y	Y	N	Y	N	N	Y	Y	Y	Y	Y	7
Yang et al. (90)	Y	Y	Y	Y	N	N	N	N	Y	Y	Y	5
Choi et al. (91)	Y	Y	N	Y	N	N	N	N	Y	Y	Y	5
Chueh et al. (92)	Y	Y	Y	Y	N	N	N	N	Y	Y	Y	6
Huang et al. (93)	Y	N	N	Y	N	N	N	Y	Y	Y	Y	5
Huang et al. (94)	Y	Y	N	Y	N	N	N	Y	Y	Y	Y	6
Hung et al. (95)	Y	N	N	N	N	N	N	Y	Y	Y	Y	4
Janssen et al. (96)	Y	Y	N	Y	N	N	N	N	Y	Y	Y	5
Janssen et al. (97)	Y	Y	N	Y	N	N	N	N	Y	Y	Y	5
Lee et al. (98)	Y	Y	N	Y	N	N	N	N	Y	Y	Y	5
Ludyga et al. (99)	Y	Y	N	Y	N	N	N	Y	Y	Y	Y	6
Mehren et al. (100)	Y	N	N	Y	N	N	N	Y	Y	Y	Y	5
Mehren et al. (101)	Y	N	N	Y	N	N	N	Y	Y	Y	Y	5
Pontifex et al. (102)	Y	N	N	Y	N	N	N	Y	Y	Y	Y	5
Smith et al. (103)	Y	Y	Y	Y	N	N	N	N	Y	Y	Y	6
Tsai et al. (104)	Y	N	Y	Y	N	N	N	N	Y	Y	Y	6
Yu et al. (105)	Y	N	N	Y	N	N	N	N	Y	Y	Y	4
Tsai et al. (106)	Y	N	N	Y	N	Y	Y	Y	Y	Y	Y	7
Tsai et al. (107)	Y	N	N	Y	N	Y	Y	Y	Y	Y	Y	7
Milligan et al. (108)	Y	N	N	Y	N	N	N	Y	Y	Y	Y	5
Chen et al. (109)	N	N	N	Y	N	N	N	Y	Y	N	Y	4
Vogt et al. (110)	Y	Y	N	Y	N	N	N	N	Y	Y	Y	5

*Criteria of the PEDro scale: 1, Eligibility criteria; 2, Group randomization; 3, Concealed allocation; 4, Baseline comparisons; 5, Blinding-subjects; 6, Blinding-therapist; 7, Blinding-assessors; 8, Missing data; 9, Intention to treat; 10, Between-group comparisons; 11, measure of variability (Detailed description in **Supplementary Table 1**); Y, Yes; N, No; Total scores are calculated by summing the number of met criteria (except the first criterion) for each individual study. A PEDro score ≥ 6 indicates low risk of bias; while a PEDro score < 6 indicates high risk of bias.*

TABLE 2 | NIH-ROB scores for the pre-post test studies.

References	1	2	3	4	5	6	7	8	9	10	11	12	Total
Brand et al. (111)	Y	Y	Y	Y	N	Y	Y	N	Y	Y	N	Y	9
LaGasse et al. (112)	Y	Y	Y	Y	N	Y	Y	N	Y	Y	N	Y	9
Choi et al. (113)	Y	N	Y	N	N	Y	Y	N	Y	N	N	Y	6
Chen et al. (114)	Y	N	Y	N	N	Y	Y	N	Y	Y	N	Y	7
Vogt et al. (115)	Y	N	N	N	N	Y	Y	N	Y	N	N	Y	6

*Criteria of the NIH-ROB scale: 1, Study questions and objective; 2, Eligibility criteria; 3, Representation of general population; 4, Participant enrollment; 5, Sample size; 6, Description of assessment/intervention; 7, Reliability and Validity of the measures; 8, Blinding assessors; 9, Missing data; 10, Pre-postest assessments and p-values; 11, Pre-post-tests in multiple time-points; 12, Statistical analysis including individual-level data (Detailed description in **Supplementary Table 1**); Y, Yes; N, No; Total scores are calculated by summing the number of met criteria for each individual study.*

Neuroimaging Assessments

The majority of the studies (25 out of 32) used EEG to assess the neural effects of movement interventions. Other neuroimaging tools that were used included functional Magnetic Resonance Imaging (fMRI; $n = 5$), functional Near-Infrared Spectroscopy (fNIRS; $n = 1$), and Diffusion Tensor Imaging (DTI; $n = 1$). Among the 23 EEG studies, one study used sleep EEG to determine the sleep quality in participating children (111), while the remaining studies recorded neural activity during resting-state ($n = 6$), or during different functional tasks assessing inhibitory control ($n = 9$), mental flexibility ($n = 3$), memory ($n = 3$), sensory gating ($n = 1$), and auditory attention

TABLE 3 | Study characteristics of studies assessing the chronic effects of physical activity/movement interventions (ADHD, LD, ID).

References	Design/ evidence level	Sample (E/C)	Age (E/C: M ± SD; Range)	Gender (E/C)	IQ (E/C)	Movement int	Min/s; s/wk; # of WKs	Intensity (% HR max/ mean ± SD)	Control int	Neural measure	Task
Attention-Deficit/hyperactivity disorder											
Cho et al. (91)	RCT/II	13/17	15.8 ± 1.7/ 16.0 ± 1.2; 13–18	13M0F/17M0F	94.9 ± 11.8/ 95.9 ± 15.2	Aerobic exercise	90; 6; 18	60%	Behavioral intervention	fMRI	Mental flexibility
Huang et al. (93)	CCT/II	15/14	7.9 ± 1.0/ 8.3 ± 1.0; 5–10	11M4F/14M0F	–/–	Water aerobic	90; 2; 8	50–60%	–	EEG	Resting state
Janssen et al. (96)	RCT/II	24/25	9.8 ± 2.0/ 9.2 ± 1.3; –	19M5F/19M6F	98.3 ± 13.8/ 100.8 ± 14.3	Physical activity	35;–;– (28 s)	70–100%	Medication	EEG	Inhibitory control
Janssen et al. (97)	RCT/II	27/25	9.8 ± 1.9/ 9.1 ± 1.1; –	21M6F/19M6F	>80/>80	Physical activity	35;–;– (28 s)	70–100%	Medication	EEG	Inhibitory control
Lee et al. (98)	RCT/II	6/6	8.8 ± 1.0/ 8.8 ± 1.0; –	6M0F/6M0F	>80/>80	Combined exercise	60; 3; 12	45–75%	–	EEG	Resting state & mental flexibility
Smith et al. (103)	RCT/I	13/16	7.2 ± 1.4/ 7.1 ± 1.1; 5–9	7M6F/8M8F	107.5 ± 14.7/ 99.3 ± 11.2	Integrated brain, body, and social	120; 3; 15	–	–	EEG	Inhibitory control
Learning disabilities											
Milligan et al. (108)	CCT/II	45/36	13.1 ± 1.7/ 12.8 ± 1.2; 11–17	41M7F/31M7F	–/–	Martial art	90; 1; 20	–	–	EEG	Inhibitory control & auditory attention
Intellectual disabilities											
Chen et al. (109)	CCT/II	14/4	22.4 ± 1.9/ 22.01 ± 1.8; –	10M4F/4M0F	–/–	Badminton	50; 5; 10	–	–	EEG	Resting state

RCT, Randomized control trials; CCT, Controlled clinical trial; Pre-Post, Pre-post-test design; E, Experimental group; C, Comparison group; M, Mean; SD, Standard deviation; M, Male; F, Female; IQ, Intelligence quotient; INT, Intervention; MIN, Minute; S, Session; WK, Week; HR MAX, Maximum heart rate; ABA, Applied Behavior Analysis; SENSE, Social Emotional NeuroScience Endocrinology; EEG, Electroencephalogram; DTI, Diffusion tensor imaging; fMRI, Functional magnetic resonance imaging.

TABLE 4 | Study characteristics of studies assessing the chronic effects of physical activity/movement interventions (ASD and DCD).

References	Design/ evidence level	Sample (E/C)	Age (E/C: M ± SD; Range)	Gender (E/C)	IQ (E/C)	Movement int	Min/s; s/Wk; # of WKs	Intensity (% HR max/ mean±SD)	Control int	Neural measure	Task
Autism spectrum disorder											
Brand et al. (111)	Pre-post/III	10/–	10.0 ± 2.3/–; 7–13	5M5F/–	–/–	Cycling & motor skill training	60; 3; 3	–/–	–	EEG	Sleep
Cai et al. (85)	CCT/II	15/14	5.1 ± 0.6/ 4.6 ± 0.7; 3–6	2M3F/13M1F	–/–	Mini-Basketball training	40; 5; 12	–/ 136.0 ± 6.1	ABA training	DTI	Resting state
Chan et al. (86)	RCT/I	20/20	11.3 ± 3.9/ 12.4 ± 3.3; 6–17	19M1F/17M3F	78.4 ± 18.9/ 80.5 ± 18.5	Nei Yang Gong	60; 2; 4	–/–	Muscle relaxation	EEG	Inhibitory control
Chan et al. (87)	RCT/I	18/17	11.9 ± 4.1/ 11.0 ± 3.3; 5–17	17M1F/15M2F	76.3 ± 17.7/ 86.5 ± 17.5	Nei Gong	60; 2; 4	–/–	Muscle relaxation	EEG	Visual memory
Corbett et al. (88)	RCT/I	17/13	11.38 ± 2.5/ 10.7 ± 1.9; 8–14	13M4F/11M2F	100.1 ± 16.8/ 95.9 ± 21.2	SENSE-theater treatment	240; 1; 10	–/–	Waitlist	EEG	Face memory
LaGasse et al. (112)	Pre-post/III	7/–	8.4 ± 2.9/–; 5–12	6M1F/–	–/–	Music therapy	35; 2; 5	–/–	–	EEG	Sensory gating
Sharda et al. (89)	RCT/I	26/25	10.3 ± 1.9/ 10.2 ± 1.9; 6–12	21M5F/22M3F	102.0 ±18.8/ 94.0 ± 18.2	Music therapy	45; 1; 8 ∼ 12	–/–	Play-Based intervention	fMRI	Resting state
Yang et al. (90)	RCT/II	15/15	4.7 ± 0.7/ 5.0 ± 0.6/ 3–6	13M2F/12M3F	–	Mini-Basketball training	40; 5; 12	60–69%/–	Behavioral intervention	fMRI	Resting state
Developmental coordination disorder											
Tsai et al. (104)	RCT/I	16/14	9.7 ± 0.4/ 9.5 ± 0.3; 9–10	9M7F/9M5F	104.6 ± 5.7/ 103.4 ± 6.1	Soccer training	50; 5; 10	–	–	EEG	Inhibitory control
Tsai et al. (107)	RCT/I	20/20	11.5 ± 0.3/ 11.5 ± 0.3; 11–12	13M7F/12M8F	108.0 ± 6.5/ 108.4 ± 7.1	Aerobic exercise	50; 3; 16	80–90%	–	EEG	Working memory

RCT, Randomized control trials; CCT, Controlled clinical trial; Pre-Post, Pre-post-test design; E, Experimental group; C, Comparison group; M, Mean; SD, Standard deviation; M, Male; F, Female; IQ, Intelligence quotient; INT, Intervention; MIN, Minute; S, Session; WK, Week; HR MAX, Maximum heart rate; ABA, Applied behavior analysis; SENSE, Social emotional NeuroScience endocrinology; EEG, Electroencephalogram; DTI, Diffusion tensor imaging; fMRI, Functional magnetic resonance imaging.

TABLE 5 | Study characteristics of studies assessing the acute effects of physical activity/movement interventions (ADHD).

References	Design/ evidence level	Sample (E/C)	Age (E/C: M ± SD; Range)	Gender (E/C)	IQ (E/C)	Movement int	Time (min)	Intensity (% HR max)	Control int	Neural measure	task
Attention-Deficit/hyperactivity disorder											
Choi et al. (113)	Pre-post/III	27/–	–/–; 12–14	14M13F/–	91–113/–	Dynamic stretching exercise	13	–/–	–	EEG	Resting state
Chueh et al. (92)	RCT/I	E1: 14 E2: 15/ C: 17	E1: 10.1 E2: 9.6/ C:10.4; 7–12	E1: 14M0F E2: 15M0F/C: 16M1F	**–/–**	Treadmill running	E1: 50; E2: 30	50–70%	Video watching	EEG	Resting state
Huang et al. (94)	Cross-Over/I	24/24	9.5 ± 1.6/ 9.5 ± 1.6; 7–12	24M0F/24M0F	105.7 ± 9.0/ 105.7 ± 9.0	Treadmill running	30	65–75%	Video watching	EEG	Resting state
Hung et al. (95)	Cross-Over/II	34/34	10.2 ± 1.7/ 10.2 ± 1.7; 8–12	33M1F/33M1F	104.9 ± 16.9/ 104.9 ± 16.9	Treadmill running	30	50–70%	Video watching	EEG	Mental flexibility
Ludyga et al. (99)	Cross-Over/I	E1: 14 E2: 14/ C: 14	E1: 12.8 ± 1.8; E2: 12.8 ± 1.8/ C: 12.8 ± 1.8	E1: 11M5F; E2: 11M5F/ C:11M5F	–/–	E1: Coordination E2: Cycling	E1: 20 E2: 20	E1:–; E2: 65–70%	Video watching	EEG	Inhibitory control
Mehren et al. (100)	Cross-Over/II	20/20	29.9 ± 9.5/ 29.9 ± 9.5; –	16M4F/16M4F	–/–	Cycling	30	50–70%	Video watching	fMRI	Inhibitory control & visual attention
Mehren et al. (101)	Cross-Over/II	20/20	31.4 ± 9.6/ 31.4 ± 9.6; –	17M3F/17M3F	–/–	Cycling	30	50–70%	Video watching	fMRI	Inhibitory control
Pontifex et al. (102)	Cross-Over/II	20/20	–/–; 8–10	14M6F/14M6F	110–121/110–121	Treadmill running	20	65–75%	Seated reading	EEG	Inhibitory control
Tsai et al. (104)	Cross-Over/I	25/25	10.5 ± 1.2/ 10.5 ± 1.2; –	23M2F/23M2F	–/–	Treadmill running	30	E1: 30%; E2: 50–60% E3: 70–80%	–	EEG	Resting state & inhibitory control
Yu et al. (105)	Cross-Over/II	24/24	9.9 ± 1.3/ 9.9 ± 1.3; 8–12	23M1F/23M1F	105.0 ± 9.8	Treadmill running	30	60–70%	Video watching	EEG	Inhibitory control

Pre-Post, Pre-post-test design; Cross-over, Cross-over design (note that the same group of participants act as the experimental and comparison groups); E, Experimental group (E1, the first experimental group; E2, the second experimental group; E3, the third experimental group); C, Comparison group; M, Mean; SD, Standard deviation; M, Male; F, Female; IQ, Intelligence quotient; INT, Intervention; MIN, Minute; HR MAX, Maximum heart rate; EEG, Electroencephalogram; fNIRS, functional near infrared spectroscopy; fMRI, Functional magnetic resonance imaging.

TABLE 6 | Study characteristics of studies assessing the acute effects of physical activity/movement interventions (ASD & ID).

References	Design/ evidence level	Sample (E/C)	Age (E/C: M ± SD; Range)	Gender (E/C)	IQ (E/C)	Movement int	Time (min)	Intensity (% HR max/mean±SD)	Control int	NeurAL measure	Task
Autism spectrum disorder											
Brand et al. (111)	Pre-post/III	10/–	10.0 ± 2.3/–; 7–13	5M5F/–	–/–	Aerobic bicycle & motor skill training	60	–/–	–	EEG	Sleep
Bremer et al. (84)	Cross-Over/I	12/12	11.1 ± 1.3/ 11.1 ± 1.3; –	12M0F/12M0F	–/–	E1: Circuit; E2: Treadmill	20	60–80%/–	Video watching	fNIRS	Inhibitory control & Sustained attention
Intellectual disabilities											
Chen et al. (114)	Pre-post/III	12/12	DS: 21.3 ± 5.4; ASD: 18.5 ± 2.0 FXS: 26.17	8M4F/–	–	Treadmill running	20	<85%	–	EEG	Resting state
Vogt et al. (115)	Pre-post/III	11/11	22.5 ± 9.9/–; –	12M0F/–	–	Running	30	–; 154.5 ± 14.4	–	EEG	Resting state
Vog et al. (110)	Cross-Over/II	11/11	16.0 ± 1.34/ 16.0 ± 1.34; –	6M5F/6M5F	–	Cycling	10	–; 143.1 ± 14.4	Music listening	EEG	Resting state & decision making

Pre-Post, Pre-post-test design; Cross-over, Cross-over design (note that the same group of participants act as the experimental and comparison groups); E, Experimental group (E1, the first experimental group; E2, the second experimental group; E3, the third experimental group); C, Comparison group; DS, Down syndrome; ASD, Autism spectrum disorder; FXS, Fragile X syndrome; M, Mean; SD, Standard deviation; M, Male; F, Female; IQ, Intelligence quotient; INT, Intervention; MIN, Minute; HR MAX, Maximum heart rate; EEG, Electroencephalogram; fNIRS, functional near infrared spectroscopy; fMRI, Functional magnetic resonance imaging.

($n = 1$). The EEG variables included: (1) Slow waves (Theta band), fast waves (Alpha and Beta bands), and their ratios (i.e., Theta/Alpha and Theta/Beta ratios) ($n = 8$). Note that the slow and fast wave activity is associated with cortical arousal, (2) Amplitude and latency of event-related potentials (ERP) during executive functioning tasks (i.e., positive peaks in the ERP waveform such as P3b and negative peaks in ERP waveform such as N2) ($n = 11$). Note that greater P3b/N2 amplitude and shorter latency are indicative of more efficient cognitive processing during inhibitory control tasks, (3) Level of right-left frontal asymmetry ($n = 2$), with increased asymmetry indicating greater motivation during exercise, and (4) Sleep EEG variables (i.e., total sleep time, duration of rapid eye movements, etc.) ($n = 1$).

The 5 fMRI studies reported Blood-Oxygen-Level-Dependent (BOLD) signals and functional connectivity (i.e., associations or activity) during resting-state ($n = 2$), or during tasks assessing inhibitory control ($n = 1$), mental flexibility ($n = 1$), or both inhibitory control and attention ($n = 1$). Greater levels of the BOLD signal indicate greater brain activation, while greater connectivity indicates increased synchronized neural activity between brain regions. Only one DTI study measured fractional anisotropy (FA) and mean diffusivity (MD) in brain tissues during sedation/resting state (85). The FA and MD measures are indicative of white matter fiber density, axonal diameter, and myelination, with increased FA and decreased MD reflecting altered white matter organization. Lastly, one fNIRS study recorded the concentration of oxyhemoglobin during an inhibitory control task (84); Typically, higher levels of oxyhemoglobin (Oxy-Hb) indicate greater activation in measured brain regions (details in **Tables 3–6**).

Chronic and Acute Neural Effects of Movement Interventions

Sixteen of the 18 studies that assessed chronic effects of movement interventions reported positive effects on at least one neural measure, whereas 12 of the 15 studies that assessed the acute effects of exercise reported significant beneficial effects in at least one neural measure after a single bout of exercise (**Supplementary Tables 4**, **5**). We were able to calculate effect sizes for 13 chronic and 9 acute effect studies based on the means and standard deviations (and/or standard errors) provided in the publications. The effect sizes of the chronic effect studies ranged from −2.34 to 2.87 (negative effect sizes indicate reduced neural activity post-intervention), with 10 studies having the 95% confidence intervals (CI) of at least 1 variable not including 0 (**Figure 2**; **Supplementary Table 6**). The effect sizes of the acute effect studies ranged from −1.1 to 1.17, with 3 studies having the 95% CI of at least 1 variable not including 0 (**Figure 3**; **Supplementary Table 6**). Although more studies are needed to investigate the differences between chronic and acute effects of movement intervention, the current literature confirms larger effect sizes following multiple sessions (chronic) vs. a single training session (acute).

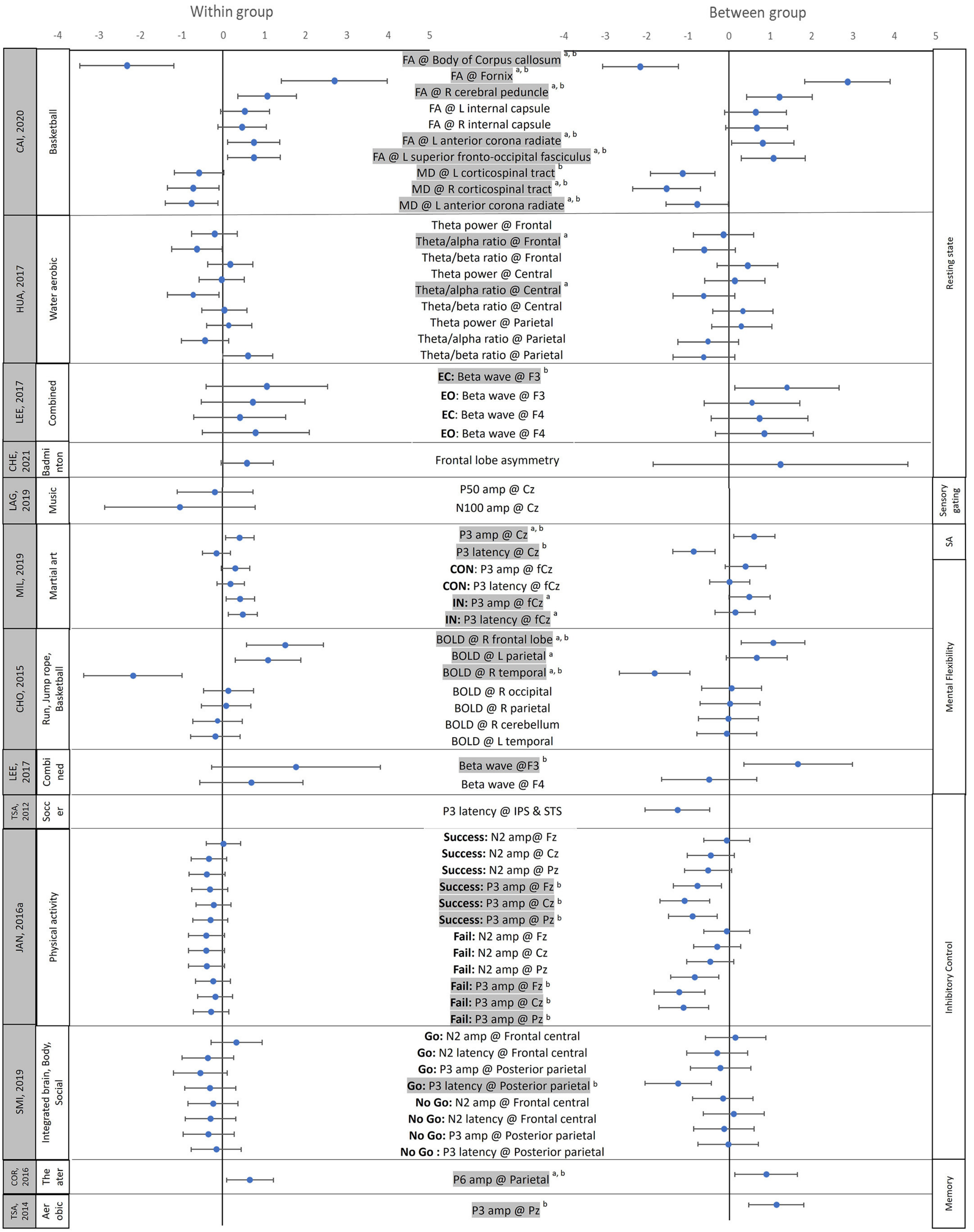

FIGURE 2 | Effect sizes for the chronic neural effects after movement interventions. The mean (solid circle) and 95% CI of the Hedges' g effect sizes were provided for studies assessing the chronic effects of physical activity/movement interventions. The data on the left side shows the effect sizes for within-group comparisons

(Continued)

FIGURE 2 | (pre vs. post), while the data on the right side shows effect sizes for between-group comparisons (Experimental group vs. control group); [a]Shows that the 95% CIs of within-group comparisons does not include 0; [b]Shows that the 95% CIs of between-groups comparisons does not include 0. Shaded variable indicates that the 95% CIs of between and/or the within-group comparisons does not include 0. FA, Fractional anisotropy; MD, Mean diffusivity; L, left; R, right; EC, Eyes closed; EO, Eyes opened; Go, the go condition during the Go-no-go task; No go, the no go condition during the Go-no-go task; CON, Congruent condition during the Flanker task, IN, incongruent condition during the Flanker task; Success, the trials when the participants successfully inhibited the impulses; Fail, the trials when the participants failed to inhibit the impulses; SA, selective attention; Fz, Cz, Pz, FCz, CPz refer to the locations on the head according to the international 10–20 system; amp, amplitude. Please note that to ensure accuracy and to allow between-study comparisons, this table only includes the effect sizes of the outcome variables for which the means, standard deviation/standard error of means, and study sample sizes were provided by the original papers.

Structural and Functional Changes as Well as Domain-Specific Neural Effects of Movement Interventions

Structural Organization

Using DTI, one study investigated the training-related changes in the structural organization of brain tissue (85). Specifically, Cai et al. found training-related improvements in social responsiveness and normalized fractional anisotropy in the fornix, fronto-occipital fasciculus, cerebellar peduncle, internal capsule, anterior corona radiate [Hedges' g = 0.46–2.70 (within); −1.51 to 2.87 (between)], as well as decreased mean diffusivity in bilateral corticospinal tracts [Hedges' g = −0.58 and −0.72 (within); −1.12 to −1.51 (between)] after 12 weeks of mini-basketball training in children with ASD (85).

Sleep Quality

There was one study that investigated the chronic and acute effects of a movement intervention on sleep quality in children with ASD (111). Specifically, Brand et al. conducted sleep EEG in children with ASD before and after 3 weeks of aerobic exercise and motor skill intervention (chronic effects) and assessed acute effects of the intervention by collecting EEG data during nights preceding the intervention as well as nights preceding days when no intervention was provided (acute effects) (111). They found improved sleep quality in children with ASD (higher sleep efficiency, % of deep sleep, % slow-wave sleep, and reduced sleep onset latency) in the nights preceding intervention days compared to the nights preceding days without intervention (positive acute effect; absolute Hedges' g = 0.15–1.39 (within); **Supplementary Table 6**) (111). Although there was no significant chronic effect of the movement intervention on sleep quality as assessed using the Sleep EEG measure [absolute Hedges' g = 0.04–0.75 (within); **Supplementary Table 6**], better ball skills and balance performance were reported after 3 weeks of aerobic and motor skill intervention (See **Supplementary Tables 4**, **5**). In short, there were greater acute compared to chronic effects of physical activity on sleep quality in children with ASD.

Emotional Responses to Movement Interventions

Three studies investigated the changes in EEG resting-state frontal asymmetry after chronic and acute movement interventions in children with ID and ADHD (92, 109, 114). Typically, greater left than right frontal activity is associated with motivation to continue physical activity/tasks, whereas greater right than left frontal activity is associated with lower levels of motivation to pursue physical activity/tasks. Although Chen et al. found reduced left frontal asymmetry after 20 min of treadmill running exercise, indicating low motivation to adhere to exercises [Hedges' g = −0.26 (within)] (114); Chueh et al. found increased left frontal asymmetry after 50 min of treadmill running compared to 30 min of treadmill running and sedentary video watching [E1 (50 min): Hedges' g = 0.78 (within), 1.17 (between); E2 30 min: Hedge' g = −0.41 (within), −0.02 (between)] (92). Moreover, Chen et al. found increased left frontal asymmetry after 10 weeks of badminton training, indicating better motivation to engage in a chronic ball skill intervention [Hedges' g = 0.59 (within), −0.66 (between); **Supplementary Tables 4–6**] (109). Due to the inconsistent results, more studies are needed to understand how duration and types of physical activity/ movement intervention might lead to different levels of motivation to pursue exercise and the subsequent effects on exercise adherence (indicated by left frontal asymmetry).

Resting-State Cortical Arousal

Using EEG, several studies found changes in resting-state slow- and fast-wave activity in children with ADHD, suggesting normalized cortical arousal level after movement interventions (91, 93, 94, 97, 104). Specifically, Janssen et al. (2016) found decreased theta activity over the midline regions (Fz, Cz, and Pz) after 28 physical activity training sessions (97), and Huang et al. found decreased EEG theta/alpha ratios over frontal (F2, F4, Fz) and central (C3, C4, Cz) regions following an 8-week water aerobics intervention compared to a control intervention [Hedges' g = −0.63 and −0.72 (within); −0.60 and −0.61 (between)] (93). Similar results were found in acute effect studies, with Huang et al. reporting reduced theta/beta ratios in the midline regions [Hedges' g = −0.04 to −0.20 (within); −0.21 to −0.35 (between)] (94), Tsai et al. reporting increased alpha power after a single bout of treadmill running [E1: Hedges' g = 0.29; E2: Hedges' g = 0.20; E3: Hedges' g = −0.11 (within)] (104), and Choi et al. (113) reporting increased alpha band and reduced theta band/theta-beta ratio after a single bout of dynamic stretching exercise, indicating improved normalized cortical arousal (113). Although the associations between neural and behavioral/symptoms remain to be explored, our review of the literature suggests that both chronic and acute movement interventions seem to lead to normalized cortico-subcortical crosstalk in children with ADHD (**Supplementary Tables 4–6**).

Resting State Connectivity

fMRI studies found training-related changes in resting-state neural activity in regions important for social communication

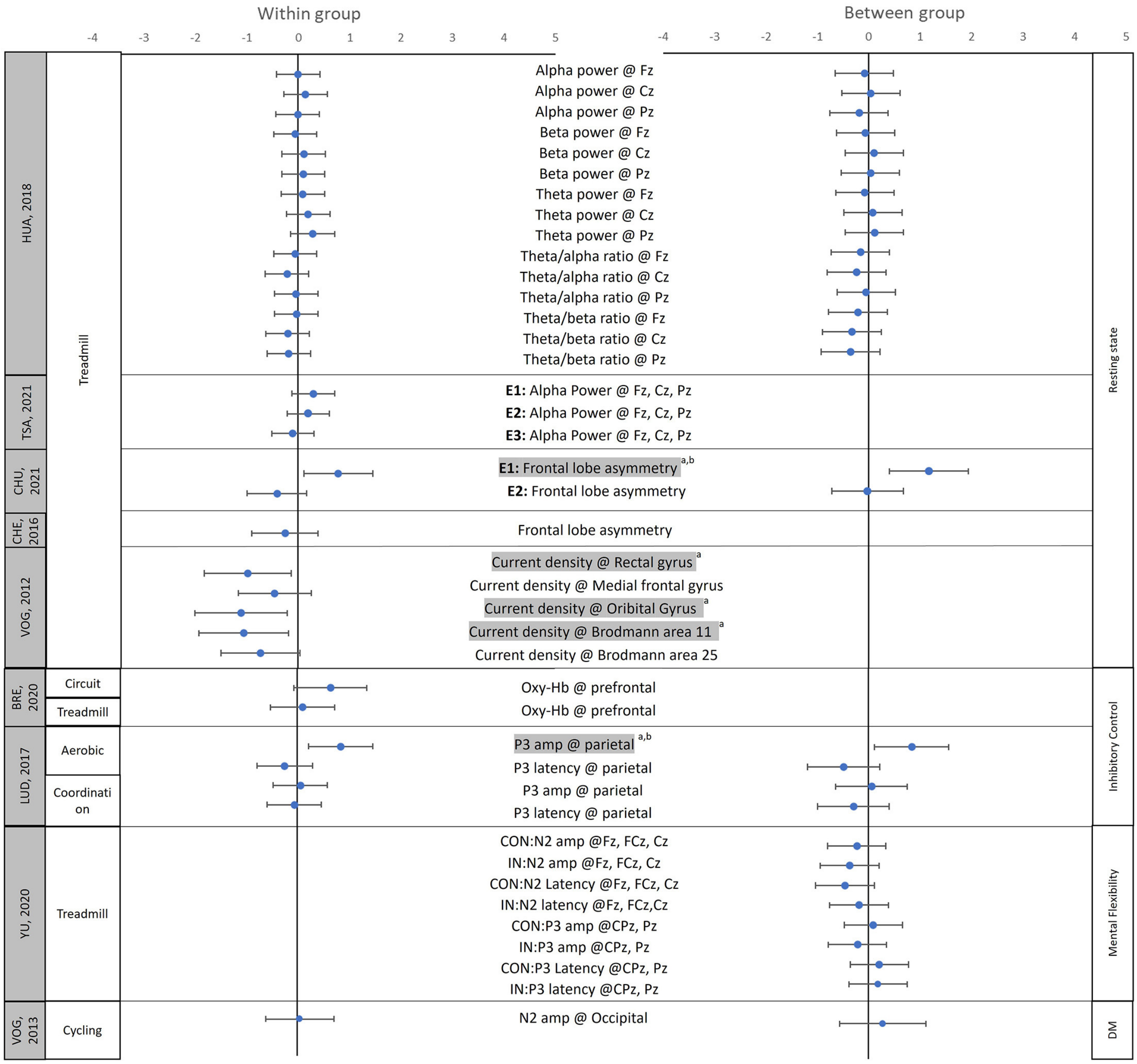

FIGURE 3 | Effect sizes of the acute neural effects after movement interventions. The mean (solid circle) and 95% CI of the Hedges' g effect sizes were provided for the studies focused on the acute effects of the physical activity/movement interventions. The data on the left side show the effect sizes for within-group comparisons (pre vs. post), while the data on the right side show the effect sizes for between-group comparisons (Experimental group vs. control group); [a]Shows that the 95% CIs of within-group comparisons does not include 0; [b]Shows that the 95% CIs of between-groups comparison does not include 0. Shaded variable indicates that 95% CIs of between- and/or within-group comparisons does not include 0; L, left; R, right; CON, Congruent condition during the Flanker task, IN, incongruent condition during the Flanker task; DM, decision making; Fz, Cz, Pz, FCz, CPz refer to the locations on the head according to the international 10–20 system. Oxy-Hb, concentration of the oxygenated hemoglobin; amp, amplitude. Please note that to ensure accuracy and to allow between-study comparisons, this table only includes the effect sizes of the outcome variables for which the means, standard deviation/standard error of means, and study sample sizes were provided by the original papers.

skills in children with ASD (89, 90). Yang et al. (90) found increased connectivity between the left inferior frontal gyrus and the right cerebellum after mini-basketball training (90). Similarly, Sharda et al. found reduced resting-state fMRI over-connectivity between the auditory and visual regions and under-connectivity between the auditory and motor regions after 8–12 weeks of music therapy in children with ASD (89). Moreover, the changes in connectivity were associated with improvements in communication skills in children (89). Overall, these findings suggest that movement interventions might benefit the social communication performance of children with ASD through more efficient social/motor information transmission (**Supplementary Tables 4–6**) (89, 90).

Inhibitory Control

Using different inhibitory control tasks (including Stop sign task, Go-no-Go, Flanker tasks, Visuospatial attention paradigm, decision making, and the attention sustained subtest of the Leiter international performance scale), multiple studies found improved behavioral performance and/or associated neuroplastic changes in EEG/fNIRS/fMRI neural activity after movement interventions in individuals with ADHD, ASD, DCD, and LD (84, 86, 96, 97, 99–103, 105, 106, 108, 110). In terms of behavioral effects of movement interventions, although a few studies failed to report significant changes in inhibitory control performance in children with developmental disabilities (101, 103, 108), others reported increased response accuracy (84, 102, 105), and reduced reaction time during inhibitory control tasks (99, 100, 106, 110), as well as improved parent-reported performance in tasks assessing self-control abilities in individuals with developmental disabilities (86).

For the EEG-related neural effects, the P3b and N2 amplitude/latency were two of the most frequently studied ERP components during inhibitory control tasks (96, 99, 102, 103, 105, 108). Overall, movement interventions led to a normalization of EEG neural activity, including increased amplitude of P3b [Hedges' g = 0.31–0.84 (within), 0.39–0.84 (between)] (99, 102, 108), and N2 peak [Hedges' g = −0.39 to 0.02 (within), −0.06 to −0.52 (between)] (96, 105), as well as reduced latency of P3b [Hedges' g = −0.15 to −0.30 (within), −0.03 to −1.26 (between)] (102, 103, 106), and N2 waves [Hedges' g = −0.18 to −0.45 (between)] (105, 110). Similarly, using fNIRS, Bremer et al. (2020) found increased oxyhemoglobin concentration over the prefrontal cortex following circuit training but not after a treadmill training intervention [Hedges' g = 0.64 and 0.10 (within), respectively] (84). For fMRI-related neural effects, two papers from the same research group found increased activation over the temporal (superior and middle temporal regions), parietal (i.e., superior and inferior parietal gyri, postcentral and supramarginal gyri), and occipital lobes during Go-no-go tasks (100), but no significant changes in brain activity during the Flanker task after a single bout of cycling exercise (101). Taken together, despite some inconsistent results, several studies found improved inhibitory control along with normalized EEG and higher levels of activation in task-appropriate neural substrates using fMRI/fNIRS (**Supplementary Tables 4–6**).

Mental Flexibility

Three studies investigated the effects of the movement-related intervention on mental flexibility in children with ADHD and found improved behavioral performance (91, 95, 98). Specifically, Lee et al. found increased color-word score during the Stroop task after 12 weeks of combined exercise (98); Hung et al. found improved reaction times during task switching after 30 min of treadmill running (95); Choi et al. found fewer preservation errors during Wisconsin Card Sorting test after the 13 min of dynamic stretching exercise (91). For neural activity findings, Lee et al. found increased EEG beta wave activity over the frontal regions (F3 & F4) in children with ADHD after 12 weeks of combined movement exercise (including balancing, jumping rope, and stretching) [Hedge' g = 0.70–1.77 (within), −0.49–1.66 (between)] (98). Similarly, Hung et al. (2016) found increased P3b amplitude over the midline regions (Fz, Cz, Pz) during rule-shifting than non-shifting conditions after a single bout of treadmill running (95). Lastly, using fMRI, Choi et al. (2015) found increased activation over the right frontal and left parietal regions [Hedges' g = 1.10–1.51 (within), 0.66–1.05 (between)], as well as decreased activation over the temporal lobe after 18 weeks of aerobic exercises [Hedges' g = −2.17 (within), −1.81 (between)] (91). Taken together, both acute and chronic movement-related interventions have positive effects on mental flexibility and led to normalized EEG and fMRI neural activity important for selective attention and stimulus processing/discrimination (**Supplementary Tables 4–6**) (91, 95, 98).

Memory

Two studies that focused on visual memory performance in children with ASD and one study that focused on the visuospatial working memory in children with DCD found positive effects of the movement-related intervention on behavioral memory tests as well as underlying neural activity performance along with training-related changes in neural activity (87, 88, 107). Specifically, while Chan et al. found enhanced memory (increased total recall) and better memory retrieval strategies (increased semantic clustering and visual scanning performance) in children with ASD after 4 weeks for Nei Yang Gong/martial art training (87), Corbett et al. found improved memory of faces with and without a delayed period in children with ASD after 10 weeks of SENSE-theater intervention (88). Similarly, Tsai et al. found enhanced response accuracy during a visuospatial working memory task (i.e., remember the spatial locations of ladybirds) in children with DCD after 16 weeks of aerobic exercise (107).

For neural effects, Chan et al. (2015) found a training-related increase in EEG theta coherence over the frontoposterior regions, indicating better cortical connectivity between brain regions (87). On the other hand, Corbett et al. (2016) found normalized ERP amplitude between 300 and 500 ms after stimuli over the parietal lobe, after SENSE theater intervention, indicating enhanced working memory (88). Lastly, Tsai et al. found increased P3b amplitude over the frontal, central, temporal, parietal, and occipital regions during the retrieval process when working on the visuomotor working memory task [Hedges' g = 1.13 (between-group)] (107). Movement-related interventions might have positive effects on memory performance including visuospatial memory, memory of faces, and working memory, and lead to changes in neural activity important for resource allocation during the retrieval process (**Supplementary Tables 4–6**) (87, 88, 107).

Associations Between Neural and Behavioral Improvements

Few studies reported the correlation between neural and behavioral improvements after movement-related intervention (91, 96, 105). Using EEG, Janssen et al. found a significant but relatively weak positive association between changes in N2 amplitude over Cz and improvements in inhibitory control (indicated by the change of reaction time during Stop Sign

Signal task) after physical activity intervention ($r = 0.22$) (96). Using fMRI, Choi et al. found moderate-sized associations between changes in right prefrontal activation and improvements in mental flexibility (shown as decreased preservation errors during Wisconsin card sorting test) and decreased ADHD symptoms after aerobic intervention ($r = 0.53–0.57$) (91). Similarly, Yu et al. found associations between increased EEG N2 amplitude/decreased N2 latency and the improvements in mental flexibility (indicated by increased accuracy during Flanker task; $r = −0.44–0.46$; **Supplementary Tables 4**, **5**) (105). The significant associations between neural and behavioral improvements suggest that the neural measures reflect the underlying neural mechanisms for behavioral improvements and may be used as objective and sensitive measures to assess intervention effects.

DISCUSSION

Summary of Main Findings

This review aimed to summarize findings on neurobiomarkers of chronic and acute effects of physical activity/movement intervention using different neuroimaging tools and quantified effect size estimates for various neural outcome measures. Our review of 32 experimental studies revealed that 84% of the studies were fair to good quality (RCT, CCT, or cross-over design studies) and supported the use of neuroimaging techniques, including EEG, fMRI, DTI, and fNIRS, as objective measures for capturing training-related changes in neural processing in individuals with developmental disabilities. Both chronic and acute movement interventions led to positive effects on behavioral measures of social communicational, emotional, and cognitive/executive functions (i.e., inhibitory control, mental flexibility, memory) as well as improved neural function/processing. We found larger effects for chronic movement interventions (Hedges' g = −2.34 to 2.87) compared to acute effects of physical activity (Hedges' g = −1.1 to 1.17). Specifically, movement training led to normalized resting-state, cortical arousal in children with ADHD, normalized resting-state neural connectivity between brain regions important for social communication performance in children with ASD, and normalized neural activity during executive functioning tasks (i.e., tasks involving inhibitory control, memory, and mental flexibility) in individuals with ADHD, ASD, DCD, and LD. Despite the promising results, more research with larger sample sizes and standardized neuroimaging methods across multiple diagnoses is needed to further explore the underlying neural mechanisms and to increase the replicability of findings within and across diagnoses.

Neural Biomarkers for the Effect of Physical Activity/Movement Intervention in Individuals With Developmental Disabilities

With advances in neuroimaging techniques, more and more intervention studies are including neuroimaging tools as objective outcome measures of intervention effects (58). Systematic reviews involving healthy populations support the use of neuroimaging tools as outcome measures and propose potential mechanisms underlying training-related improvements (73, 79). The current systematic review extends these findings to individuals with developmental disabilities. A large proportion of the studies included in the current systematic review showed significant changes in at least one neural measure after movement intervention (Chronic: 16 out of the 18 included studies; Acute: 12 out of the 15 included studies). Moreover, the training-related changes in neural activity were correlated with behavioral improvements as indicated by a few studies included in the review (91, 96, 105). In short, neuroimaging tools may serve as promising outcome measures to objectively report training effects in individuals with developmental disabilities. Below, we summarize the key findings of the review in terms of neural effects and associated biomarkers of movement interventions in individuals with developmental disabilities.

Normalized Resting-State Cortical Arousal and ERP Components During Executive Functioning Tasks in Individuals With Developmental Disabilities

The EEG resting-state fast-wave (i.e., Alpha and Beta band), slow-wave (i.e., Theta band), and their ratios (i.e., Theta/alpha and Theta/Beta ratios) are said to reflect the cortico-subcortical crosstalk/arousal, which in turn affect executive functioning performance (116). Most studies assessing cortical arousal have focused on individuals with ADHD and found reduced resting-state fast-wave activity (i.e., alpha and beta bands), increased slow-wave activity (i.e., Theta band), and increased theta/alpha, theta/beta power ratios in individuals with ADHD compared to healthy individuals (117, 118). The ADHD-related differences in resting-state activity might reflect atypical cortical-subcortical crosstalk/arousal and a lack of inhibition of irrelevant sensory inputs (116, 119). Studies included in the current systematic review found normalized EEG resting-state activity [i.e., increases in alpha power (91, 104), as well as decreases in theta power (91, 97) and theta/alpha (93) and theta/beta ratios (91, 94)] after aerobic physical activity, suggesting normalized cortico-subcortical crosstalk/arousal in children with ADHD.

Apart from resting-state neural activity, several ERP components are said to be reflective of neural processing during executive functioning tasks. For example, greater P3b/N2 amplitudes and shorter P3b/N2 latency indicate more efficient stimuli processing, response monitoring, and memory storage (66). Case-control studies suggested reduced P3b and N2 amplitudes and increased latencies during inhibitory control and mental flexibility tasks in individuals with ASD, ADHD, and/or LD (64–66). Moreover, children with DCD were found to have smaller P3b amplitude during a visuospatial working memory task compared to their TD peers (106). Studies included in the current systematic review found training-related behavioral improvements along with increased P3b amplitude (99, 102, 107, 108), N2 amplitude (95, 96, 105), as well as reduced P3b latency (102, 103, 106) and N2 latency (105, 110) in children with ASD, ADHD, LD, and DCD during inhibitory control, mental flexibility, and working memory tasks. Similar neural mechanisms were found in healthy individuals, with increased P3b amplitude and reduced P3b latency during executive functioning tasks associated with higher fitness levels (74, 75).

It is postulated that aerobic exercise may lead to changes in cerebral metabolism, increased blood flow, and the release of neurotransmitters/ neurotrophic factors, such as norepinephrine and dopamine, and serum brain derived neurotrophic factors, leading to changes in cortical arousal which in turn increase the efficacy of stimuli processing, response monitoring, and memory storage during executive functioning tasks (120–122).

Increased Social Brain Connectivity in Children With ASD

Children with ASD are known to have abnormalities in cortico-cortical and cortico-subcortical connectivity (123–126). For example, excessive short-range connectivity (prefrontal, temporal, etc.) and reduced long-range connectivity between cortical regions (fronto-parietal, fronto-temporal, etc.) as well as between various cortical and subcortical structures (cortico-cerebellar and cortico-striatal connections) are well-documented in children and adolescents with ASD (123–129). DTI studies have found that children with ASD have lower fractional anisotropy and higher mean diffusivity values in the corpus callosum, internal capsule, fronto-occipital fasciculus, and corticospinal tract, and these differences were associated with their social communication deficits (127, 129). The DTI and fMRI studies in this systematic review reported training-related changes in resting-state neural activity in regions important for social communication performance in children with ASD (85, 89, 90). After 12 weeks of mini-basketball training in children with ASD, training-related improvements in social responsiveness were reported (85, 90). Additionally, using DTI and fMRI, researchers also found normalized white matter integrity (including increased fractional anisotropy in the corpus callosum, fornix, fronto-occipital fasciculus, cerebellar peduncle, internal capsule) and mean diffusivity in the corticospinal tract, as well as increased connectivity between left inferior frontal gyrus and right cerebellum (85, 90). Movement interventions such as mini-basketball training are team sports that require children to set goals, make decisions, take turns, communicate with each other, and manage conflicts in a supportive environment, which in turn, might improve social responsiveness of children with ASD. At a neural level, this may present as increasing efficacy of social/motor information transmission and normalizing of white matter integrity (85).

Similarly, Sharda et al. found reduced resting-state fMRI overconnectivity between the auditory and visual regions and underconnectivity between the auditory and motor regions after 8–12 weeks of music therapy in children with ASD (89). Moreover, the changes in connectivity were associated with improvements in children's communication skills (89). Music and movement interventions/experiences are known to have multisystem and multimodal effects on social, language, and cognitive performance of typically developing children/healthy adults and those with developmental disabilities (49). Musical training involves turn-taking and tuning to the actions of partners during duet/group musical performance which engages the social brain networks in the fronto-temporo-parietal cortices (130, 131). One study found greater fNIRS activation in the temporo-parietal and sensori-motor regions of musicians when they played the second violin part as followers compared to when they played the first violin part as leaders which required greater individual motor planning (132). Such repeated experiences may shape the cortical connectivity of individuals over the long term. DTI measures in musicians with 15 years of experience found reduced diffusivity and greater fiber coherence in effector-specific pathways including corticospinal tracts, superior longitudinal fasciculus, and corpus callosum (133). Additionally, structural MRI studies have widely confirmed that musical training leads to enhancements in the gray and white matter of auditory and effector-specific motor cortices which were in turn associated with musical performance of the participants (134, 135). These findings further confirm the neuroplastic changes following musical training reported by Sharda et al. (89). They postulated an increase in bottom-up sensory processing following music therapy which may contribute to the functional connectivity changes within the auditory and motor cortices. Nevertheless, there is limited literature on cascading social communication effects of physical activity/movement interventions on the neural functioning of individuals with disabilities, and results from this review need to be further confirmed by other studies with larger samples and long-term follow-ups.

Increased Functional Activation/Connectivity Within Frontal-Parietal Network During Executive Functioning Tasks in Individuals With Developmental Disabilities

The frontoparietal network, primarily composed of the lateral prefrontal, inferior parietal lobe, and posterior inferior temporal lobes, plays an important role in executive functioning, including inhibitory control, mental flexibility, and memory retrieval (136–139). Specifically, the prefrontal cortex is important for monitoring and sending top-down signals to other cortical/subcortical regions (140); while the parietal regions are particularly important for selective attention whereby the information is selected for preferential processing (136, 139). Case-control studies had found hypoactivation over the frontoparietal network in individuals with ASD and ADHD during executive functioning tasks (41–43, 59). Using fNIRS, Bremer et al. found increased prefrontal cortex activation during inhibitory control tasks after a circuit-based intervention (84). Similarly, fMRI studies found increased connectivity between the left inferior frontal gyrus and right cerebellum, increased parietal activation during inhibitory control, and increased frontal and parietal activation during mental flexibility tasks, following movement interventions (90, 100, 113). Physical activity/movement interventions might benefit executive functioning performance by improving the top-down monitoring and selective attention for stimulus processing.

Diagnosis-Specific Intervention Program and Related Outcome Measures

Most studies that focused on individuals with ADHD used structured physical activity/aerobic interventions, such as treadmill running and cycling, to promote their executive functioning. Despite some inconsistency, the results generally support the use of physical activity/aerobic interventions to promote executive functioning in individuals with ADHD. Using fMRI and EEG measures, studies suggested normalized resting-state cortical arousal, as well as normalized ERPs and increased activation over the frontoparietal network during executive functioning tasks. Compared to the studies in individuals with ADHD, studies in individuals with ASD have used more multisystem, creative movement interventions (i.e., martial arts, theater, and music and movement interventions) to improve a wide range of skills, including ASD symptoms, social communication skills, and executive functioning. ASD is a multisystem disorder that not only leads to core impairments in social communication skills and repetitive behaviors, but also affects children's motor performance, sensory processing, and cognitive functioning from infancy through adolescence (2–29). Our current review suggests improved sleep quality, social communication skills, executive functioning, as well as enhanced social brain connectivity along with normalized EEG/ERP variables and increased activation over the frontoparietal network during executive functioning tasks. Similar behavioral and neural findings of the effects of physical activity/movement intervention on executive functioning were found in individuals with DCD and LD. Studies of individuals with ID focused on emotional changes and motivation toward physical activity/movement interventions, and found greater motivation to adhere to exercise following an enjoyable badminton training program compared to a treadmill running program. In terms of limitations of the examined literature, the majority of the studies were conducted in school-age children between 6 and 18 years needing less support (i.e., high-functioning children) perhaps, because neuroimaging tools generally require compliance and persistence through testing. Few studies included children with ID, LD, and DCD while the majority assessed intervention effects in children with ADHD/ASD. Lastly, the majority of the studies did not examine follow-up retention effects.

Limitations

Our effect size calculations might not be representative of all studies investigating neural effects of physical activity/movement interventions because we were only able to calculate effect sizes if the mean and standard deviations of outcome variables were provided by the authors. We also did not include theses and dissertations in our review. Lastly, due to the scarcity of literature on neural effects of movement interventions, we included studies examining effects of various perceptuomotor interventions including multisystem, creative movement (music, dance, etc.), and targeted physical activity (treadmill, cycling, etc.). As discussed earlier, readers should be careful to differentiate when postulating the neural mechanisms of the various movement interventions included in this review. Although multiple cross-over design studies used a counterbalancing approach, they did not report details such as the method of allocation to intervention order or allocation ratio. In general, neuroimaging studies reporting effects on neurobiomarkers post-intervention should comply with CONSORT guidelines when reporting study details (141).

Implications and Recommendations for Clinical Practice

In terms of the duration of physical activity/movement interventions, our systematic review found larger effects for chronic compared to acute interventions. This is also confirmed by recent reviews and meta-analyses of physical activity interventions in healthy and neurologically affected individuals reporting significant positive effects on working memory after chronic but not acute physical activity interventions (142, 143). Clinicians should recommend longer intervention periods within and across bouts for their clients (i.e., 50 min or more, 1–2 sessions/week, up to 10 weeks or more) to yield better results compared to a single session/shorter periods of physical activity/movement interventions. Weekly consistency and continued physical activity/movement interventions over the long term will likely have a greater positive impact on neural, social, and cognitive functioning. In terms of physical activity/movement intervention types, circuit-based exercise led to greater cognitive/executive functioning improvements compared to continuous treadmill training perhaps, due to the greater cognitive demands of switching between exercises (84). Certain other exercise forms such as badminton training have led to greater exercise adherence suggesting that motivation and enjoyment will be crucial in continuing exercise in the long-term (109, 114). Aerobic exercise (e.g., cycling at 65–70% Heart Rate max) may have more cognitive benefits compared to gentler coordination exercises requiring static and dynamic balance (99, 143). Lastly, after the onset of the COVID-19 pandemic, there has been a rise in use of telehealth as an alternative intervention delivery method. It will be important to understand the differences in behavioral and neural effects of physical activity/movement interventions delivered through virtual vs. traditional, face-to-face approaches (144–147). Further research is needed to understand how different types and delivery methods of physical activity/movement interventions might lead to differential neural effects on social communication and cognitive performance.

Implications and Recommendation for Future Research

Our review of studies supports the use of different neuroimaging tools as objective measures for intervention effects including MRI/fMRI, DTI, EEG, and fNIRS. The majority of the studies included in the current systematic review used EEG to investigate the movement-related changes in neural activity, probably due to its low-cost and child-friendly nature. EEG-based neurobiomarkers (i.e., slow and fast-wave EEG activity, and the ERPs such as P3b, N2 peaks) could be used to study neural effects of movement interventions on children's networks related to cognitive/executive functioning and social functioning. Besides EEG, other non-invasive, child-friendly techniques include fNIRS (58, 84). Using fNIRS, our research group has reported differences in cortical activation in infants at-risk for and children with ASD during socially embedded actions (i.e., actions performed with adults and caregivers), solo movements, and action observation compared to healthy children and adults during social interaction as well as interpersonal synchrony tasks involving reaching and whole-body movements (67–72). We have consistently found lower fNIRS activation in the superior temporal sulcus and middle/inferior frontal gyri in infants at-risk for and children with ASD compared to controls (67–72). In certain tasks involving synchronous reaching and body sway, fNIRS activation was associated with ASD severity and communication performance (69, 71). Moreover, in an ongoing RCT study, we are investigating the neural effects of creative movement and physical activity/exercise-based movement interventions compared to sedentary, standard of care interventions using fNIRS to track the intervention-related differences during executive functioning and interpersonal synchrony tasks in children with ASD (147). In short, there are alternative, child-friendly approaches robust against motion artifacts that should be considered to study intervention-based changes in neurobiomarkers in individuals with wide-ranging severity in developmental disabilities. Despite the promising results from the studies covered in this review, a lot more remains to be done to develop a deeper understanding of neural mechanisms underlying movement intervention-related improvements. Studies should make it a point to report relationships between changes in neural activity and behavioral performance (imaging task and standard measures). There is little understanding about how certain subgroups based on impairment severity (e.g., level of cognitive or social impairment) and intervention characteristics (e.g., type and intensity of exercise) might have differential impacts on neurobiomarkers. Future studies should include individuals from different subgroups based on age, sex, ethnicity, diagnoses, impairment levels, and use interventions of different types (e.g., aerobic vs. circuit training), intensities (moderate, vigorous, etc.), and durations (30–90 min, etc.) to investigate relations between neural effects and sample/intervention characteristics.

CONCLUSION

We conducted a comprehensive review of studies that investigated the neural effects of physical activity/movement interventions in individuals with developmental disabilities. Several intervention-related neurobiomarkers were identified along with behavioral improvements in cognitive and social functioning in individuals with developmental disabilities. Specifically, following movement interventions, individuals with developmental disabilities were found to have normalized resting-state cortical arousal, normalized resting-state social brain connectivity, and changes in neural activity during executive functioning tasks. More research with larger sample sizes and standardized neuroimaging tools is needed to further explore the different neural mechanisms underlying the behavioral effects of physical activity/movement interventions and to increase the replicability of findings across studies.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

W-CS, SS, and AB contributed to conception and design of the study. W-CS developed, organized the literature database, and wrote the first draft of the manuscript. SS, CC, and AB assisted with establishing coding reliability. NA and W-CS performed the statistical analysis. SS and AB wrote several sections of the manuscript. All authors contributed to manuscript revision, proof reading, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.794652/full#supplementary-material

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"On-Time Autism Intervention": A Diagnostic Practice Framework to Accelerate Access

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It is well-documented that autism can be reliably diagnosed by age two and that early signs emerge most often between 18 and 24 months. However, despite the increased awareness and focus on early diagnosis, the average age of diagnosis is over 4 years old; even later for Black children and those who are Medicaid-eligible. In this paper, we will propose a framework for accurate and accelerated autism diagnosis for children before age three. The proposed framework emphasizes a collaborative diagnostic process, which relies heavily on Birth to Three provider knowledge and expertise. Considerations for next steps are presented. This approach could increase access to diagnosis of young children soon after first signs of autism emerge.

Keywords: autism, autism (autism spectrum disorders), early intervention (EI) services, early autism diagnosis, early autism intervention

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INTRODUCTION

Autism Spectrum Disorder (ASD) is a neurodevelopmental disability that impacts social communication and repetitive behaviors that can be identified within the first 3 years of life (1, 2). In the United States (US), despite the recent focus on early detection and diagnosis of ASD in young children, a practice gap persists that disproportionately affects young children of color (3–6). Timely diagnosis and quick entry into intensive, comprehensive, and developmentally appropriate intervention services has long been recommended following the emergence of symptoms of ASD (7, 8). It is imperative to address the gap between the emergence of ASD and starting ASD-specific intervention to address the developmental needs of young children and their families (9). Prioritizing referral to Birth-to-Three (B-3) early intervention in this diagnostic process may help close this gap (10).

EARLY DETECTION AND HEALTH INEQUITIES

Most children show clear signs of ASD (2) by 24 months, with some individuals manifesting characteristics earlier (11, 12). Some of the earliest detectable signs of ASD include lower rates of social smiles, reduced time spent looking at faces, little or no babbling, reduced eye contact, no pointing or sharing interests, and limited verbalizations (13, 14). Despite the emergence of symptoms by 24 months, diagnosis typically occurs after age 4 in the US (1). The average age of diagnosis is later for low-resource and non-White children. Latinx children are diagnosed later than White children and receive fewer services (6). The mean age of diagnosis of Black children is 64.9 months, with Black parents waiting more than 3 years on average from first concern to diagnosis (3). This gap even persists for Black children with intellectual disability; a co-occurring condition that usually results in earlier identification (1). Medicaid-eligibility, as well as racial, ethnic, and socioeconomic factors are also associated with decreased access to timely and accurate diagnosis (15, 16). Non-white children are less likely than White children to have a personal doctor or nurse and non-White parents are more likely to report their doctor does not spend enough time with them, does not make them feel like a partner in care, and is not sensitive to their family values or customs (17). Other factors that may contribute to these continuing inequities include maternal education level (18), providers dismissing caregiver concerns (19), and variability in the implementation of ASD screenings and referral following a positive screen in pediatric offices, suggesting the possible need for more culturally sensitive ASD screening tools (20). Innovative approaches to provide timely diagnosis are needed to ensure access to services for all children and families.

B-3 SERVICE DELIVERY SYSTEM

The B-3 service delivery system, established by Part C of the Individuals with Disabilities Education Act (IDEA), is a federal program that supports states in providing individualized services for infants and toddlers with disabilities and their families (21). This system is well-situated to facilitate a more timely and equitable approach to early detection and early intervention for young children with ASD in the US (10, 22). For additional information on the B-3 system and IDEA see https://sites.ed.gov/idea/

Increased collaboration between B-3, medical providers, and diagnostic clinicians is an innovation that may improve outcomes for pediatric populations. For example, better integration of B-3 and newborn screening programs, programs that serve the same population but have different funding structures, recruitment approaches, and approaches to intervention, may improve services for children with Fragile X syndrome (23). Fragile X and ASD share many characteristics and Fragile X is often initially misdiagnosed as ASD (24). Similarly, systematic coordination of the B-3 system with medical and diagnostic providers may benefit children with ASD. Such integration, although requiring coordination and effort, holds promise for improving equitable access and outcomes for young children with ASD and their families.

20 years ago, the National Research Council recommended that services for children with ASD should begin as soon as ASD is suspected (7). This goal has not yet been achieved for many children, especially children of color and those with fewer resources (1, 3, 6, 15, 16). Innovations in the diagnostic process are needed so that entry into ASD-specific services as soon as symptoms emerge is no longer considered *early* intervention, but rather is considered *on-time* intervention.

SHIFTING TO "ON-TIME" IDENTIFICATION AND DIAGNOSIS

The 'On-Time Autism Intervention' project (OTAI) is a collaboration at the University of Washington (UW) in Seattle, Washington lead by the UW Autism Center and UW Haring Center for Inclusive Education. OTAI staff consists of researchers, clinicians, and educators with expertise in ASD diagnosis and intervention for young children. The goal of OTAI is to develop, with community partners, innovative strategies to increase equitable access to "on-time" diagnostic and ASD-specific intervention services for young children and their families.

TABLE 1 | Questions about parent orientation towards diagnosis from 'Birth-3 Team Input' Form.

Instructions: Please circle all that apply. Use additional space provided to answer each question.

1. **Parent's Overall Level of Concern about their child and ASD**: Mild/Minimal, Moderate, High
2. **How is family approaching an autism evaluation and possible diagnosis**: Hesitant, anxious/nervous, only doing it because told to/not ready, couple is in conflict-one wants this and other does not, they seem to know s/he has ASD and are ready (other—please explain)
3. **How do you anticipate this parent will respond to an ASD diagnosis**: Denial/Refusal to accept this, Sadness Acceptance/positive thinking, Anger, Self-Blame, Worry, Other
4. **Is there anything else that the team thinks would be important for us to know**: (e.g., trauma, homelessness, language barriers, family culture, financial barriers, marital issues, CPS reports, etc.)

The OTAI identification and diagnosis practice framework consists of practice recommendations in five areas: (1) universal screening by B-3 staff, (2) supporting parental orientation toward diagnosis, (3) collaborative referral to diagnostic evaluation, (4) accelerated diagnostic evaluation, and (5) seamless transition to ASD navigation and intervention.

To develop the framework, OTAI staff engaged community B-3 partners by visiting B-3 centers, meeting with and observing the work of B-3 providers. From there, a preliminary collaborative, accelerated diagnostic framework was developed and tested with a partner B-3 organization and revised based on observations and feedback from B-3 providers, parents, and OTAI staff. The framework employs reliable and valid clinical measures in the diagnostic process. The measures considered the 'gold standard' include the Autism Diagnostic Observation Schedule (ADOS) (25), to directly assess ASD characteristics, the Autism Diagnostic Interview (ADI-R) (26) to provide parent-report of ASD characteristics, a standardized developmental measure to determine developmental level [e.g., Battelle Developmental Inventory (27)] and a measure of adaptive functioning [e.g., the Vineland Adaptive Behavior Scale, 3; VABS-3 (28); or Adaptive Behavior Assessment System-III; ABAS-III (29)] (30–32). However, no specific measure is intended to super cede the clinical judgement by an experienced clinician; thus, clinical judgement is considered the ultimate 'gold standard' for ASD diagnosis. As such, the OTAI diagnostic framework includes a developmental interview with the caregivers that covers the same domains as the ADI-R, an ASD evaluation using the ADOS, and standardized testing of the child. The most important innovation of the framework, is instead of redoing the standardized developmental assessment in the diagnostic evaluation, we utilize the developmental testing conducted by the B-3 team. This functionally accelerates

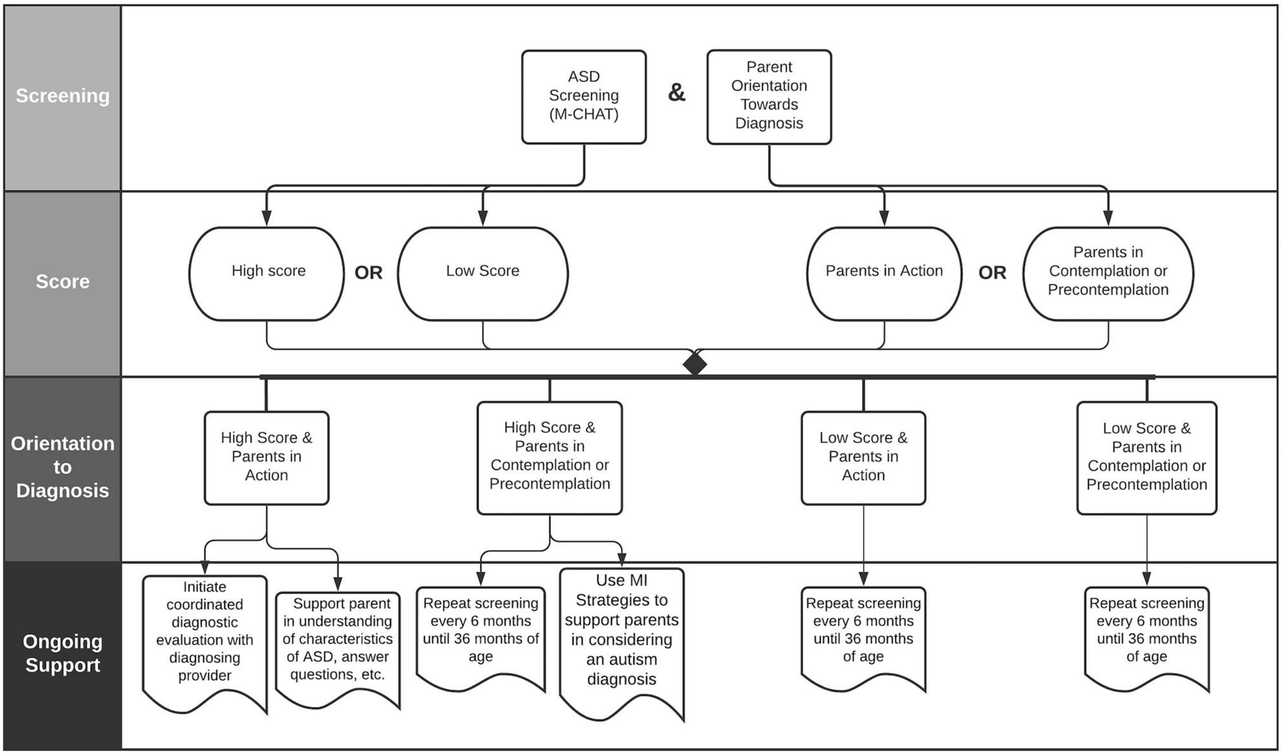

FIGURE 1 | Parent orientation toward diagnosis flowchart.

the diagnostic process. But also, by combining information across organizations and practitioners, a collaborative process is initiated that fits within the context of the publicly funded B-3 system.

The OTAI framework is informed by efforts over the past decade to help primary care physicians, B-3 early interventionists, and psychologists learn and implement universal screening for ASD and reduce health inequities (33). A fundamental framework tenet is that when there are developmental concerns about a child, *all roads should lead to B-3 programs as the first stop*. This means that whoever raises concerns about ASD or developmental characteristics associated with ASD; pediatrician, parent, day care provider, or extended family member, the child should be referred to B-3 for evaluation for services. We propose that the following practices, implemented by B-3 centers, can reduce the gap between emerging ASD and accessing ASD services.

PRACTICE 1: UNIVERSAL SCREENING BY B-3 STAFF

Conduct ASD Screening

Based on existing recommendations for universal ASD-specific screening for primary care medical providers (8) and leveraging the broad reach of the B-3 system, we recommend that B-3 organizations ensure ASD screening is carried out for all children during their eligibility assessment. Specifically, B-3 providers may either:

- Review existing pediatric ASD screening records prior to B-3 evaluation, OR
- If screening has not yet been conducted, or is not made available, B-3 centers should intentionally screen all children for ASD at their eligibility intake meeting.

Standardized developmental testing, including parent reports, is conducted as part of the B-3 eligibility assessment. The OTAI model suggests universal screening, a novel addition to the standard B-3 assessments and questionnaires. B-3 staff should:

- Administer and score the Modified Checklist for Autism in Toddlers (M-CHAT-R/F), using the standardized follow-up questions (34) or
- Review results of any recent M-CHAT screening from a community provider (see **Figure 1**).
  - If the M-CHAT score indicates further ASD evaluation is warranted, the B-3 provider should assess the parent's orientation toward a diagnosis
  - If the M-CHAT does not indicate further evaluation is warranted, B-3 staff should:
    - ∗ Determine whether direct observation or reports from collateral contacts warrant further ASD evaluation.

* If there is no need for further assessment, B-3 staff should make note of the administration date, continue surveillance for ASD signs, and repeat the M-CHAT every 6 months until 36 months of age (35, 36).
* If at any point concerns about ASD are raised by parents or B-3 team, the B-3 provider should initiate the M-CHAT screening process as above.

Introduce the Idea of ASD

The OTAI framework proposes that services should be adapted to meet the needs of parents with different orientations toward receiving, understanding, and acting on diagnostic information. The OTAI framework is designed to help B-3 staff provide support consistent with parental orientation to a diagnosis to move the parent toward engagement with ASD-specific intervention when the time is right for them and in a way that is responsive to parental concern.

Parental responses to early signs of ASD and referral for a diagnostic evaluation range from hesitancy due to fear of labels or stigma, to defensiveness when concerns are brought up by providers, to acceptance or feelings of validation (37, 38). When a child shows characteristics of ASD, the OTAI model suggests the B-3 provider should individualize a plan for working with parents. The first step is to determine the level of caregiver concern about the child and orientation toward diagnosis. The Stages of Change Theory (39) and Motivational Interviewing (MI) strategies (40) have been incorporated into the OTAI framework to help families prepare for diagnostic evaluations when they are ready. These models have been applied in parent coaching for ASD (41) but, to our knowledge, have not yet been applied to support parents in the initial screening and diagnostic referral process.

Parents respond to screening results differently depending upon their orientation toward diagnosis.

- Action: Some parents have been thinking and learning about ASD and are waiting for a provider to suggest they seek out a diagnostic appointment.
- Contemplation: Some parents may be open to the possibility of ASD but are weighing the pros and cons and are still not quite ready to act and schedule a diagnostic evaluation.
- Precontemplation: Some parents may be adjusting to the developmental concerns that led them to B-3 services and have not considered the idea that their child may have ASD. These parents are unlikely to schedule a diagnostic evaluation and if they do, they may not be comfortable with the diagnosis or with seeking ASD-specific services.

PRACTICE 2: PREPARE FOR DIFFICULT CONVERSATIONS AND SUPPORT

If concerns about ASD are indicated on the M-CHAT, but parents are contemplating or not yet contemplating a diagnosis, clinicians should support parental orientation toward a diagnosis and intervention by preparing for difficult conversations and engaging families in conversation.

- Prepare for difficult conversations: B-3 providers should prepare to engage parents using MI strategies to collaboratively explore the ASD characteristics that need further evaluation and to highlight a child's strengths in addition to behavioral and developmental concerns (42).
- Engage in conversations: B-3 providers can engage in ongoing conversations with families about child developmental concerns and positive ASD screens thereby avoiding the pitfall of implicitly or explicitly encouraging families to "*wait and see.*" B-3 providers are experts at supporting families. Sharing additional information about ASD and engaging families in these conversations should aim to support parental orientation toward diagnostic evaluation.

- Parents in the action stage may benefit from:
  - Information about local diagnosing providers
  - Ongoing discussion and information specific to their child
  - Help scheduling and completing the diagnostic evaluation
  - Post-diagnosis navigation support.

- Parents in the contemplation and precontemplation stages may benefit from:
  - Discussing the behaviors on the M-CHAT that suggest ASD
  - Opportunities to ask questions about the assessment, their child's behavior, and other concerns.
  - Conversations about ASD using MI strategies to support orientation towards diagnostic evaluation over the first few months in B-3 services.

In collaboration with B-3 partners, OTAI developed a tool to measure parental orientation towards diagnosis and collect other information relevant to the diagnostic process. This B-3 provider-rated form (available upon request) is designed to support the B-3 provider in tailoring discussions to the parental level of concern and, once a parent decides to pursue a diagnosis, to facilitate efficient and relevant conversations between the B-3 team and the diagnosing clinician. Utilizing the knowledge and expertise of the B-3 provider specific to each family and child is a novel contribution that could support both parents and diagnosing providers when it comes to accelerating access to timely diagnosis. Information for the diagnostic clinician includes:

- Services the child is currently receiving through B-3 agency
  - Child skills and needs in relevant developmental domains (communication, play, social, sensory behaviors, restricted/repetitive behaviors)

- B-3 team impressions of likelihood of ASD
- B-3 team impressions of parental concern regarding ASD (see **Table 1**)
- Child strengths
- Family support needs

PRACTICE 3: REFERRAL TO COLLABORATIVE DIAGNOSTIC EVALUATION

Once a parent decides to pursue a diagnostic evaluation, an innovative collaborative diagnostic model is recommended. The OTAI model suggests the formation of partnerships between B-3 agencies and local diagnosing clinician(s); psychologists, pediatricians, neurologists, or other professionals, consistent with state law. The collaborative diagnostic model delineates roles for the B-3 provider and diagnostic clinicians and weaves these roles together in a meaningful way to best support the family and accelerate the diagnostic process. B-3 referral for a collaborative diagnosis includes two steps:

- Parental release of information to share B-3 records with diagnostic clinician
- Conversation between B-3 and diagnostic clinician to share relevant information about the child and family

PRACTICE 4: ACCELERATED DIAGNOSTIC EVALUATION

The accelerated diagnostic evaluation utilizes recommended practices (32) for accurate, high-quality diagnosis modified for use in a collaborative partnership with B-3 providers to reduce the amount of time and resources required for diagnosis.

- Diagnostic clinician - Pre-meeting data review:
  - Contact family and schedule first diagnostic visit. Diagnosing clinicians should set a goal to complete the first visit as soon as possible and track how long this takes.
  - Contact B-3 provider to discuss case with child's team.
  - Review records and assessment results provided by B-3 team; medical and developmental history, standardized developmental assessment, M-CHAT screening results, and other relevant records.

Following the pre-meeting data review, the diagnostic clinician will conduct a single, 3-h diagnostic appointment consisting of a parent interview, child-parent play observation, ADOS administration, and diagnostic disclosure. The child, caregivers, and B-3 provider should be in attendance. Involving the B-3 provider in the diagnostic evaluation and disclosure as standard practice is novel and facilitates a coordinated transition between diagnosis and post-diagnosis services. The diagnostic disclosure should include examples of observed child behaviors across the core ASD diagnostic categories, intervention recommendations, and individualized family support information.

Following the diagnostic appointment in accordance with existing clinical practice recommendations, the diagnostic clinician will write a diagnostic report to be shared with the family and B-3 intervention team. The report should include behavioral observations, diagnostic information and scores, intervention recommendations (including a prescription for ABA), and family support resources.

PRACTICE 5: SEAMLESS TRANSITION TO ASD NAVIGATION AND INTERVENTION

Once a family has received an ASD diagnosis, they should immediately be offered ASD navigation support as part of their ongoing B-3 services. Navigators can be B-3 service providers of any discipline who have additional training in helping families find ASD-specific services and resources. The family should be assigned an ASD navigator and meet quickly (e.g., within a week) to review the evaluation process, psychologist feedback, and recommendations. The primary role of the navigator is to provide parents with follow-up support, information, and resources after diagnosis. Navigators help parents understand their child's ASD characteristics, seek out resources, pursue and evaluate interventions for the child, and process emotions related to the diagnosis.

DISCUSSION

The OTAI project suggests that, with adequate funding and support, B-3 intervention service systems can serve a critical and novel role in the effort to increase equitable access to timely diagnosis of ASD through community partnerships with diagnosing clinicians. Novel practices are proposed that are in line with accepted clinical practice and use valid and reliable measures. Telephone surveys conducted with B-3 providers in the state of California found that although 85% of agencies conduct screening for ASD, only 39% offer diagnostic evaluations prior to age three (43). The OTAI framework, based on partnerships and pilot work in the Pacific Northwest of the US, resulted in the diagnosis of over 120 children by a single provider working part time over 2 years. Parents waited less than 3 months for a diagnosis once they were referred.

Studies examining the parent perspective of diagnosis suggest a need for improvement and innovation. When given opportunities to share about their experiences of the diagnostic process, parents highlighted a need for more information and follow-up after diagnosis (37, 44). Similarly, parents indicated a need for more time during diagnostic feedback meetings, additional follow-up visits, and additional resources about ASD (45). Embedding the diagnostic process into the B-3 experience addresses these concerns since children and families are already working with and receiving support from B-3 providers and programs.

There are several limitations and considerations for future work. Our project staff engaged closely with community providers to increase acceptability and feasibility of the referral and diagnostic process. Despite our efforts to ensure a good fit in our region, this may not be applicable to other communities. Finding diagnostic providers to engage in novel, collaborative diagnosis may be challenging due to structural barriers like low insurance reimbursement or lack of providers with expertise in diagnosis of children under age three. Furthermore, there are questions related to costs of training B-3 providers and logistics, such as who will provide the training, that could impede the implementation of this framework. Finally, the OTAI project was small and focused locally. Scaling up the project to meet the complex and different needs of other regions has not yet been tested. Future efforts are needed to engage community partners to make adaptations to the model that will increase acceptability and feasibility. Additionally, well-designed implementation research is needed to better understand the impact of these practices.

The OTAI Project to date has focused on conducting development field work with partner B-3 agencies. OTAI staff have conducted all diagnoses. The next phase of research will implement the OTAI framework with community diagnostic clinicians and new B-3 agencies. In this next phase, OTAI will provide training but will not provide direct services within B-3 agencies. This will achieve two major purposes, (1) larger scale implementation and testing of the framework, and (2) feedback from community partners to inform novel design and implementation considerations. Further refinement of the OTAI framework will help ensure acceptability and feasibility in a wide range of communities.

For decades large-scale studies have documented delays between first concerns and ASD diagnosis, with greater delays for children of color and those with fewer resources. This research and practice gap suggests the need for innovative advances toward sustainable implementation (46). The OTAI framework presented here is the outcome of an iterative process of co-creating an innovative practice to begin addressing this gap. Children and families received services and the framework was refined collaboratively with providers in the B to 3 system. Within this framework, novel and collaborative concrete actions are proposed which could lead to increased widescale implementation of faster and more equitable diagnosis through the B-3 system, which is available to all regardless of ability to pay. Randomized trials and implementation research methods are needed to further evaluate this model. It is our hope that by reframing ASD diagnosis and intervention to "on-time" rather than "early" and by community replication and refinement of the OTAI practice framework, that other communities may benefit from this work.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

AP, JG, IS, and AE devised the project, main conceptual ideas, and framework outline. AP wrote the manuscript with input from all authors. JG implemented and field tested the framework. IS and AE were in charge of overall direction and planning of the project. All authors discussed the results and commented on the manuscript.

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ORIGINAL RESEARCH
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Prenatal GABAB Receptor Agonist Administration Corrects the Inheritance of Autism-Like Core Behaviors in Offspring of Mice Prenatally Exposed to Valproic Acid

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This study was performed to evaluate the effects of prenatal baclofen (a GABAB receptor agonist) treatment on the inheritance of autism-like behaviors in valproic acid (VPA)-exposed mice. VPA model mice (first generation, F1) that were prenatally exposed to VPA exhibited robust core autism-like behaviors, and we found that oral administration of baclofen to F1 mice corrected their autism-like behavioral phenotypes at an early age. Based on a previous epigenetics study, we mated the F1 male offspring with litter females to produce the second generation (F2). The F2 male mice showed obvious inheritance of autism-like phenotypes from F1 mice, implying the heritability of autism symptoms in patients with prenatal VPA exposure. Furthermore, we found prenatal baclofen administration was associated with beneficial effects on the autism-like phenotype in F2 male mice. This may have involved corrections in the density of total/mature dendritic spines in the hippocampus (HC) and medial prefrontal cortex (mPFC), normalizing synaptic plasticity. In this research, GABAB receptor agonist administration corrected the core autism-like behaviors of F1 mice and protected against the inheritance of neurodevelopmental disorders in the offspring of F1 mice, suggesting the potential of early intervention with GABAB receptor agonists in the treatment of neurodevelopmental disorders.

Keywords: autism spectrum disorder (ASD), valproic acid (VPA), baclofen, GABAB, inheritance, mice

INTRODUCTION

Autism is a lifelong neurodevelopmental disease and one of the most serious developmental psychiatric disorders known today; in 2013, the diagnoses of "autism" and several other disease categories were incorporated into the single diagnostic category "autism spectrum disorder" (ASD) (Diagnostic and Statistical Manual of Mental Disorders, DSM-5) (1, 2). The new diagnostic criteria include social/communication deficits (criterion A) and restricted, repetitive patterns of behaviors, interests, or activities (criterion B). These symptoms are present beginning in early childhood (criterion C) and limit or impair daily life (criterion D) (2, 3).

In recent years, the incidence of ASD has increased persistently (4, 5). Based on its complex pathophysiological mechanism and lack of effective drug treatments, ASD has attracted attention worldwide (6–9). While autism has a strong genetic component, environmental factors, including intrauterine exposure to drugs, toxins, pesticides, and infection, are known to confer susceptibility to autism (6, 10, 11). Accumulating clinical evidence suggests that prenatal exposure to the anti-epileptic drug valproic acid (VPA) is associated with an increased risk of ASD, neurodevelopmental delay, and cognitive deficits in children (10–12). Consistent with clinical evidence, rodents prenatally exposed to VPA exhibit behavioral deficits resembling autism-like symptoms (12).

Animal studies have shown that *in utero* exposure to VPA in rodents represents a robust model of autism that exhibits face, construct and predictive validity (6, 11). This model has been widely used in preclinical research to reveal the etiology of environmental factors contributing to ASD and identify new drug treatment targets (12). Studies have found that VPA rodent models exhibit robust behavioral changes and molecular pathology involving dysfunctional GABAergic signaling, extensive alterations in neuronal morphology and local neocortical microcircuit disruption (13–22). Dysregulation of the GABAergic system and excitatory-inhibitory (E-I) imbalance have commonly been observed in rodent models of autism (16, 23), and correction of these changes with pharmacological interventions normalizes core autism-like phenotypes in these animals (24, 25). According to recent studies, the autism-like symptoms in a genetically defective mouse model of ASD were corrected by the GABAB2 receptor agonists baclofen and arbaclofen (STX209, an exploratory drug comprising the single, active R-enantiomer of baclofen) (26–30). Although the results of the majority of clinical trials also supported the therapeutic effect of R-baclofen (31–35), the phase 3 clinical trial of arbaclofen for the treatment of patients with fragile X syndrome presenting the ASD phenotype was prematurely terminated due to lack of efficacy (but the highest dose exerted a beneficial effect on treated children) (36). Hence, we infer that GABAB receptor agonists are effective treatments for some but not all subgroups of patients with ASD. The possible therapeutic effect of GABAB agonists on children with ASD caused by environmental factors (such as VPA) aroused our attention. In addition, there are no relevant reports have assessed oral baclofen administration in mice/children prenatally exposed to VPA. Part of the present study showed that long-term oral treatment with baclofen attenuated autism-like behaviors in young F1 mice, suggesting that the GABAB receptor agonist treatment could correct the core autism-like symptoms in mice prenatally exposed to VPA.

Additionally, ASD is also accompanied by a high risk of transmission to the next generation (37–40), and epigenetics may play an important role in this process (41–43). Studies have verified that epigenetics might be implicated in the mechanisms underlying neurodevelopmental disorders caused by VPA (10–12, 44). Recent research showed that the offspring of male mice prenatally exposed to VPA (F1) mated with control female mice transmit the autism-like phenotype to the F2 and F3 generations (45, 46), suggesting that prenatal exposure to VPA causes autism-like symptoms with strong heritability. Meanwhile, a report showed that pregabalin (a GABA analog) administered during the pregnancy period could correct autism-like behavioral defects in rats prenatally exposed to VPA (47). Based on the above results, prenatal intervention with baclofen in the offspring (F2) of VPA-exposed mice (F1) with autism-like behaviors aroused our interest.

The results indicated that (1) the offspring produced by mating within the same litter of F1 mice exhibited obvious autism-like behaviors, suggesting that the autism-like symptoms of F1 mice were inherited by the next generation; and (2) prenatal administration of baclofen corrected autism-like symptoms in F2 mice by correcting the defects in the density of total/mature dendritic spines in the hippocampus (HC) and medial prefrontal cortex (mPFC). The morphology and density of dendritic spines play crucial functional roles in synaptic plasticity and, consequently, in learning and memory processes (48). Therefore, the activation of the GABAergic pathway may exert beneficial and profound effects on early brain development in F2 mice.

MATERIALS AND METHODS

Animals

Breeding pairs of C57BL/6J mice were purchased from Ningxia Medical University Laboratory Animal Center (Ningxia, China) and housed in a conventional mouse vivarium at the Feeding Unit of Ningxia Medical University Craniocerebral Laboratory (Ningxia, China). Each male mouse was housed in a single cage, and female mice were housed in groups of 2 (random allocation). Standard rodent chow and tap water were available ad libitum. All mice were maintained under standard laboratory conditions at 22 ± 22°C with 50 ± 10% relative humidity and a 12-h light/dark cycle. For the present experiments, a total of 67 male offspring from 22 dams have been used.

Breeding Process

Breeding pairs mice aged ∼10 weeks, with female mice weighing 20–25 g and male mice weighing 22–25 g. Precontact between male and female mice was established for 3 days to regulate the fertility cycle, and when the females were in a proestrus state, the animals were allowed to mate overnight, namely, from 5 p.m. to 8 a.m. the next day. Detection of a vaginal plug in female mice was designated 0.5 days of pregnancy. Because of the precontact procedure, female pregnancy and pup birth occurred within a 3-day period. All mice were handled according to protocols approved by the Institutional Animal Care and Use Committee of Ningxia Medical University (IACUC Animal Use Certificate No. 2019-152). All efforts were made to minimize the number of animals used and their suffering.

Prenatal VPA Exposure

The pregnant mice (F0 mice) were housed separately and divided into vehicle- and VPA-exposed groups. VPA (Sigma Aldrich, St. Louis, MO, USA) was purchased and dissolved in 0.9% saline at a 10 mg/ml concentration. Prenatal VPA exposure was induced using a new method (49) in which female mice in the VPA-exposed group received two doses each of 300 mg/kg VPA on embryonic days 10 (E10) and E12, and vehicle-exposed group females were injected with the same amount of physiological saline (NS) on the same days. The female mice raised their litters. Male offsprings (F1 mice) of VPA-exposed group females and male offsprings (CTRL mice) of vehicle-exposed group females were weaned on postnatal day 21 (P21) and labeled with ear tags. Because the ASD-related behavior of male VPA-exposed mice is more stable than that of female mice in this model (10, 44, 50), male offspring were used in all subsequent experiments (**Figure 1A**). Considering the differences in characteristics between different breeding pairs, we equally divided the litters of VPA model mice into a baclofen intervention group and a control group, excluding the last mouse when the number of males in a litter was odd. We also ensured that the fathers of the CTRL and F1 mice were the same male mice to the greatest extent possible to reduce the "litter effect" (51).

Breeding of F2 Mice

Breeding pairs of F1 mice with no oral baclofen treatment were obtained from the same litter and were ∼10 weeks of age. Female mice weighing 20–25 g and male mice weighing 22–25 g were used. The breeding process was the same as that mentioned above (**Figure 1A**), and male offspring (F2 mice) were used in all subsequent experiments.

Drug Administration

Baclofen Administration to F1 Mice

Baclofen (MedChemExpress, New Jersey, USA) was administered to male F1-Int group mice (F1 mice with oral baclofen treatment) through the drinking water at a dose of 0.5 mg/ml, and CTRL group mice and F1-Con group mice (F1 mice with no oral baclofen treatment) were provided normal drinking water (control water) from weaning (P21) until the end of the experiment (P60) (**Figure 1G**). The baclofen dose was selected based on the effective dose for neuropathy and ASD-like symptoms in experimental animal studies (26, 30, 52, 53). We implemented many measures to ensure that each animal received the exact dose of baclofen. These measures include ensuring a constant temperature and humidity in the room, changing drinking water containing drugs daily, placing mice of approximately the same weight in the same cage, and restricting the number of breeding animals in the cage (not more than 4 mice per cage).

Aspartame (MedChemExpress, New Jersey, USA) was added at a concentration of 0.1% to reduce the bitter taste of baclofen. Control water contained aspartame only. All drinking water was refreshed three times a week.

Baclofen Administration to F2 Mice

Baclofen was administered through the drinking water using the method described above 3 days before mating to ensure that a stable baclofen concentration was achieved in breeding pairs. The pregnant F1 mice were administered baclofen until delivery. Control pregnant females received normal drinking water during the same period (**Figure 1G**).

Growth and Development

The body weight and tail length of all offspring mice (F1 and F2 mice with no oral baclofen treatment) were recorded at weeks 3, 4, and 5 after birth. Pup weight was measured by placing the mouse on the balance and obtaining the reading after the mouse had remained still for 2 s. Pups were weighed twice, and the mean value was calculated. The pup tail length measurement started from the root of the tail, and the length of the tail was measured in the straight state.

A crooked tail was observed in mice and recorded at week 2 after birth (**Figure 1B**).

Autism-Related Behavioral Tests

The social interaction test and marble-burying test were completed with F1 and F2 mice in the 8th week after birth, the novel object recognition task was completed in the 7th week after birth, and the open-field task and open-field habituation task were completed in the 7th week after birth. All behaviors of the animals were recorded using a computerized video tracking system (SMART 3.0, Panlab, Spain).

Social Interaction Test

The mice were tested in an automated three-chambered social approach apparatus as previously described (27, 28). The test had two testing phases: (A) the sociability phase (scene 1), in which an unfamiliar mouse (stranger 1) was placed inside a plastic cage in one of the side chambers, an empty cage was placed in the other chamber, and the test mouse was allowed to freely explore the apparatus for 5 min; and (B) the preference for social novelty phase (scene 2), in which a second unfamiliar mouse (stranger 2) was placed inside the cage in the opposite chamber, and the test mouse was allowed to freely explore the apparatus for 5 min. The total time spent in each region and the time spent sniffing the stranger mouse and the empty cage were recorded. The social preference index (SPI) was calculated as (stranger 2 time)/(stranger 1 time + stranger 2 time) in scene 2. The tasks started at ∼9:30 a.m.

Novel Object Recognition Task

The novel object recognition task was performed using a previously reported method with slight modifications (30, 54). The animals were placed in a box containing two identical objects and allowed to explore for 5 min (scene 1). After an interval of 30 s, one object was replaced with a novel object, and the animals were allowed to explore the objects for 5 min (scene 2). The discrimination index (DI) was calculated as (novel object time)/(novel object time + familiar object time). The tasks started at ∼9:30 a.m.

Open-Field Task and Open-Field Habituation Task

The open-field boxes were made of wood (50.0 × 50.0 × 40.0 cm), and an overhead camera was used for automatic tracking of animal behaviors using SMART 3.0 software. The box was divided into two zones: an "inner" zone (a 30 × 30 cm^2 central square) and an "outer" zone (10 cm from the walls). The duration of the test was 10 min (task 1).

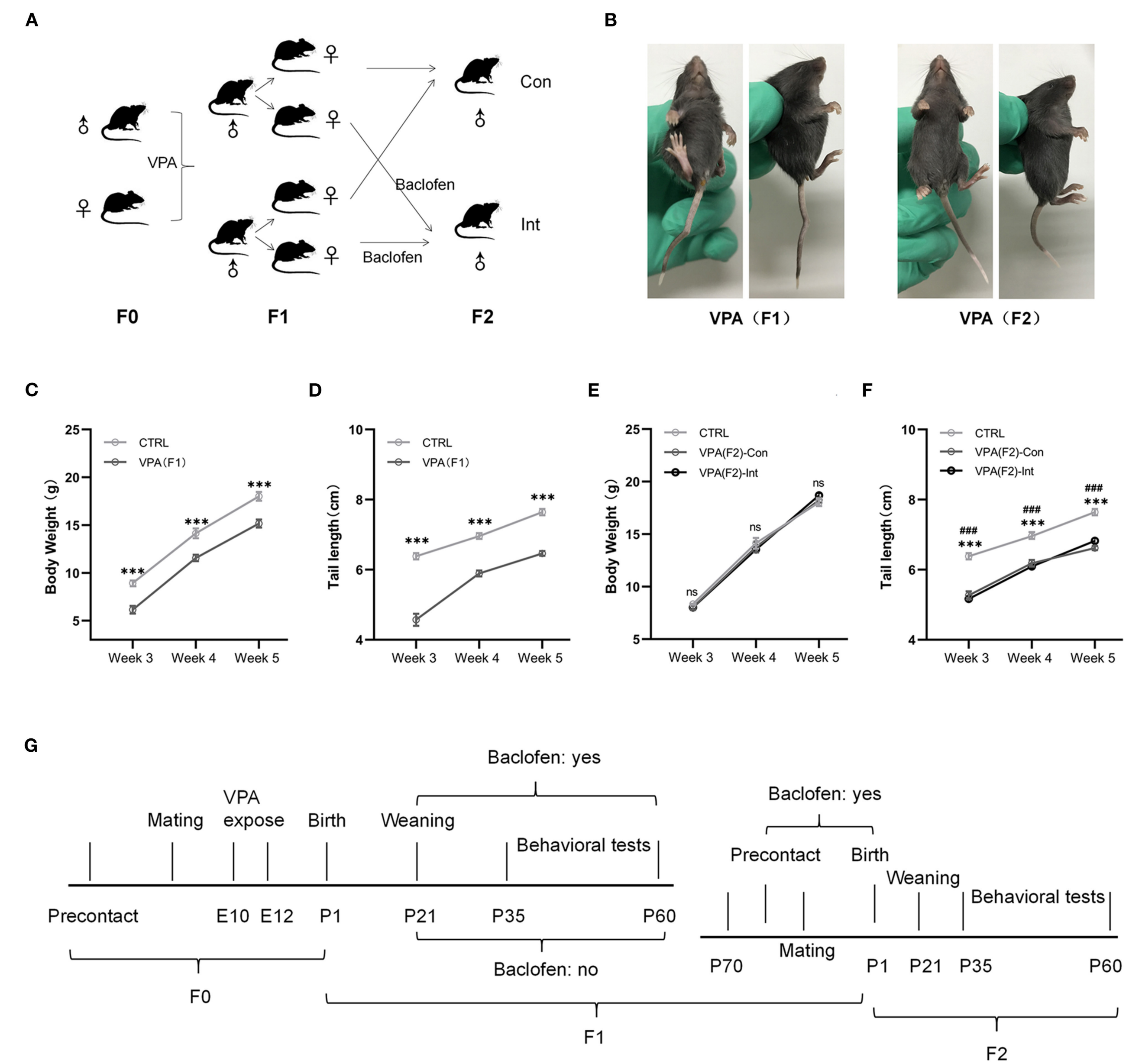

FIGURE 1 | F1 mice exhibited delayed growth and tail malformations, and F2 mice exhibited delayed tail growth without malformation. **(A)** The schematic diagram of F1 and F2 mice breeding. **(B)** The pictures of F1 mice show a tail deformity, and F2 mice did not show any tail deformity. **(C,D)** The body weight and tail length of male F1 mice were lower than those of male control mice from postnatal week 3–week 5 [two-way analysis of variance (ANOVA) followed by Bonferroni *post-hoc* test, *n* (CTRL vs. F1) = 14:14, $^{***}p < 0.001$]. **(E,F)** Compared to CTRL group mice, male F2-Con (without prenatal baclofen intervention) and male F2-Int (with prenatal baclofen intervention) mice did not show a significant difference in body weight, but the tail length of F2-Con and F2-Int mice was lower than that of male CTRL group mice in postnatal week 3–week 5 [two-way analysis of variance (ANOVA) followed by Bonferroni *post-hoc* test, *n* (CTRL vs. F2-Con vs. F2-Int) = 14:12:13, $^{***}p < 0.001$]. All data for all figures are plotted as the mean ± SEM. **(G)** A representative timeline of the experimental process. E: embryonic day; P: postnatal day; F0: CTRL mice; F1: first-generation mice (VPA-exposed mice); F2: second-generation mice (offspring of VPA-exposed mice); F1-Con: F1 mice with no oral baclofen treatment; F1-Int: F1 mice with oral baclofen treatment; F2-Con: F2 mice with no prenatal baclofen treatment; F2-Int: F2 mice with prenatal baclofen treatment; **#** indicates a comparison between the CTRL group and F2-Con groups; * indicates a comparison between the control (CTRL) group and F2-Int groups.

Inspired by a previous report (30), we repeated the open-field test at 24-h intervals and measured the same indexes (task 2). The open-field exploration index (OFEI) was calculated as the distance traveled in the inner zone/the total distance traveled. The tasks started at ∼9:30 a.m.

Marble-Burying Test

The tested mouse was placed in a black cage containing 16 marbles arranged in a 4 × 4 grid on clean rice husk bedding up to 5 cm in height. Before the test began, each mouse was acclimated to the cage with rice husk bedding without marbles for 3 min of habituation. The duration of the test was 10 min. Marbles with >75% of their surface buried in the bedding were counted and recorded. Digital images and movies of the marbles were captured during the test period. The numbers of buried marbles and actions (strong and obvious digging or burial movement) were counted from the digital images and movies by trained persons ($n = 3$) who were not associated with this experiment. The operation of the marble-burying test is relatively simple, does not require much energy from the experimental researchers, and observes the active state of mice at night. We performed the test at ∼21:30 at night to save time in the experiment.

Golgi-Cox Staining

In this study, we used the Golgi-Cox staining method to observe the dendritic spines of cerebral neurons. Golgi staining is a powerful technique for providing a complete, detailed representation of a single neuron. With this staining procedure, neuronal spines are observed, which are located on dendrites, receive electric signals from other neurons and are involved in neuronal plasticity. After deep anesthesia was induced with isoflurane, the mice were decapitated, and the brains were removed in a low-temperature environment (operating on ice) and soaked in a mixed AB liquid (FD Rapid GolgiStain™ Kit, NeuroTechnologies, Ellicott City, MD, USA). After 3 weeks, brain tissues were sliced with a vibrating slicer (VT1000S; Leica, Germany) and soaked in liquid C. The thickness of each slice was 100 μm. Five days later, slices were stained with dye solution (solution D:solution E:distilled water; 1:1:2) for 10 min, after which the slices were rinsed with distilled water, dehydrated with an ascending series of ethanol solutions, and cleared in xylene for more than 2 h. Finally, the slices were sealed on slides with neutral resin and dried in the dark.

Dendritic Spine Analysis

Images of spines in selected brain regions (mPFC; ventral and dorsal HC) were obtained with the Extended Depth of Focus module of a Nikon Eclipse microscope (Shanghai, China), 3D dendritic spine images were combined into a plan view, and ImageJ (Fiji) analysis software was used to evaluate the dendritic spine density in the images.

Statistical Analysis

Statistical analyses were performed using GraphPad Prism 8.0 software. The results of the statistical tests were considered significant at $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$. Data are presented as the means ± SEM. The body weight and tail length of mice recorded weekly were analyzed using two-way ANOVA. The data from the social interaction test, novel object recognition task and the spine morphological study were analyzed using one-way ANOVA. Open-field task (task 1) and open-field habituation task (task 2) were analysed using paired Student's t-test for comparing the differences between different tasks in the same group and one-way ANOVA for comparing the differences among groups in the same task. Marble burying test data were analysed using Pearson correlation, linear regression analysis and one-way ANOVA. All ANOVAs were followed by Bonferroni *post hoc* test to compare the differences among the groups.

RESULTS

Tail Malformations in F1 Mice but Not in F2 Mice

Neural tube defects (NTDs) may result from genetic mutations, malnutrition or exposure to teratogens during gestation (55). Tail malformations are often used as a sign of successful modeling in F1 mice (11, 56). The crooked tail phenotype was observed in all F1 mice but was not observed in all F2 mice in the present experiment (**Figure 1B**), indicating that the crooked tail phenotype associated with NTDs caused by VPA exposure in F1 mice was not transmitted to F2 mice.

Growth Retardation in F1 Mice

We measured the body weight and tail length of male pups weekly between postnatal days 14 and 35 (**Figures 1C,D**). The body weight of F1 mice was significantly lower than that of control (CTRL) mice in weeks 3–5 ($F_{1,78} = 67.47$, week 3: $^{***}p < 0.0001$; week 4: $^{***}p < 0.0004$; week 5: $^{***}p < 0.0001$). The tail length of F1 mice was also significantly shorter than that of control mice in weeks 3–5 ($F_{1,78} = 255.0$, week 3: $^{***}p < 0.0001$; week 4: $^{***}p < 0.0001$; week 5: $^{***}p < 0.0001$). The results indicated that F1 mice exhibited severe postnatal growth retardation. This finding is consistent with the characteristics of developmental delay in VPA model mice.

Normal Body Weight Growth but Tail Dysplasia in F2 Mice

The body weights of F2-Con (offspring of F1 mice without prenatal baclofen intervention) mice and F2-Int (offspring of F1 mice with prenatal baclofen intervention) mice were not significantly different from those of male CTRL mice in weeks 3–5. However, the tail length of F2-Con and F2-Int pups was significantly shorter than that of CTRL mice in weeks 3–5 ($F_{2,108} = 143.6$, CTRL vs. F2-Con, week 3: $^{\#\#\#}p < 0.0001$; week 4: $^{\#\#\#}p<0.0001$; week 5: $^{\#\#\#}p < 0.0001$); ($F_{2,108} = 143.6$, CTRL vs. F2-Int, week 3: $^{***}p < 0.0001$; week 4: $^{***}p<0.0001$; week 5: $^{***}p < 0.0001$). No significant difference was observed in tail length between F2-Con and F2-Int pups (**Figures 1E,F**). Based on these results, F2 mice exhibited tail dysplasia but did not exhibit an altered body weight. The explanation for this result may be related to the reduced VPA exposure-induced damage in F2 mice compared with F1 mice, but the decrease in tail length in F2 mice may be related to a mild NTD.

Baclofen Treatment Corrected Sociability Deficits in F1 Mice

During scene 1, "sociability" was defined as the propensity to spend time in the cage containing stranger 1 compared with the time spent alone in the identical but empty opposite cage. The session indicates the interest in social cues of tested mice (6, 57–60).

As the **Figure 2A** showed, the F1-Con mice (F1 mice with no oral baclofen treatment) spent more time examining the empty cage than the CTRL mice ($F_{2,39} = 5.56$, $^{**}p = 0.0082$) in scene 1 (**Figure 2C**). F1-Con mice spent less time in the region of the cage containing stranger 1 than CTRL mice and F1-Int mice (F1

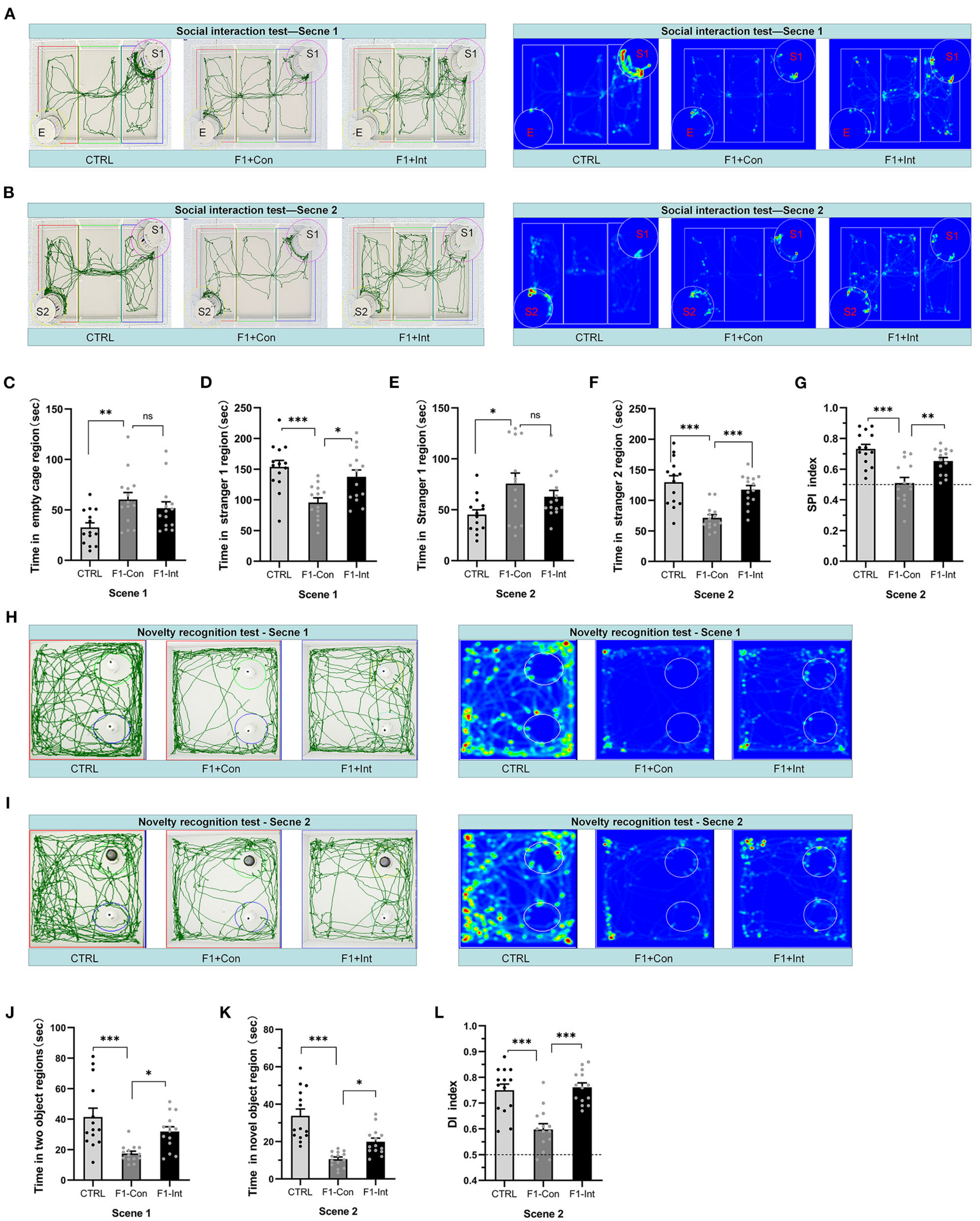

FIGURE 2 | Baclofen treatment corrected social interaction and novelty recognition deficits in F1 mice. S1 = stranger 1 mouse; S2 = stranger 2 mouse; E = empty. **(A)** Representative traces and heatmaps of mice in the sociability phase (scene 1). **(B)** Representative traces and heatmaps of mice in the preference for the social novelty phase (scene 2). **(C)** The time that tested mice entered the region of empty cage for sniffing in scene 1. **(D)** The time that tested mice entered the region containing stranger 1 for sniffing in scene 1. **(E)** The time that tested mice entered the region containing stranger 1 for sniffing in scene 2. **(F)** The time that tested mice

(Continued)

FIGURE 2 | entered the region containing stranger 2 for sniffing in scene 2. **(G)** The SPI of tested mice in scene 2. **(H,I)** Representative traces and heatmaps of tested mice in the novel object recognition task. **(H)** Traces of mice exploring the regions containing the two similar objects (white plastic bottles) in phase 1 (scene 1). **(I)** Traces of mice exploring the region containing the novel object (black glass bottle) in phase 2 (scene 2). This test was used to assess novelty recognition ability. **(J)** The total time spent sniffing the two objects by each group of mice in scene 1. **(K)** The time spent sniffing the novel object by each group of mice in scene 2. **(L)** The discrimination index (DI) for each group of mice in scene 2. **(C–G,J–L)** One-way ANOVA followed by the Bonferroni *post-hoc* test was used: $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$. All data for all figures are plotted as the mean ± SEM. Each group had 14 mice ($n = 14$).

mice with oral baclofen treatment) ($F_{2,39} = 9.37$, CTRL vs. F1-Con: $^{***}p = 0.0005$; F1-Con vs. F1-Int: $^{*}p = 0.0131$, **Figure 2D**). Therefore, F1-Con mice exhibited obvious sociability deficits, and baclofen treatment corrected the deficits.

Baclofen Treatment Corrected Deficits in the Preference for Social Novelty in F1 Mice

As the **Figure 2B** showed, during scene 2, "preference for social novelty" was defined as the propensity to spend time with a new stimulus mouse (stranger 2) rather than with the same stimulus mouse (stranger 1) encountered in scene 1. The session indicates interest in novel social cues of the tested mouse (6, 57–60).

In scene 2, F1-Con mice spent less time in the chamber containing stranger 2 than CTRL/F1-Int mice ($F_{2,39} = 15.58$, CTRL vs. F1-Con:$^{***}p < 0.0001$; F1-Con vs. F1-Int:$^{***}p = 0.0005$, **Figure 2F**); F1-Con mice spent more time in the chamber containing stranger 1 than CTRL mice ($F_{2,39} = 4.26$, CTRL vs. F1-Con: $^{*}p = 0.0179$, **Figure 2E**). More importantly, the SPI of CTRL/F1-Int mice was significantly higher than that of F1-Con mice ($F_{2,39} = 14.14$, CTRL vs. F1-Con: $^{***}p < 0.0001$; F1-Con vs. F1-Int: $^{**}p = 0.005$, **Figure 2G**). The results revealed that the F1-Con mice exhibited an obvious deficit in the preference for social novelty and that baclofen corrected the deficits.

Baclofen Treatment Corrected Novelty Recognition Deficits in F1 Mice

As the **Figures 2H,I** showed, similar to previous reports using other ASD mouse models (28, 30), F1-Con mice showed deficits in the preference for novel objects compared with CTRL mice (CTRL vs. F1-Con: $F_{2,39} = 9.48$, $^{***}p = 0.0003$, scene 1, **Figure 2J**; $F_{2,39} = 22.22$, $^{***}p < 0.0001$, scene 2, **Figure 2K**). Baclofen treatment increased the amount of time F1 mice spent in the region containing the novel object (F1-Con vs. F1-Int: $F_{2,39} = 9.48$, $^{*}p = 0.0395$, scene 1, **Figure 2J**; $F_{2,39} = 22.22$, $^{*}p = 0.0339$, scene 2, **Figure 2K**). The DI is a valuable index that reflects object recognition memory and the preference for novel objects. The DI of F1 mice without baclofen treated, was lower than that of CTRL mice ($F_{2,39} = 18.51$, CTRL vs. F1-Con: $^{***}p < 0.0001$, scene 2, **Figure 2L**) and baclofen-treated F1 mice (F1-Con vs. F1-Int: $F_{2,39} = 18.51$, $^{***}p< 0.0001$, scene 2, **Figure 2L**). Thus, baclofen treatment corrected the deficits in the preference for novel objects in VPA-exposed mice.

Baclofen Treatment Corrected Locomotor and Exploratory Activity Deficits in F1 Mice

As the **Figure 3A** showed, in the open-field task (task 1), F1-Con mice showed lower locomotor and exploratory behaviors than CTRL mice, including decreases in the distance traveled in the inner area (CTRL vs. F1-Con: $F_{2,39} = 4.095$, $^{*}p = 0.0210$, **Figure 3D**) and the OFEI (CTRL vs. F1-Con: $F_{2,39} = 8.992$, $^{***}p = 0.0007$, **Figure 3E**). However, no significant differences in the time traveled in the inner area were observed compared with CTRL mice (CTRL vs. F1-Con: $F_{2,39} = 2.118$, $^{ns}p = 0.3932$, **Figure 3C**). Baclofen treatment did not increase the indicators of locomotor/exploratory activity in F1 mice in task 1 (F1-Con vs. F1-Int: $F_{2,39} = 2.118$, $^{ns}p > 0.9999$, **Figure 3C**; $F_{2,39} = 4.095$, $^{ns}p = 0.3090$, **Figure 3D**; $F_{2,39} = 8.992$, $^{ns}p > 0.9999$, **Figure 3E**). Based on these results, VPA model mice exhibited deficits in locomotor and exploratory activity in a new open environment, and treatment with baclofen did not exert a positive effect on ameliorating these changes in locomotor and exploratory behaviors in F1 mice in task 1.

Inspired by a previous report (30), we redesigned the open-field habituation task (task 2; the two tasks were performed at a 24 h interval) to further evaluate the therapeutic effects of baclofen. As the **Figure 3B** showed, in contrast to task 1, CTRL mice and F1-Int mice traveled a greater distance in the inner area in task 2 (CTRL: $t = 5.612$, df = 13, $^{***}p < 0.0001$; F1-Int: $t = 6.114$, df = 13, $^{***}p < 0.0001$, **Figure 3D**), but not VPA-exposed mice (F1-Con: $t = 0.3125$, df = 13, $^{ns}p = 0.7596$, **Figure 3D**). In addition, in contrast to task 1, the OFEI of F1-Int mice was also increased in task 2 (F1-Int: $t = 6.172$, df = 13, $^{***}p < 0.0001$, **Figure 3E**), but not in F1-Con mice (F1-Con: $t = 0.2737$, df = 13, $^{ns}p = 0.7886$, **Figure 3E**).

In addition, the indicators of the distance traveled in the inner area or the OFEI of F1-Con mice were lower than those of CTRL mice (CTRL vs. F1-Con: $F_{2,39} = 16.77$, $^{***}p = 0.0001$, **Figure 3D**; $F_{2,39} = 9.218$, $^{*}p = 0.0224$, **Figure 3E**) and F1-Int mice (F1-Con vs. F1-Int: $F_{2,39} = 16.77$, $^{***}p < 0.0001$, **Figure 3D**; $F_{2,39} = 9.218$, $^{***}p = 0.0004$, **Figure 3E**) in task 2. Baclofen treatment also increased the time traveled in the inner area by F1 mice in task 2 (F1-Con vs. F1-Int: $F_{2,39} = 4.997$, $^{*}p = 0.0119$, **Figure 3C**). The results revealed that baclofen treatment corrected locomotor and exploratory activity deficits in F1 mice in an open environment that they had been habituated to 24 h previously.

In conclusion, we propose that the differences in the results of the two tasks may have been related to decreases in anxiety and fear. This anxiolytic effect may have been caused by previous experience exploring the same apparatus and familiarity with the environment. However, treatment with baclofen substantially corrected the deficits in F1 mice in recognizing a familiar environment in the open-field habituation task.

Linear Correlation Between the Number of Buried Marbles and Burying Actions in the Marble-Burying Test

We counted the number of marbles buried and burying actions of all groups of mice in the marble-burying test and found that

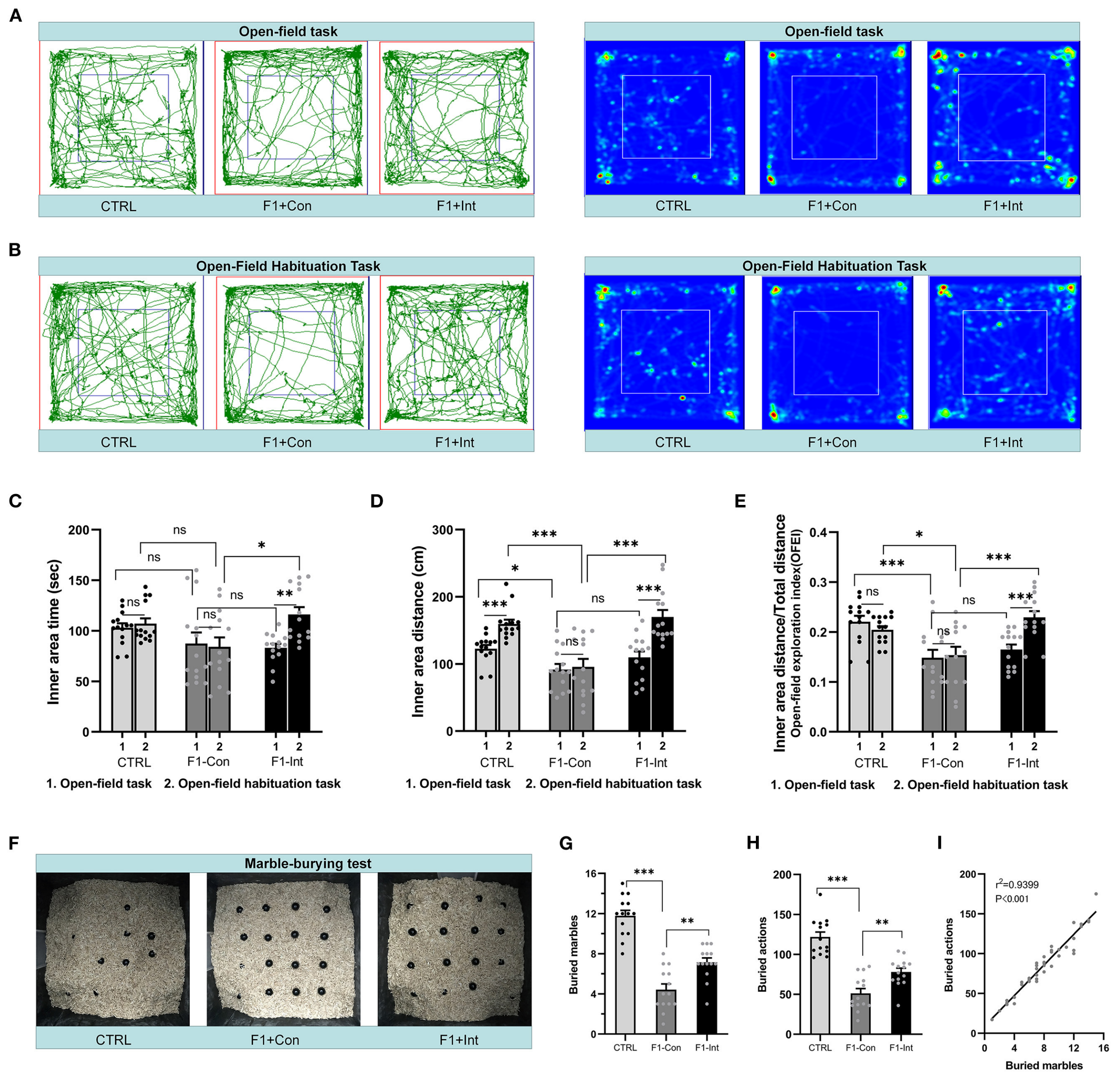

FIGURE 3 | Baclofen treatment corrected the locomotor, exploratory activity and marble-burying deficits in F1 mice. **(A,B)** Representative traces and heatmaps of mice in the open-field task (task 1) and open-field habituation task (task 2). **(C)** Time traveled in the inner zone by mice in the two open-field tasks. **(D)** Distance traveled by mice in the inner zone in the two open-field tests. **(E)** The open-field exploration index (OFEI = distance traveled in the inner zone/the total distance traveled) of mice in the two open-field tasks. In (**C–E**), Student's paired *t*-test was used to compare the differences in behavior in the two tasks between each group of mice, and one-way ANOVA followed by the Bonferroni *post-hoc* test was used to compare the difference in the same task across the four groups; $^{*}p < 0.05$, $^{**}p < 0.01$ $^{***}p < 0.001$. All data for all figures are plotted as the mean ± SEM. Each group had 14 mice ($n = 14$). **(F)** Representative marble-burying maps after the marble-burying test. **(G)** The numbers of buried marbles for each group of mice. **(H)** The number of burying actions for each group of mice. In **(G,H)**, one-way ANOVA followed by the Bonferroni *post-hoc* test was used to compare the differences among groups; $^{**}p < 0.01$, $^{***}p < 0.001$. All data for all figures are plotted as the mean ± SEM. Each group had 14 mice ($n = 14$). **(I)** Pearson correlation and linear regression analysis between the number of buried marbles and the number of burying actions. All mice were included ($n = 42$) in the analysis, and there was a linear correlation between the number of buried marbles and the number of burying actions.

these two measures were linearly correlated ($r^2 = 0.9399$, $^{***}p < 0.001$/Y = 9.628*X + 8.733) (**Figure 3I**). This showed that the marble burying actions in the test were effective, and the time of test is appropriate.

Baclofen Treatment Corrected Marble-Burying Deficits in F1 Mice

As the **Figure 3F** showed, the numbers of buried marbles and burying actions were lower in F1 mice than in CTRL mice (CTRL vs. F1-Con: $F_{2,39} = 51.94$, $^{***}p < 0.0001$, **Figure 3G**; $F_{2,39} = 40.452$, $^{***}p < 0.0001$, **Figure 3H**), indicating that F1 mice showed marble-burying deficits. Baclofen treatment increased these parameters in F1 mice (F1-Con vs. F1-Int: $F_{2,39} = 51.94$, $^{**}p = 0.0019$, **Figure 3G**; $F_{2,39} = 40.452$, $^{**}p = 0.005$, **Figure 3H**), indicating that baclofen exerted a therapeutic effect on marble-burying deficits in F1 mice.

Baclofen Treatment Corrected Sociability Deficits in F2 Mice

As the **Figure 4A** showed, the results did not reveal a significant difference in time spent in the empty cage in scene 1 between the three groups of mice (**Figure 4B**). F2-Con mice spent less time in the region of the cage containing stranger 1 than the CTRL mice and F2-Int mice ($F_{2,36} = 6.722$, CTRL vs. F1-Con: $^{**}p = 0.0032$; F2-Con vs. F2-Int: $^{*}p = 0.0362$, **Figure 4C**).

Based on these results, the F2-Con mice exhibited obvious sociability deficits, and baclofen treatment corrected the deficits.

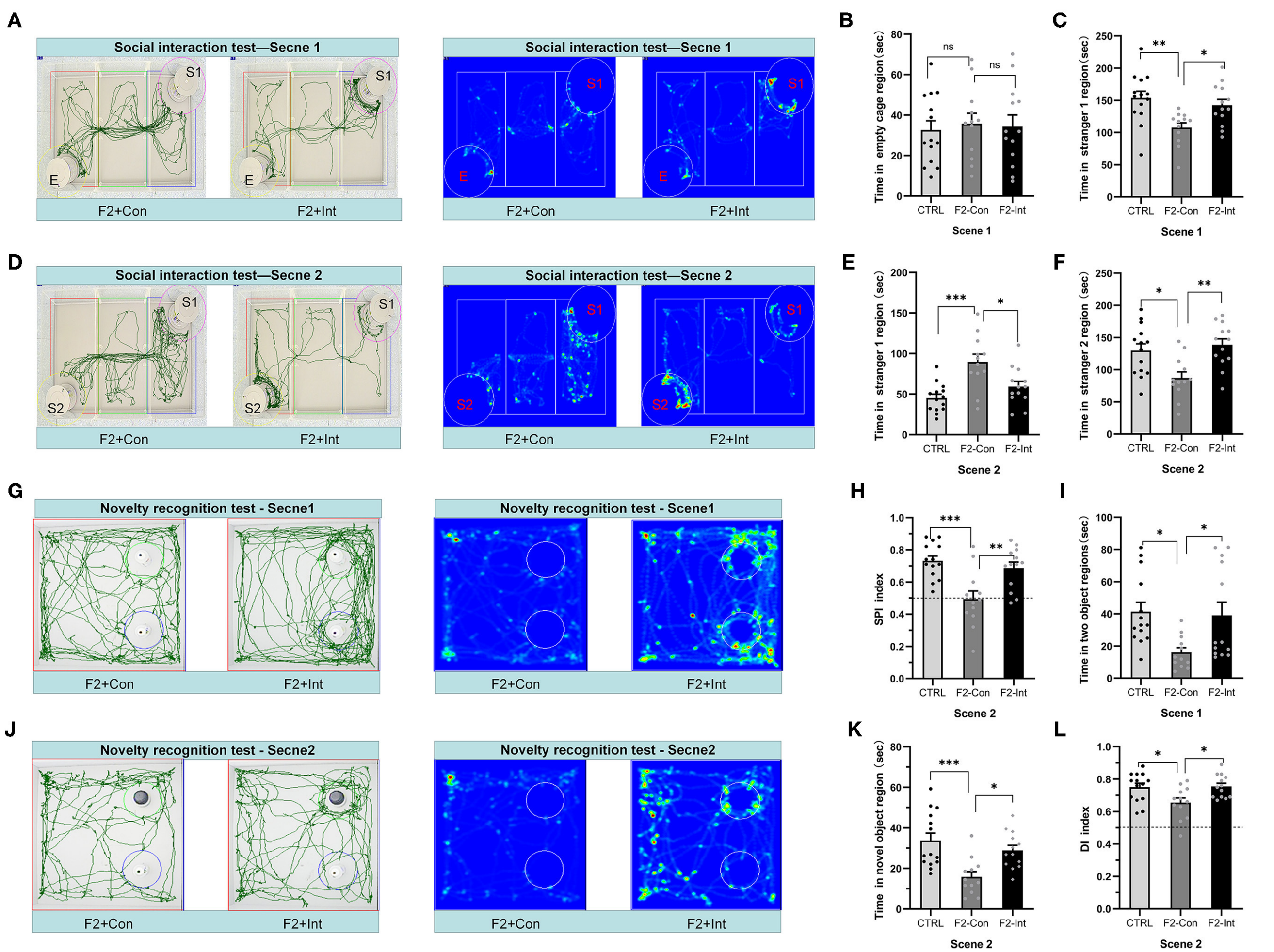

FIGURE 4 | Prenatal baclofen administration corrected social interaction deficits and novelty recognition deficits in F2 mice in the social interaction test. **(A,D)** In the social interaction test, representative traces and heatmaps from tested mice in the sociability phase (scene 1) and preference for social novelty phase (scene 2). **(B)** The time that tested mice entered the region of empty cage for sniffing in scene 1 of the social interaction test. **(C)** The time that tested mice entered the region containing stranger 1 for sniffing in scene 1 of the social interaction test. **(E)** The time that tested mice entered the region containing stranger 1 for sniffing in scene 2 of the social interaction test. **(F)** The time that tested mice entered the region containing stranger 2 for sniffing in scene 2 of the social interaction test. **(G,J)** Representative traces of tested mice in the novel object recognition task. **(G)** Traces and heatmaps of mice exploring the regions containing the two similar objects (white plastic bottles) in phase 1 (scene 1). **(H)** The SPI of tested mice in scene 2 of the social interaction test. **(I)** The total time spent sniffing the two objects by each group of mice in scene 1 of the novel object recognition task. **(J)** Traces and heatmaps of mice exploring the region containing the novel object (black glass bottle) in phase 2 (scene 2) of the novel object recognition task. This test was used to assess novelty recognition ability. **(K)** The time spent sniffing the novel object by each group of mice in scene 2 of the novel object recognition task. **(L)** The discrimination index (DI) for each group of mice in scene 2 of the novel object recognition task. **(B,C,E,F,H,I,K,L)** One-way ANOVA followed by the Bonferroni *post hoc* test was used to compare the differences among groups: $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$. All data for all figures are plotted as the mean ± SEM. n (CTRL: F2-Con: F2-Int) = 14:12:13.

Baclofen Treatment Corrected Deficits in the Preference for Social Novelty in F2 Mice

As the **Figure 4D** showed, in scene 2, F2-Con mice spent less time in the chamber containing stranger 2 than the CTRL/F2-Int mice ($F_{2,36} = 7.465$, CTRL vs. F2-Con: $^{*}p = 0.0128$; F2-Con vs. F2-Int: $^{**}p = 0.0027$, **Figure 4F**); F2-Con mice spent more time in the chamber containing stranger 1 than the CTRL mice and F2-Int mice ($F_{2,36} = 10.46$, CTRL vs. F2-Con: $^{***}p = 0.0002$; F2-Con vs. F2-Int: $^{*}p = 0.0136$ **Figure 4E**). More importantly, the SPI of CTRL/F2-Int mice was significantly higher than that of F2-Con mice ($F_{2,36} = 10.42$, CTRL vs. F2-Con: $^{***}p = 0.0003$; F1-Con vs. F2-Int: $^{**}p = 0.004$, **Figure 4H**). The results revealed that the F2-Con mice exhibited an obvious deficit in the preference for social novelty and that baclofen corrected the deficits.

Prenatal Baclofen Treatment Corrected Novelty Recognition Deficits in F2 Mice

As the **Figures 4G,J** showed, F2-Con mice showed deficits in the preference for novel objects compared with CTRL mice (CTRL vs. F2-Con: $F_{2,36} = 5.020$, $^{*}p = 0.0184$, scene 1, **Figure 4I**; $F_{2,36} = 9.076$, $^{***}p = 0.0006$, scene 2, **Figure 4K**; $F_{2,36} = 5.175$, $^{*}p = 0.0264$, scene 2, **Figure 4L**). Prenatal baclofen treatment increased the DI and the amount of time F2 male mice spent in the region containing the novel object (CTRL vs. F2-Con: $F_{2,36} = 5.020$, $^{*}p = 0.0401$, scene 1, **Figure 4I**; $F_{2,36} = 9.076$, $^{*}p = 0.0153$, scene 2, **Figure 4K**; $F_{2,36} = 5.175$, $^{*}p = 0.0213$, scene 2, **Figure 4L**). Prenatal baclofen treatment corrected deficits in the novel object preference of F2 mice.

Prenatal Baclofen Treatment Corrected Locomotor and Exploratory Activity Deficits in F2 Mice

As the **Figures 5A,B** showed, in the open-field task, F2-Con mice showed lower locomotor and exploratory behavior than CTRL mice, including decreases in the time traveled in the inner area (CTRL vs. F2-Con: $F_{2,36} = 8.584$, $^{***}p = 0.0007$, **Figure 5D**) and in the OFEI (CTRL vs. F2-Con: $F_{2,36} = 12.650$, $^{***}p < 0.0001$, **Figure 5F**). F2-Int mice showed greater exploratory and locomotor behaviors than F2-Con mice, including increases in the time traveled in the inner area (F2-Con vs. F2-Int: $F_{2,36} = 8.584$, $^{*}p = 0.025$, **Figure 5D**), the distance traveled in the inner area (F2-Con vs. F2-Int: $F_{2,36} = 4.193$, $^{*}p = 0.026$, **Figure 5E**), and the OFEI (F2-Con vs. F2-Int: $F_{2,36} = 12.650$, $^{*}p = 0.0343$, **Figure 5F**). Thus, F2 male mice exhibited lower levels of locomotor and exploratory behaviors than CTRL mice, and prenatal treatment with baclofen exerted a positive effect on ameliorating locomotor or exploratory behavioral deficits in F2 mice.

Prenatal Baclofen Treatment Corrected Marble-Burying Deficits in F2 Mice

As the **Figure 5C** showed, the numbers of buried marbles and burying actions were lower in F2-Con mice than in CTRL mice (CTRL vs. F2-Con: $F_{2,36} = 7.638$, $^{**}p = 0.0015$, **Figure 5G**; $F_{2,36} = 6.548$, $^{**}p = 0.0037$, **Figure 5H**), indicating that F2 male mice exhibited marble-burying deficits. Baclofen treatment increased these parameters in F2 mice (F2-Con vs. F2-Int: $F_{2,36} = 7.638$, $^{*}p = 0.0302$, **Figure 5G**; $F_{2,36} = 6.548$, $^{*}p = 0.0401$, **Figure 5H**), indicating that prenatal baclofen treatment exerted a certain therapeutic effect on the marble-burying deficits in F2 mice.

The marbles buried and the burying actions of all groups of mice (CTRL, F2-Con, F2-Int) were linearly correlated in the marble-burying test ($r^2 = 0.8545$, $^{***}p < 0.001$/Y = 9.372*X + 11.49) (**Figure 5I**).

Prenatal Baclofen Treatment Corrected Alterations in Dendritic Spine Density on CA1 Pyramidal Neurons in the HC of F2 Mice

Because dendritic spines play critical roles in synaptic plasticity, we sought to determine whether F2 mice exhibited changes in the total spine density and mature spine density on CA1 pyramidal neurons in the HC. Because the functions of the ventral HC (related to stress, emotion, and affect) and dorsal HC are different (related to cognitive functions) (61), we measured the densities of total dendritic spines and mature dendritic spines on basal and apical dendrites of vertebral neurons in the ventral HC and dorsal HC in the CA1 region.

As the **Figures 6H,I,L** showed, the analysis of mouse brain slices of the dorsal HC with Golgi staining showed that the total spine density and mature spine density (mushroom-shaped + stubby-shaped spines) were significantly lower on pyramidal neurons from F2-Con mice than on those from CTRL mice, including basal dendrites (CTRL vs. F2-Con, total spine density: $F_{2,55} = 19.52$, $^{***}p < 0.0001$, **Figure 6J**; mature spine density: $F_{2,55} = 13.87$, $^{***}p < 0.0001$, **Figure 6K**) and apical dendrites (CTRL vs. F2-Con, total spine density: $F_{2,53} = 22.33$, $^{***}p < 0.0001$, **Figure 6M**; mature spine density: $F_{2,53} = 24.74$, $^{***}p < 0.0001$, **Figure 6N**). Our analysis revealed that prenatal baclofen treatment corrected spine density defects in the dorsal HC of F2 mice (F2-Int), including basal dendrites (F2-Con vs. F2-Int, total spine density: $F_{2,55} = 19.52$, $^{***}p < 0.0001$, **Figure 6J**; mature spine density: $F_{2,55} = 13.87$, $^{***}p = 0.0001$, **Figure 6K**) and apical dendrites (F2-Con vs. F2-Int, total spine density: $F_{2,53} = 22.33$, $^{***}p = 0.0001$, **Figure 6M**; mature spine density: $F_{2,53} = 24.74$, $^{***}p = 0.0001$, **Figure 6N**).

Similarly, as the **Figures 6A,B,E** showed, though there were no difference in spine density on basal dendrites of CA1 pyramidal neurons in the ventral HC obtained from three groups (total spine density, $F_{2,51} = 0.7057$, CTRL vs. F2-Con: nsp = 0.8001; F2-Con vs. F2-Int: nsp > 0.9999, **Figure 6C**) (mature spine density, $F_{2,51} = 1.709$, CTRL vs. F2-Con: nsp = 0.2264; F2-Con vs. F2-Int: nsp > 0.9999, **Figure 6D**), the analysis showed a lower spine density on apical dendrites of CA1 pyramidal neurons in the ventral HC obtained from F2-Con mice than that obtained from CTRL mice (total spine density: $F_{2,47} = 13.77$, $^{**}p = 0.0040$, **Figure 6F**; mature spine density: $F_{2,47} = 14.98$, $^{***}p = 0.0008$, **Figure 6G**). Prenatal baclofen treatment corrected the altered spine density on apical dendrites in F2 mice (total spine density: $F_{2,47} = 13.77$, $^{***}p < 0.0001$, **Figure 6F**; mature spine density: $F_{2,47} = 14.98$, $^{***}p < 0.0001$, **Figure 6G**). In the ventral

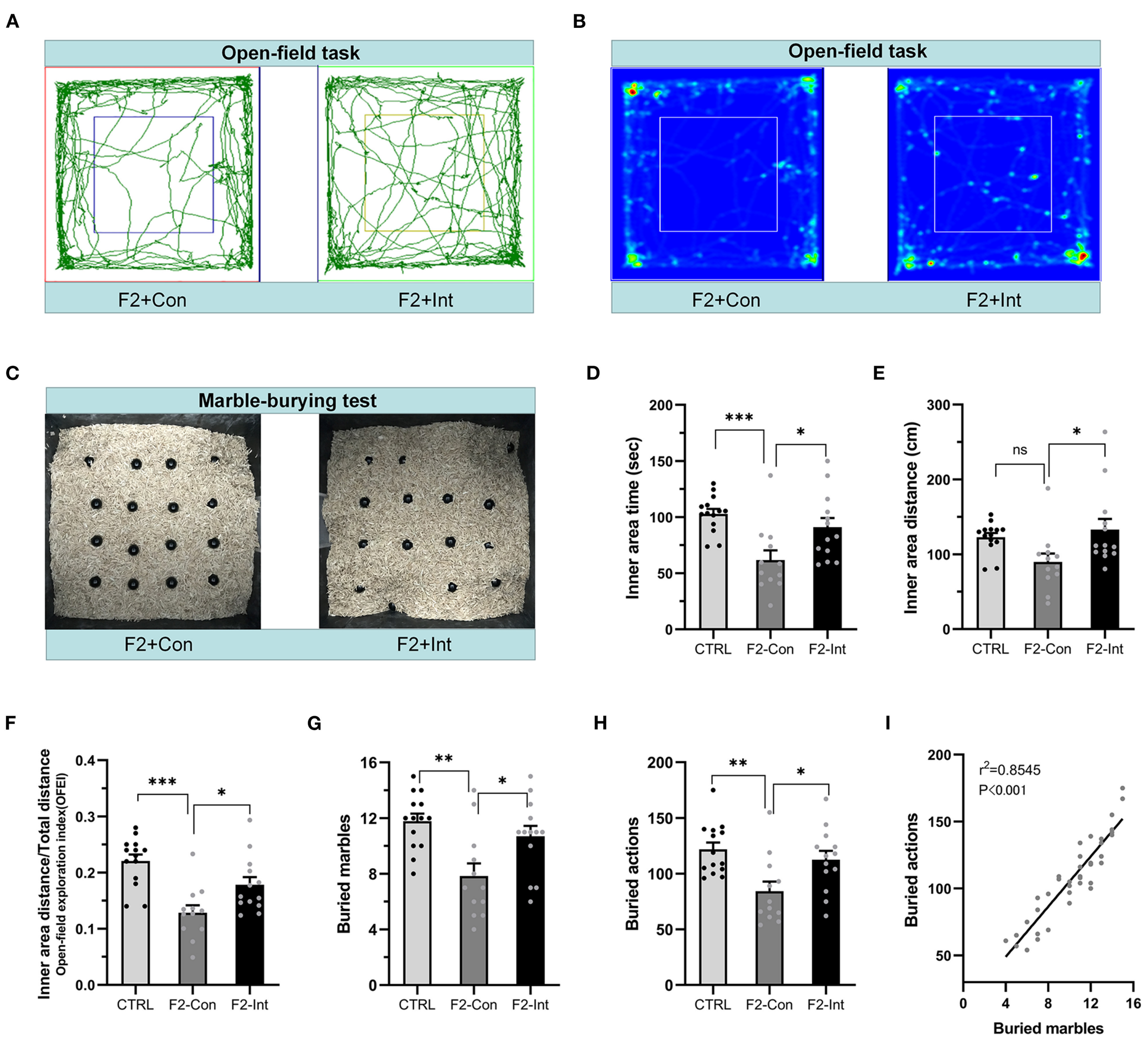

FIGURE 5 | Prenatal baclofen administration corrected locomotor, exploratory activity, and marble-burying deficits in F2 mice. **(A)** Representative traces of mice in the open-field task. **(B)** Representative heatmaps of traces of mice corresponding to **(A)**. **(C)** Representative marble-burying maps after the marble-burying test. **(D)** Time traveled in the inner zone by mice. **(E)** Distance traveled in the inner zone by mice. **(F)** The open-field exploration index (OFEI = distance traveled in the inner zone/the total distance traveled) of mice. **(G)** The numbers of buried marbles of mice. **(H)** The number of burying actions of mice. In **(D–H)** and **(G–I)**, one-way ANOVA followed by the Bonferroni *post-hoc* test was used to compare the differences among groups: $^{*}p < 0.05$, $^{**}p < 0.01$ $^{***}p < 0.001$. All data for all figures are plotted as the mean ± SEM. n (CTRL: F2-Con: F2-Int) = 14:12:13. **(I)** Pearson correlation and linear regression analysis between the number of buried marbles and the number of burying actions. All mice were included ($n = 39$) in the analysis, and there was a linear correlation between the number of buried marbles and the number of burying actions.

HC, we did not observe significant differences in the spine density on basal dendrites of CA1 pyramidal neurons among the CTRL, F2-Con, F2-Int groups of mice.

Prenatal Baclofen Treatment Corrected Defects in Dendritic Spine Density on Pyramidal Neurons in the mPFC of F2 Mice

As the **Figures 7A,B** showed, the analysis of mouse mPFC brain slices with Golgi staining showed a lower total spine density and mature spine density on basal dendrites of pyramidal neurons of layer V in F2-Con mice than those in CTRL mice (CTRL vs. F2-Con, total spine density: $F_{2,74} = 18.79$, $^{***}p < 0.0001$, **Figure 7C**; mature spine density: $F_{2,74} = 7.046$, $^{**}p = 0.0025$, **Figure 7D**). Prenatal baclofen treatment corrected the spine density defects in F2 mice (F2-Con vs. F2-Int, $F_{2,74} = 18.79$, $^{***}p = 0.0001$, **Figure 7C**; mature spine density: $F_{2,74} = 7.046$, $^{*}p = 0.0151$, **Figure 7D**).

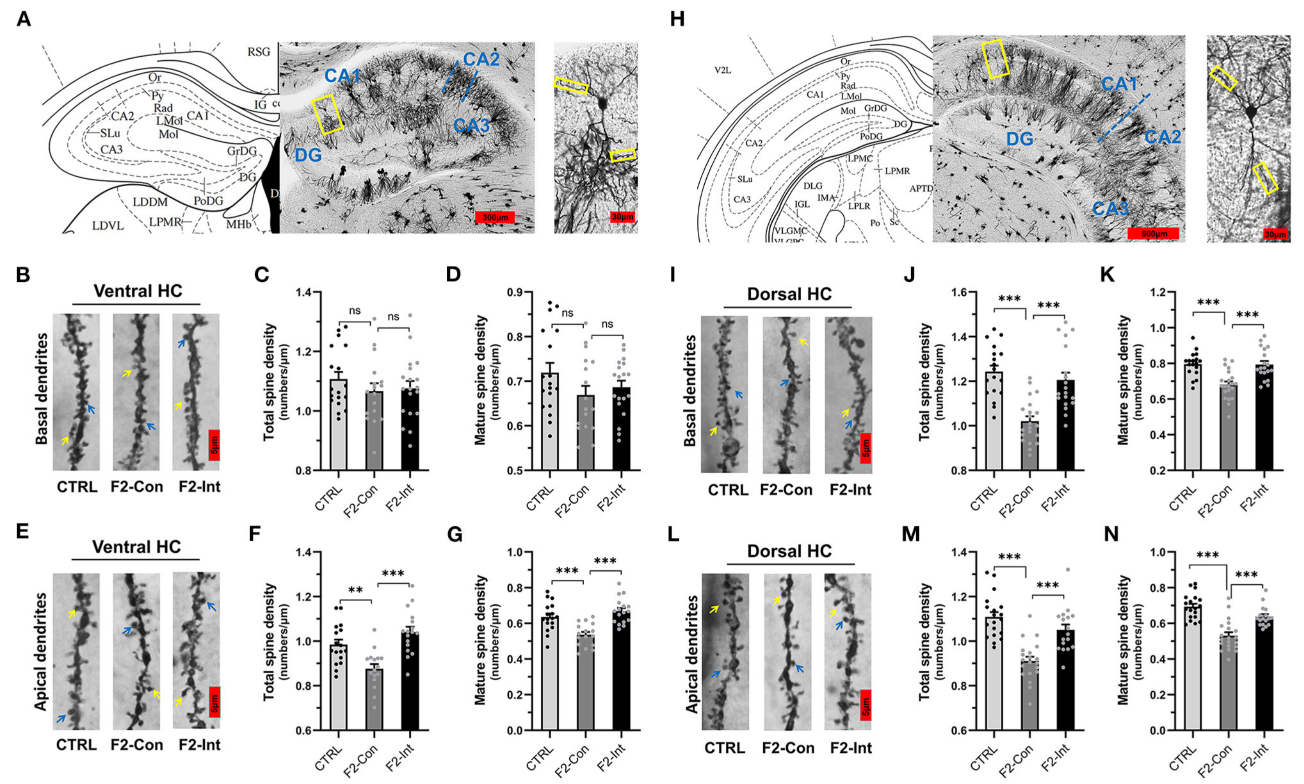

FIGURE 6 | Prenatal baclofen administration corrected the defects in dendritic spines density of CA1 pyramidal neurons in the HC in F2 mice. **(A)** A composite of a representative scanned image of Golgi-Cox-stained slices of the ventral HC and the mouse brain map from *The Mouse Brain in Stereotaxic Coordinates*; scale bar: 300 and 30 μm. **(A/H)** The part inside the yellow rectangle is the neurons and dendrites selected for analysis. The spines were selected from grade 3 basal dendrites and grade 6/7 apical dendrites for analysis. **(B/E)** Representative three-dimensional reconstructed images of the basal/apical dendrites of pyramidal neurons in the CA1 of the ventral HC obtained from CTRL, F2-Con and F2-Int mice. The yellow arrow points to a mushroom spine, and the blue arrow points to a stubby spine. Scale bar: 5 μm. **(C,D)** Summary of spine density on the basal dendrites of CA1 pyramidal neurons in the ventral HC. Mature spines = mushroom spines + stubby spines (CTRL: *n* = 18 dendrites from 3 mice; F2-Con: *n* = 17 dendrites from 3 mice; F2-Int: *n* = 19 dendrites from 3 mice). **(F,G)** Summary of spine density on the apical dendrites of CA1 pyramidal neurons in the ventral HC. Mature spines = mushroom spines + stubby spines (CTRL: *n* = 17 dendrites from 3 mice; F2-Con: *n* = 16 dendrites from 3 mice; F2-Int: *n* = 17 dendrites from 3 mice). **(H)** A composite of a representative scanned image of Golgi-Cox-stained slices of the dorsal HC and the mouse brain map from *The Mouse Brain in Stereotaxic Coordinates*; scale bar: 500 and 30 μm. **(I/L)** Representative three-dimensional reconstructed images of the basal/apical dendrites of pyramidal neurons in the CA1 of the dorsal HC. The yellow arrow points to the mushroom spine, and the blue arrow points to the stubby spine. Scale bar: 5 μm. **(J,K)** Summary of spine density on the basal dendrites of CA1 pyramidal neurons in the HC (CTRL: *n* = 18 dendrites from 3 mice; F2-Con: *n* = 21 dendrites from 3 mice; F2-Int: *n* = 19 dendrites from 3 mice). **(M,N)** Summary of spine density on the apical dendrites of CA1 dorsal neurons in the dorsal HC. Mature spines = mushroom spines + stubby spines (CTRL: *n* = 19 dendrites from 3 mice; F2-Con: *n* =20 dendrites from 3 mice; F2-Int: *n* = 17 dendrites from 3 mice). One-way ANOVA followed by the Bonferroni *post-hoc* test was used to compare the differences among the four groups; $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$. All data for all figures are plotted as the mean ± SEM.

DISCUSSION

In present preclinical study, we designed a rigorous mouse breeding process and behavioral tests to evaluate the rigor and repeatability of assessments evaluating the efficacy of drug therapy. Baclofen has been used in the clinic for many years as a treatment for spasticity in children and adults with cerebral palsy. Placebo-controlled trials in patients with fragile X syndrome and autism using R-baclofen have shown that the drug is safe and well tolerated in patients with other developmental brain disorders (30). In addition, baclofen crosses the placental barrier. We first designed a long-term oral baclofen experiment for weaned VPA-exposed mice (F1) and found that baclofen administration improved the core autism-like behaviors of F1 mice. Long-term moderate activation of GABAB receptors exerted therapeutic effects on F1 mice during the developmental stage. Subsequent prenatal baclofen treatment of F2 mice showed a similar beneficial effect on ameliorating autism-like behavioral dysfunction. Thus, moderate activation of GABAB receptors during the pregnancy period exerts therapeutic effects on the inheritance of autism-like core behaviors in F2 mice.

Social interaction tests (6, 57–60), novel object recognition tests (30, 54), and open-field tests (11, 30) are classic experiments used to detect autism-like behavior of core symptoms of the ASD diagnosis: social communication and interaction impairments, restricted interests and anxiety-like behaviors. F1 mice that were prenatally exposed to VPA (300 mg/kg) on the gestational day 10 and 12 showed autism-like behaviors, including (1) decreased

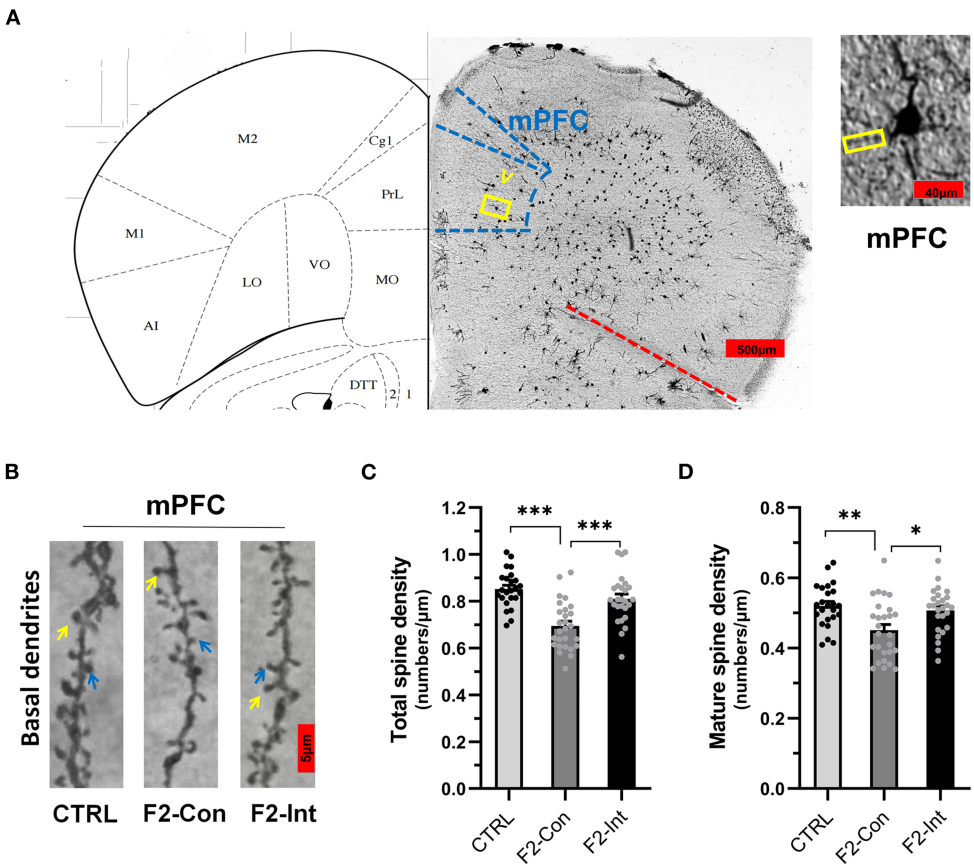

FIGURE 7 | Prenatal baclofen administration corrected the defects in dendritic spines density of pyramidal neurons in the mPFC in F2 mice. **(A)** A composite of a representative scanned image of Golgi-Cox-stained slices of the mPFC and the mouse brain map from *The Mouse Brain in Stereotaxic Coordinates*; scale bar: 500 and 40 μm. **(B)** The part inside the yellow rectangle is the neurons and dendrites selected from layer V in the mPFC for analysis. The spines were selected from grade 3 basal dendrites for analysis. The yellow arrow points to a mushroom spine, and the blue arrow points to a stubby spine. Scale bar: 5 μm. **(C,D)** Summary of spine density on the basal dendrites of mPFC pyramidal neurons. Mature spines = mushroom spines + stubby spines (CTRL: $n = 24$ dendrites from 3 mice; F2-Con: $n = 27$ dendrites from 3 mice; F2-Int: $n = 26$ dendrites from 3 mice). One-way ANOVA followed by the Bonferroni *post-hoc* test was used to compare the differences among the four groups; $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$. All data for all figures are plotted as the mean ± SEM.

social interaction parameters; (2) decreased novel object recognition parameters; (3) decreased open-field parameters; and (4) significantly decreased conditioned defense responses in the marble-burying test, as assessed as buried marbles and burying actions. The marble-burying test is commonly used to detect repetitive and stereotypic behavioral indicators. Our experimental results are not consistent with several previous studies (62–64), showing that the numbers of buried marbles and burying actions were lower in F1 mice than in CTRL mice and baclofen exerted a therapeutic effect on marble-burying deficits in F1 mice. This discrepancy may be due to differences in the total test time, acclimation period, test days, standard buried marble, volume and color of the test cage, number of marbles, and other parameters. We suggest that our experimental results provided more support for the marble-burying test as a conditioned defense response (65–67). The behavior of marble burying is more similar to adaptation to a new complicated environment. In addition, our results showed that F2 male mice obviously inherited their parents' core autism-like phenotypes.

The intrinsic pathology of VPA-exposed mice is presumed to provide a model of the environmental/epigenetic origins of epigenetic changes induced by prenatal exposure to VPA. Compared with transgenic models carrying mutations in single autism-associated genes, the model can better reflect many clinical cases of idiopathic autism (11). Neurotransmission regulated by VPA, as a key mechanism, could influence neurodevelopment (11, 68, 69) and regulate gene expression through chromatin remodeling by inhibiting histone deacetylase (HDAC) activity (41, 70). These molecular disturbances have been shown to induce epigenomic disturbances in gametes that may result in abnormal transcription of brain-related genes during fetal and early development, resulting in abnormal neurobehavioral phenotypes in offspring, such as F2 mice (71–74). Furthermore, F2 mice were not only affected by epigenetic information based on changes in histone acetylation but were also exposed to VPA during the gonad development of F1 mice. In other words, F2 mice were also directly exposed to VPA (45). This result may help explain the high degree of inheritance of autism-like behavior in the F2 generation of mice from the F1 mice. Our results showed that after oral treatment with baclofen, the core autism-like behavioral indicators in F1 mice were ameliorated to varying degrees (**Figures 2** and **3**). Encouraged by the results, we continued to investigate whether prenatal baclofen treatment ameliorated the core autism-like deficits in the F2 generation. The results were similar to those in F1 mice and included the following changes: prenatal baclofen treatment in the F2 generation (1) increased the social time and index, (2) increased the exploration of new objects, (3) increased locomotor and exploratory activities in the open-field test, and (4) increased the number of buried marbles and burying actions.

Synaptic development, maintenance and plasticity under both physiological and pathological conditions are frequently associated with abnormalities in the morphology and numbers of dendritic spines. Disruptions in synaptic plasticity are considered to be the basic neural mechanism underlying various mental diseases. Dynamic changes in dendritic spines play an important role in the formation and refinement of neural circuits and in higher brain neurobehavioral functions. When the density and morphology of dendritic spines change, the structure and function of synapses change accordingly (48). In our previous study, we found that arbaclofen increased the density of basal dendritic spines on neurons in the CA1 region of the dorsal HC in VPA mice (unpublished results). In some studies, the same changes have been reported in F1 mice, and medications can correcte the defect (75–77). Based on these result, we used the Golgi-Cox staining method to study the spine density in the brains of F2 mice, as this parameter is closely related to autism-like behaviors. The spine density was abnormal in the ventral HC, dorsal HC, and mPFC of F2 mice, including reductions in the total spine density and mature spine density. These findings indicated that important brain regions associated with autism in F2 mice exhibited prominent defects in synaptic plasticity and that connectivity was reduced. After prenatal baclofen treatment, this deficiency in F2 mice was reversed.

GABA signaling plays pivotal roles in the initial formation of neuronal networks in the embryonic and early postnatal brain (78), of which GABAB receptors have an extremely important effects in early neural development, involving neuronal survival and migration, developmental pruning, and synaptic formation and maturation (79–81). Previous studies confirmed that mouse models with mutations in GABA receptor subunits showed obvious social deficits and other ASD-relevant behavioral phenotypes (82–85). In addition, defects in GABA receptors, including a reduction in the number and density of GABAB and GABAA receptor subunits, have also been found in postmortem brain tissues from many patients with ASD (86). In conclusion, GABA receptor dysfunction is an important pathological mechanism in some children with ASD. Based on the facts described above, we boldly infer that a large number of patients with ASD also have dysfunction in the GABAB pathway during the fetal period. Our results indicated that the activation of the GABAB receptor by prenatal baclofen treatment exerts a beneficial effect on fetal neurodevelopment in F2 mice, which may compensate for epigenetic and VPA exposure-induced molecular perturbations. The results supported the hypothesis that therapeutic strategies designed to enhance inhibitory synaptic transmission during pregnancy and early in life may improve symptoms associated with the autism diagnosis in some children with ASD.

While the experimental results are encouraging, the current study has limitations. The complex genetic and environmental conditions of real children with ASD are impossible to replicate in animals due to the homogeneity between experimental animals and exposure to the same experimental environment. Meanwhile, the determination of whether the drug baclofen will exert adverse effects on the fetus when administered during pregnancy is difficult, although no obvious abnormalities were observed in this study. However, the results show the possibility of early intervention with GABAB receptor agonists for the treatment of children with ASD. These results are undoubtedly encouraging. In addition, our results also support the hypothesis that GABABR is a promising drug target for the treatment of neuropsychiatric disorders and developmental disorders (78, 87), which may be an important direction for the development of new drugs for ASD treatment.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The animal study was reviewed and approved by the Institutional Animal Care and Use Committee of Ningxia Medical University (IACUC Animal Use Certificate No 2019-152).

AUTHOR CONTRIBUTIONS

FW and TS are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. SJ, MH, and LX made major contributions to the conception, design and the acquisition, analysis, or interpretation of data for the work. A part of material preparation, data collection were performed by YS, JD, WL, BG, LW, YW, and CG. The first draft of the manuscript was written by SJ and all authors commented on previous versions of the manuscript. All authors contributed to the study conception and design. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.835993/full#supplementary-material

Supplementary Figure 1 | Flowchart for eliminating the "litter effect".

Supplementary Figure 2 | Flowchart for behavioral test.

Supplementary Video 1 | Social interaction test(scene 2, F2-Con).

Supplementary Video 2 | Novel object recognition task(scene 2, F2-Con).

Supplementary Video 3 | Novel object recognition task(scene 2, F2-Int).

Supplementary Video 4 | Open-field task (F2-Int).

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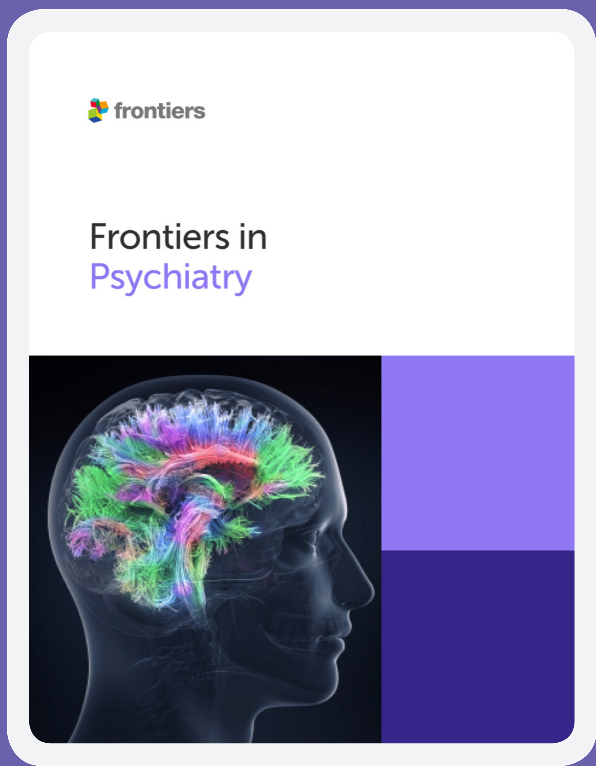

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