Unlocking cognitive potential: a comprehensive review of neurocognitive interventions in Down Syndrome

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Abstract.
Background: Down Syndrome (DS) poses unique challenges in cognitive functioning, characterized by deficits in language, memory, and executive functions. This review synthesizes current research across educational, behavioral, pharmacological, and physical interventions to enhance cognitive capabilities in individuals with DS. Methods: A comprehensive literature review was conducted, incorporating studies that explored diverse interventions for cognitive enhancement in DS. Educational interventions, behavioral strategies, pharmacological approaches, and physical modalities were systematically analyzed to provide a holistic overview of the current landscape. Objectives: This review aims to consolidate findings from various intervention studies, offering insights into the efficacy of educational, behavioral, pharmacological, and physical approaches in ameliorating cognitive deficits in DS. The diverse range of interventions and their respective outcomes were critically examined to guide future research and intervention strategies. Discussions: Educational interventions, such as language and speech therapy, technology-assisted learning, and working memory training, displayed promising outcomes. Behavioral approaches, including responsive teaching and motor skill-focused interventions, added valuable insights to cognitive enhancement. Pharmacological interventions exhibited varying degrees of success, emphasizing the need for tailored approaches. Physical interventions, particularly regular physical activity and assisted cycle therapy, emerged as potential catalysts for cognitive improvement. This review highlights the multifaceted nature of cognitive deficits...
in DS and underscores the importance of personalized perspectives in intervention strategies. The discussions provide a comprehensive understanding of the current interventions' effectiveness, contributing to the ongoing discourse on cognitive enhancement in DS. Future research should focus on personalized approaches, considering the heterogeneity in DS phenotypes, to optimize cognitive outcomes for individuals with DS.

**Keywords:**
- Down Syndrome
- cognitive defects
- responsive teaching
- personalized intervention
**Introduction**

Down syndrome (DS) is a genetic disorder resulting from the trisomy of chromosome 21 [1]. This is known to have a multitude of phenotypic presentations, among which is the development of a learning disability [2], with DS being its most common genetic cause [3]. DS affects multiple aspects of neurocognitive development, including IQ, memory, executive function, and language, as seen in a 2015 study [4].

Standardized IQ scores have been noted to decrease in young children in studies conducted in the past [5], with relatively stable IQ scores in older children and adults [4] and IQ scores across the board being lower than their normally developed peers. In the same 2015 study, IQ scores were observed to influence memory, executive function, and language, with all having similarly low levels compared to their non-DS counterparts [4]. At older ages, DS patients are also at increased risk of Alzheimer's dementia [6].

Due to its influence on neurological development, DS patients face difficulties in regular functioning in their daily lives. Hence, it is important to address these aspects when managing DS.

DS poses a distinctive challenge in the realm of cognitive disorders, characterized by a complex interplay of deficits profoundly impacting individuals [1]. The pursuit of interventions to ameliorate cognitive impairments in DS has spurred extensive research across various domains. This comprehensive review endeavors to synthesize findings from educational, behavioral, pharmacological, and physical intervention studies, providing a nuanced perspective on the current landscape of cognitive enhancement in DS. DS manifests cognitive deficits spanning diverse domains, including language, memory, and executive functions [2]. The multifaceted nature of these deficits underscores the intricate processing of cognitive functions, as outlined by DSM-5, which categorizes cognitive function into six components [3]. Despite well-established cognitive deficits associated with DS, considerable variability is noted both between individuals and within individuals themselves [7].

This variability accentuates the need for personalized approaches to effectively comprehend and address cognitive
deficits. A personalized perspective, as suggested by studies such as Onnivello et al., enables interventions to be precisely targeted, potentially leading to improved cognitive outcomes [7]. This review encompasses a range of interventions spanning educational, behavioral, pharmacological, and physical modalities, each contributing unique insights into the multifaceted challenges of cognitive enhancement in DS. Educational interventions, exemplified by language and speech therapy, technology-assisted learning, and working memory training, present promising outcomes [17-24].

Behavioral strategies, including responsive teaching and motor skill-focused interventions, provide valuable perspectives on cognitive enhancement [25-27]. Pharmacological interventions, from traditional acetylcholinesterase inhibitors to innovative agents like GABAA-α5 negative allosteric modulators, are explored for their potential to address cognitive dysfunction in DS [8-34]. Physical interventions, such as regular physical activity and assisted cycle therapy, are examined as potential catalysts for cognitive improvement [35-37]. In navigating the complex terrain of DS, a holistic understanding and integration of diverse interventions remain imperative for optimizing cognitive outcomes.

This review aims to contribute to the evolving discourse on cognitive enhancement in DS, offering insights that may guide future research and intervention strategies for individuals with DS.

**Methodology**

A thorough search was conducted across Google Scholar and PubMed. The following criteria were employed to select and screen relevant literature and data.

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<td>- Include randomized controlled trials (RCTs), longitudinal studies, and intervention studies.</td>
<td>- Exclude studies published in languages other than English due to potential language barriers.</td>
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<td>- Exclude non-peer-reviewed literature, conference abstracts, and unpublished studies to maintain the quality of evidence.</td>
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Table continuation

- Include studies evaluating cognitive interventions, including pharmacological, behavioral, and educational approaches.
- Cover interventions explicitly designed to enhance cognitive functions, such as memory, attention, or executive function.
- Include studies published within the last 15 years to ensure relevance to current practices.

- Exclude studies that do not specifically address cognitive enhancements or neurocognitive interventions for individuals with Down Syndrome.
- Exclude purely observational studies or those not explicitly assessing the impact of interventions on cognitive outcomes.

The Manuscript was drafted using the SANRA guidelines [38].

**Intervention Effectiveness**

DSM-5 defines cognitive function into 6 components: Complex attention, executive function, learning and memory, language, perceptual-motor control, and social cognition. Down syndrome presents as a range of cognitive deficits. This includes language, memory, and executive functions being particularly affected, as indicated in various studies and literature. However, many studies including this study by Onnivello et al, show that considerable variability is noted both between individuals and within individuals themselves in the phenotype of Down syndrome [7]. Therefore, comprehending these deficits from a personalized perspective can lead to more effective targeting of interventions and improved cognitive outcomes.

Various therapies, both pharmacological and non-pharmacological, are currently employed to enhance treatment outcomes. Pharmacological interventions such as DYRK1a inhibitors, selective serotonin reuptake inhibitors (Fluoxetine), sonic hedgehog agonists, and antioxidant vitamin E are among the treatments being explored. Additionally, drugs like acetylcholinesterase inhibitors (Aricept/Donepezil, Rivastigmine), N-methyl-D-aspartate
receptor antagonists (Memantine), and selective gamma-aminobutyric acid-A α5 receptor negative allosteric modulator (Basmisanil/RG1662) are undergoing investigation for their efficacy [8]. These drugs act by reducing the extra amyloid buildup and are particularly being studied to treat Alzheimer's disease in Down syndrome.

Boada et al. conducted a study on the cognitive effects of memantine, primarily focusing on memory, in 40 patients aged 18-30 years. Their findings revealed that memantine improves verbal memory, as assessed by the California Verbal Learning test-II (CVLT-II) [9].

Rehearsal training has been recognized as beneficial for enhancing working memory. Numerous studies have also highlighted the positive impact of exercise on memory function [10], with some studies even suggesting additional benefits on attention and executive functions [11]. Ptomey et al. demonstrated that acute or short-term (less than 12 weeks) moderate-vigorous physical activity (MVPA) improves attention, memory, and executive functions, enhancing overall quality of life in individuals with Alzheimer's disease in Down syndrome [12].

Overall, numerous studies have been conducted to evaluate the effectiveness of pharmacological and non-pharmacological treatments for Down syndrome. However, most of these studies primarily measure cognitive improvement through memory assessment as the key factor.

Numerous researchers are dedicating their efforts to developing pharmaceutical therapies aimed at improving cognitive abilities in individuals with DS. Several studies provide evidence of abnormal hippocampal pathways in individuals with DS, leading to cognitive deficits. Alexandria. M et al. conducted a study on Ts65Dn mice demonstrating reduced synaptic activation of N-methyl-D-aspartate (NMDA) receptors, resulting in inadequate depolarization upon receiving afferent stimuli. This deficiency was addressed by administering picrotoxin, a GABA_A receptor antagonist, to restore normal conduction [13]. Several studies suggest that targeting GABA_A receptors could serve as a potential treatment target for cognitive deficits in many pathologies [14].
The symptoms of olfactory loss and male infertility observed in individuals with DS have been found to parallel those of Gonadotropin-releasing hormone (GnRH) deficiency, similar to those seen in Kallmann syndrome [15]. Multidisciplinary interventions play a fundamental role in modifying neurocognitive outcomes in children with Down Syndrome. They included 20 children with DS. The experimental group received early treatment (0-36 months), while the control group only underwent cognitive assessments. To examine the outcome of long-term cognitive functioning, our study evaluated assessments of the children at 5 years of age, by administering the Wechsler Preschool and Primary Scale of Intelligence 3 (WPPSI-III) scale [17].

Manfredi-Lozano et al. conducted a study on Ts65Dn mice to investigate the influence of GnRH hormone on cognition and olfactory defects. They identified dysfunctional strands of mRNA that regulate GnRH production on chromosome 21. Additionally, they conducted a pilot study involving 7 individuals with DS, administering pulsatile GnRH therapy for 6 months. The total Montreal Cognitive Assessment (MoCA) scores increased in 6 out of 7 patients, with minimal effects observed on the reproductive hormone profile [16].

Multifaceted Approaches to Enhance Cognitive Function in Down Syndrome

Cognitive function is a broad term that encompasses the mental abilities of acquiring knowledge, processing information, and engaging in reasoning, thus utilizing the various faculties of memory, perception, learning, attention, decision-making, and linguistic proficiency [17].

Hence, different clinical trials have evaluated the cognitive function, of individuals with Down’s Syndrome and the efficacy of their interventions, in different disciplines using suitable distinct parameters. The interventions adopted can be categorized into 4 principal groups- educational, behavioral, physical, and pharmacological.

Educational Interventions

A multitude of studies have assessed the efficacy of different interventions in the domain of memory, especially working memory. Working memory has distinct specialized systems for interacting with verbal and visuospatial
information: verbal short-term memory and visuospatial short-term memory respectively [18].

Targeting the verbal short-term memory in a randomized controlled trial with a waiting-list control design, an individualized educational intervention in the form of language and speech therapy in daily 20-minute sessions involving the use of regular past tense over 10 weeks, was associated with improved performance of the intervention group as compared to the delayed intervention group, in various assessments, before the latter had received the intervention. However, immediately following delayed intervention, the control group managed to demonstrate significant improvement in their performance in the particular assessments as well. Furthermore, it was assessed at the same time, that the intervention group maintained their gains, thus displaying retention of the linguistic skills acquired [19].

Another clinical trial used a similar strategy of intervention and study design to tackle the challenges associated with reading and linguistic comprehension. Trained teaching assistants delivered daily 40-minute sessions in children’s schools on an individual basis which combined reading instructions centered around phonetic principles and vocabulary enrichment in the form of a variety of short, fast-paced tasks over 20 weeks. The intervention resulted in greater progress, for the participants receiving it, in the realms of single-word reading, phonemic awareness, phoneme blending, and trained expressive vocabulary as compared to the children in the waiting-list group, being taught as usual. However, the performance and skills of the latter improved significantly upon receiving the intervention during their first 20-week period, confirming the effectiveness of the intervention [20].

In another trial designed to support phonetic awareness in children with Down’s Syndrome, a software- GraphoGame- was used to deliver computer-based phonic intervention for reading development, letter knowledge, word decoding, and phonological processing. The software algorithm modifies the intervention to adapt to each subject’s performance and maximize benefit. A daily practice of 10 minutes for 20 school
days correlated with improved decipherment of trained word material in all the children across the spectrum of intellectual disability. When complemented with regular schooling, improved performance in letter naming as well as decoding both trained and untrained word material could be observed [21].

Mean Level of Utterance (MLU) is a parameter that measures the average number of morphemes used in a sentence and thereby has the potential to analyze the development of morphosyntax in children with Down’s Syndrome. Intervention in the form of a morphosyntactic training program over 3.5 months demonstrated superior performance as well as a significant improvement in the performance of children with Down’s Syndrome in the morphology, syntax, and semantics sections of the BLOC-C test, a language evaluation assessment when compared to a control group receiving regular speech and language treatment [22].

Augmentation of regular speech and language therapy with naturalistic teaching of sign language was chosen to be the intervention to combat deficits in linguistic skill acquisition, speech articulation, and speech clarity in yet another clinical trial. Enhanced Milieu Teaching (EMT) and Joint Attention, Symbolic Play, Engagement, and Regulation (JASPER) strategies were implemented to teach the participants a set of 32 signs paired with at least 80% of the verbal communication as a form of intervention in association with the baseline of engagement in interactive play, carried out in bi-weekly sessions of 20-30 minutes, which was associated with an increase in the rate and number of expressive spontaneous signing along with a smaller increase in the use of words, not only during the intervention but also in a separate environment (home) and with an untrained partner (parent). However, it was also observed that 50-80% of the total words learned continued to be used as signs and could not be verbally articulated as words by the children during the intervention [23].

In one of the few studies that have aimed to improve visuospatial short-term memory, intense training in computerized working memory tasks tailored to their approximate mental age under a Junior Cogmed Working Memory
Training Programme thrice weekly for 10-12 weeks has been chosen as the intervention. Similar improvement was observed in the performance of each of the study participants in all 7 tasks of the training program. After completion of the program, the intervention group demonstrated significant improvement in terms of both visuospatial short-term memory and visuospatial working memory, tested using Automated Working Memory Assessment (AWMA), compared to the waiting-list population, and the gains were maintained even after 4 months. This result was replicated in the realm of visuospatial short-term memory by the waiting-list group upon receiving the intervention, thus confirming it to be both effective and feasible for use in children with Down’s Syndrome. As for the domains of verbal short-term memory and verbal working memory, the intervention group showed no significant improvement after the training program while the waiting-list group rather showed a decline in the realm of verbal working memory without the intervention and no significant improvement even with the intervention. Assessing the executive functions of the participants, significant progress was noted in the sectors of shift and working memory in the intervention group, sustained over 4 months, while in the absence of intervention in the waiting-list group, no improvement could be detected in either of the fields of inhibition, shift, emotional control or planning/organize [18].

Challenges in the field of Mathematics were attempted to be dealt with in a clinical trial, through a numerical skills training program designed especially by the cognitive profile of children with Down’s Syndrome to augment their skills of basic mathematics and logical reasoning. The training program was conducted bi-weekly by a trained instructor for a duration of 30 minutes, each, over 2 months in an individualized manner. During the evaluation of the performance of the subjects in trained tasks following the training program, significantly higher scores were observed for the intervention group children on the Numerical Intelligence Scale, particularly in the subscales of counting, pre-syntactic processes, mental calculation, written calculation, and number knowledge, as compared to the control group.
participants, who did not receive numerical skills training. The gains on the Numerical Intelligence Scale were higher in the case of children with lower levels of Numerical Intelligence. Assessing the utility of the training program in solving untrained tasks successfully, it was noted that the training group had a greater improvement in performance compared to the control group, however, the study intervention failed to elicit any significant time x group interaction effect in terms of logical thinking and the ability to draw correspondences in either the children with Numerical Intelligence at the lower end of the spectrum or those with comparatively higher score. These results were confirmed using Cohen’s d. [24]

Impaired memory span that primarily hampers linguistic skills, along with vocabulary acquisition, syntactic awareness, and reading ability, in patients with Down Syndrome was addressed in a clinical trial that explored a parent-led auditory-only verbal rehearsal intervention, following the overt cumulative rehearsal strategy, conducted in the home setting in 10-minute sessions, five times per week, over 3 months to aid the auditory memory span and associated memory processes in children suffering from the disease. Outcome measures were classified into proximal (by assessing the performance of the participants in similar tasks) and distal (by assessing their performance in dissimilar tasks) measures and they were tested using the WISC digits-forward subtest and a combination of the Memory for Sentences subtest of the Woodcock-Johnson Psycho-educational Battery-Revised and the counting span task respectively. The proximal measure was significantly improved after the implementation of the verbal rehearsal intervention, however, there was only a marginally significant correlation between the two when compared to the active control group which was involved in merely visual activity. As for the distal measure, the performance improvement following the overt cumulative rehearsal was found to be significant whereas the gain following visual activity (active control) was not found to be significant, indicating the success of the intervention in augmenting the auditory-verbal memory, to enable them to perform untrained tasks. [25].
The intervention of Milieu Communication Teaching (MCT) at different frequencies— one session weekly and 5 sessions per week, with a duration of an hour each, were compared in terms of improvement in expressive vocabulary and intellectual abilities in children with Down’s Syndrome. At a controlled level of intellectual ability, the enhancement of vocabulary observed within the high-frequency group was greater than the progress noted in the low-frequency group, albeit not statistically significant [26].

**Behavioral Interventions**

Several studies have implemented various behavioral intervention strategies to enhance the cognitive abilities of patients with Down’s Syndrome.

One study has notably compared the effectiveness of two different behavioral interventions— Cognitive Orientation to Daily Occupational Performance (CO-OP) and Conductive Education (CE) in improving cognitive function in terms of coordinated fine motor activity skills. A two-arm crossover study was designed and COPM was administered to the children and their parents, to choose the target activity for each child in distinct spheres such as productivity, self-care, and leisure. The evaluation of participants' performance post-intervention was meticulously conducted, employing COPM and PQRS as primary outcome metrics. Additionally, The Bruininks-Oseretsky Test of Motor Proficiency – Second Edition Brief Form (BOT-2-BF) was employed as a secondary measure, enabling a nuanced assessment of motor activities, including fine manual dexterity, coordination, strength, and agility, thereby ensuring a comprehensive evaluation. PQRS scores revealed significantly enhanced performance due to intervention by Conductive Education (CE) compared to Cognitive Orientation to Daily Occupational Performance (CO-OP), whereas such significant statistical differences were not reflected in the COPM or BOTS-BF outcomes [27].

Another study has explored the potential of Responsive Teaching as a relationship-focused behavioral intervention, which has earlier been used for a plethora of other conditions, in catalyzing cognitive development, among other aspects of functioning, in children with Down’s Syndrome. Parents of the study subjects were instructed to engage in
communication and interactions corresponding to their child’s level of functioning, for 1.5 to 2 hours every week over a six-month study period, rather than externally directing their behaviors, which is commonly observed in mothers while dealing with their offspring with the condition. Both the intervention and control groups received an additional standard set of bi-weekly sessions at their local rehabilitative centers, organized by the Government of Turkey. Assessing the development of the participants, using the Turkish Version of the Denver Developmental Screening Test-II and the Ankara Developmental Screening Inventory, it was noted that the children in the intervention group made a significantly higher improvement as compared to those in the control group, in all 4 sub-domains of the two child developmental assessments, therefore rendering the intervention effective and feasible in augmenting child development [28].

A rather speculative behavioral intervention was designed in yet another clinical trial in which the relationship between correction of visual acuity using unifocal or bifocal glasses and cognitive function has been explored. The practice of urging children of the intervention group with Down’s Syndrome to wear glasses can be considered as a behavior modification and hence the associated intervention has been grouped along with other behavioral interventions. Study participants were randomly allocated to one of the two intervention groups- one in which bifocal glasses were prescribed and another in which unifocal glasses were advised for 9 months, following which the alterations in their ability to perform different executive functions were assessed using the Minnesota Executive Function Scale (MEFS) complemented by Behavior Rating Inventory of Executive Function (BRIEF) questionnaires of different age groups. MEFS scores demonstrated a significant improvement in the executive functions of the children in the bifocal intervention group, whereas, for the unifocal group, this improvement was small and not statistically significant. Additionally, the difference in the average post-treatment performance of the two intervention groups was found to be rather insignificant [29].
Pharmacological Interventions

Researchers are actively exploring ways to improve cognition in individuals with Down syndrome using pharmacological interventions.

A short-term study of 10 weeks was conducted to evaluate the effectiveness of Donepezil, an acetylcholinesterase inhibitor, in improving cognitive dysfunction in children aged 10-17 with mild to moderate DS. The study was a randomized, double-blind, placebo-controlled multicenter trial with 129 participants. The children were administered donepezil 2.5-10mg/day. However, the trial did not demonstrate any significant benefit of Donepezil over placebo in improving cognitive dysfunction [30].

A 20-week double-blind placebo-controlled trial was conducted to evaluate the effectiveness of Rivastigmine, a cholinesterase inhibitor, in improving cognition in individuals with Down syndrome. The study involved 22 children and adolescents between the ages of 10-17. The study evaluated the efficacy of Rivastigmine using various measures, including parental assessments of adaptive behavior and executive function, direct language, and memory measures. However, at the end of the trial, no significant changes were observed between the two groups [31].

Memantine is an antagonist of the N-methyl-D-aspartate receptor (NMDAR) subtype of glutamate receptor. Clinical trials were conducted to evaluate the effectiveness of Memantine in improving cognition. A 52-week randomized, double-blind, and placebo-controlled trial was conducted on participants over the age of forty, who showed no improvement in cognitive function [32]. Similarly, a 16-week randomized, double-blind, placebo-controlled trial (20mg/day orally) was conducted on participants aged between 17-32 years and failed to demonstrate any significant benefit of using Memantine [33].

Trials have been conducted to test the efficacy of epigallocatechin gallate (EGCG), which is a green tea extract. One such trial involved administering EGCG at a daily dose of 10mg/kg for six months, followed by a 3-month follow-up period. However, this trial did not show any improvement in cognition [34]. On the other hand, another trial involved administering cognitive training alongside EGCG (9mg/kg daily...
dose) for 12 months, followed by a 6-month follow-up period. The participants had regular cognitive training sessions (30-50 minutes per session, three days per week) and were provided with software kits (Feskits) to access various online training programs and exercises. This combination of cognitive training and EGCG significantly improved visual recognition memory, inhibitory control, and adaptive behavior [35].

Vitamin E has antioxidant properties. Research has indicated that oxidative damage is a leading factor in the development of Alzheimer's Disease (AD) and Down Syndrome (DS) [36]. A three-year randomized controlled trial (RCT) was conducted using a dose of 1000 IU of Vitamin E. However, the study results showed that Vitamin E failed to slow the progression of cognitive decline [36].

A clinical trial was conducted to test the effectiveness of a drug called Basmisanil. This drug is a GABAA-α5 negative allosteric modulator that is used to attenuate GABAergic function and restore the excitatory/inhibitory balance in the brain. The trial lasted for six months and involved participants taking either 120 or 240mg of the drug twice daily. For younger participants aged 12-13 years, the dose was reduced to 80 or 160mg. Unfortunately, the trial showed no improvement in cognitive function [37].

**Physical Intervention**

Recent trials conducted by researchers have shown that physical activity can significantly improve cognitive functions, including attention, memory, and executive control, in patients with DS. These findings highlight the importance of incorporating exercise into the daily routine of individuals with DS, not only for their physical health but also for their cognitive well-being [38].

According to a study, attending two weekly sessions of a 30-minute physical activity intervention conducted online through Zoom has been found to improve visual memory and new learning, as assessed by paired associates learning after 12 weeks of the intervention. Participants who only attended one session per week did not show the same level of improvement. However, it was found that there was no change in reaction time and attention time between the two groups [38].

In a study conducted for 8 weeks, the effects of assisted cycle therapy (ACT), no cycling (NC), and voluntary cycling
(VC) were compared on cognitive components such as language fluency, reaction time, inhibition, and set-shifting ability in adolescents with Down Syndrome (DS). The reaction time was measured using a Lafayette Instrument Visual Choice Reaction Time Apparatus and an economy clock/counter. Set-shifting ability was tested with a modified Wisconsin Card Sorting Test (MCST) adapted from Wilson et al. (1996). Response inhibition was assessed with the NEPSY Knock-Tap task (KT; Korkman et al. 1998). Language fluency was tested by the number of appropriate words participants articulated within 1 minute that fit the theme for the trial (NEPSY; Pennington et al. 2003). At the end of the trial, it was found that participants of ACT demonstrated an improvement in reaction time, inhibition, and language fluency compared to those who did not cycle or who cycled voluntarily. Moreover, ACT was found to be more beneficial than VC for executive function [39].

In a similar study evaluating ACT, it was found that it can improve manual dexterity. Manual dexterity causes a sudden increase in activity in the motor cortex, which results in a temporary increase in the levels of dopamine and norepinephrine. This increase in neurotransmitters can lead to an improvement in motor and executive function. The study concluded that after eight weeks, ACT was more effective than VC in improving manual dexterity and cognitive planning [40].

Conclusion

This comprehensive exploration of cognitive enhancement strategies for Down Syndrome (DS) provides a nuanced understanding of interventions across educational, behavioral, pharmacological, and physical modalities. The multifaceted nature of cognitive deficits in DS, encompassing language, memory, and executive functions, necessitates a diverse and tailored approach to intervention [2].

Educational interventions, highlighted by language and speech therapy, technology-assisted learning, and working memory training, demonstrate promising outcomes in ameliorating cognitive impairments [17-24]. The significance of behavioral interventions, including responsive teaching and motor skill-focused approaches, adds valuable insights to the cognitive enhancement landscape [25, 26, 27].

Pharmacological avenues, ranging from traditional
Acetylcholinesterase inhibitors to innovative agents like GABAA-α5 negative allosteric modulators, exhibit varied degrees of success in addressing cognitive dysfunction in DS [8-34]. Physical interventions, notably regular physical activity and assisted cycle therapy, emerge as potential catalysts for cognitive improvement [35-37]. The variability observed in the DS phenotype underscores the importance of personalized perspectives in comprehending and addressing cognitive deficits [7].

A holistic understanding and integration of diverse interventions remain imperative for optimizing cognitive outcomes in DS. The review serves as a valuable contribution to the evolving discourse on cognitive enhancement in DS, offering insights that may guide future research and intervention strategies for individuals with DS.

In conclusion, the multifaceted approaches presented in this review collectively contribute to the advancement of cognitive enhancement strategies in DS. As we navigate the intricate terrain of DS, acknowledging the diversity in cognitive presentations and exploring tailored interventions will be pivotal in achieving optimal cognitive outcomes for individuals with DS.

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