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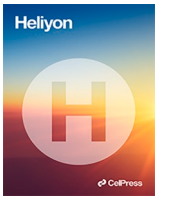

Research article

Cognition and communication in patients with spinal muscular atrophy: A systematic review

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1. Background

Spinal muscular atrophy (SMA) is a devastating inherited disorder caused by a ubiquitous deficiency in the Survival Motor Neuron (SMN) protein, with an incidence of around 1 in 6000 to 1 in 10,000 births [1]. It is the second most common autosomal recessive disorder leading to infant deaths if left untreated. Biallelic deletion of the coding region for the Survival Motor Neuron 1 (SMN1) gene is responsible for 95 % of cases of SMA [2]. SMA's main features are the progressive loss of motor activity caused by motor neuron degeneration and the functional and structural dysfunction of neuromuscular synapses, leading to muscle atrophy. SMA encompasses a broad continuum of disease severity that has been classified into five types, from type 0 to type 4 according to maximum motor milestones achieved [3].

Type 1 SMA (SMA1) is the most common form, affecting about 60 % of patients [3]. The Dubowitz decimal classification further stratifies SMA1 into subtypes based on clinical severity and onset age: type 1a denotes the acute form with onset within the first month, type 1b is the intermediate form with onset after the first month but before six months, and type 1c, the chronic form with onset after six months, where patients may achieve some motor milestones such as head control [4]. Patients with SMA1 typically present

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symptoms before the age of 6 months, are unable to sit independently, and without treatment, have a life expectancy of less than 2 years. They cannot sit down unsupported and are thus referred to as 'non-sitters.' Although SMA1 is often characterized by severe physical limitations, cognitive abilities are an area of ongoing research; early reports suggest patients may exhibit normal cognitive function and attentiveness at diagnosis, yet this remains to be thoroughly validated across the spectrum of the disease [5].

In children with type 2 SMA (SMA2), symptoms usually start later, though before the age of eighteen months. Children with SMA2 can sit independently but are unable to walk. They typically survive into early adulthood [3].

Children with type 3 SMA (SMA3) have relatively milder symptoms that begin after eighteen months. They can stand independently and are able to walk, although they may lose this ability in adolescence or later. They typically have a normal life expectancy [6].

Finally, people with type 4 SMA (SMA4) have the mildest form of the disease. Symptoms begin in adulthood and progress very slowly, and patients have a normal life span [6].

The severity of SMA is generally inversely correlated to SMN2 copy number, i.e., a larger number of SMN2 copies is associated with increased production of SMN protein and a less severe form of disease. This is because the SMN2 gene can partially compensate for the loss of function of the SMN1 gene, which is mutated in SMA [1].

Three disease modifying treatments Nusinersen, Onasemnogene abeparvovec-xioi (Zolgensma), and Risdiplam have been developed and shown to improve survival (particularly in SMA1), as well as motor function and milestone acquisition, with the observation of different new disease trajectories. However, the most impressive results have been observed when treatment is initiated before the first clinical symptoms appear [7,8].

1.1. Cognition and communication development in SMA patients

Prior studies have begun to shed light on the cognitive landscape of SMA. Polido et al. (2019) conducted a systematic review to assess cognitive performance in children with SMA, revealing mixed outcomes. Their findings suggest a possible correlation between the severity of motor impairment and cognitive function, with more pronounced cognitive challenges observed in SMA1 [9]. This underscores the importance of considering cognitive evaluations alongside motor assessments in SMA, particularly given the variability of cognitive outcomes across different SMA types. Such insights pave the way for a deeper understanding of the multifaceted impact of SMA on patient development and highlight the need for standardized cognitive assessment protocols in this population.

The clinical phenotype and natural history of SMA is well known in terms of motor, respiratory, and bulbar/swallowing complications [10], whereas the cognitive development and communication skills of children and adolescents with this disorder have not received much attention. It is, however, critical to monitor other developmental aspects that are important for patients' participation in society and quality of life, such as communication, social interaction, learning and problem-solving capacity.

In this review, 'communication' encompasses both the motoric aspects, which pertain to the physical ability to produce speech or gestures, and cognitive-communication competencies, which involve understanding, processing, and using language to interact effectively. While SMA's impact on motor functions is well-documented, its effect on cognitive-communication skills has not been as clearly defined, necessitating further exploration into how individuals with SMA comprehend and use language for effective communication. Moreover, communication has important implications in neurodevelopment, particularly for socialization, learning, and education, and it is strongly affected by the disease [11].

Studies on the development of cognitive and communicative skills in children with SMA remain limited. Also, existing studies do not reach a straightforward consensus, likely due in part to the constraints posed by the limited methods and tools available for assessing cognition and communication within this severely handicapped population. Furthermore, the lack of standardization compounds these challenges [12].

Recent therapeutic advances in SMA have shown promise in altering disease progression, particularly with early treatment regimens using Nusinersen and Onasemnogene abeparvovec-xioi (Zolgensma) [13]. While these treatments primarily target motor function improvements, their indirect effects on the assessment of cognitive and communicative skills warrant further investigation. As such, the full impact of these therapies on the methodologies for cognitive and communicative evaluations in SMA patients remains an important area for ongoing research.

In SMA1, the high mortality rate before age two, coupled with the difficulties in evaluating cognitive and communicative abilities in survivors who require a tracheostomy, complicates the study of these skills' interdependent development. Similarly, assessing the cognitive and social development of infants and toddlers is intricately linked to their communication skills. In order to evaluate these aspects, it is necessary to gather a body of knowledge on the natural history and development of communication and cognitive skills in SMA.

Thus, the evaluation of the cognitive skills of infant patients with SMA may require alternative methods and tools. For instance, there is a growing trend towards the use of an eye tracker device to measure such patients' reaction during pair-matching tasks and verbal requests to match visuals [14].

In this systematic review, we therefore aim to report on an updated and comprehensive review of the available literature about cognition and communication in patients with SMA.

2. Methodology

2.1. Research strategy

A systematic literature study was conducted on PubMed/Medline and ScienceDirect covering articles available between 2017 and November 2023.

The search included the following keywords: "*cognition*", "*communication skills*", "*language*", "*spinal muscular atrophy*" and/or "*SMA*". A detailed search strategy can be found in Table1b and Table 1a.

2.2. Screening of studies and selection criteria

This study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist. Two researchers (SA and ND) independently screened the titles and abstracts of the articles for relevance. Subsequently, full texts were reviewed comprehensively to determine their eligibility. We expanded our search to include references from the identified articles to ensure comprehensive coverage and to capture studies potentially missed in the initial search. Language was not a barrier to inclusion, and duplicates were systematically removed. Any disagreements regarding inclusion were resolved through consensus with a third researcher (HS).

We excluded papers published before 2017, as these were previously reviewed by Polido et al., in 2019, and also omitted reviews and studies focusing on neuromuscular diseases other than SMA. Inclusion criteria encompassed studies published between 2017 and 2023 that investigated cognition and communication in the context of SMA (see Table 1a and Table 1b).

Ultimately, twelve studies specifically addressing 'SMA and communication skills' or 'SMA and cognition' satisfied the selection criteria and were included in this review. These studies are further enumerated in Tables 2–5.

Table 5
Measure and results of cognition and communication profiles in untreated SMA patients.

Reference	Study design	Sample			Outcomes	Results
		Size	Type of SMA	Age range at evaluation (year)		
Hoshi et al. (2017)	Cross-sectional study	n = 36, no treatment	1	0.9–15	The CSBS DP Infant-Toddler Checklist survey	The most commonly used communication methods among SMA1 children were: 1) signs 2) electronic communication devices and 3) nonelectronic communication devices. 19.4 % of the children were unable to use any communication method to convey their intentions. The study did not report any p-values
Ball et al. (2019)	Cross-sectional study	n = 32, no treatment information	1	0.5–30	A researcher-developed online survey	Severe impairment of motor and communication development. Severe speech deficits related to clarity, independence, and intelligibility. Speech, gesture, speech-generating devices, and nontechnological pictures or symbol boards or books were the most commonly used communication method.
Zappa et al. (2021)	Retrospective chart review study	n = 22: children with SMA (no treatment)	1	3–11 Median: 5	Raven's Colored Progressive Matrices Test (RCPM) ALS Severity Score (ALSSS)	IQ of SMA 1children is on average in the high category with a mean score of 96.4 (SD = 15.4) Significant lower score in the more severe phenotypes (types 1 A and B SMA) than in type C ($p < 0.001$).
Lenzoni et al. (2021)	Cross-sectional study	n = 44, n = 22 type 3 SMA patients and n = 22 healthy controls	3	8–56	Comprehensive neuropsychological battery	SMA patients showed poorer performance in visuospatial abilities, executive functions and language as compared to healthy controls. Patients with greater motor difficulties had lower performance in attention, but higher performance in measures of language, verbal fluency, and memory. In men, but not women, cognitive test performance was associated with motor functioning

Table 6
Measure and results of cognition and communication profiles in SMA 1 Patients Receiving SMN Modulating Therapies.

Reference	Study design	Sample			Outcomes	Results
		Size	Type of SMA	Age range at evaluation (year)		
Pane et al. (2018)	Cross-sectional study	n = 122, treated with Nusinersen	1, with 12 of type 1.1, 73 of type 1.5, and 37 of type 1.9.	0.25–22	A structured pro forma to collect current and retrospective clinical data, including on speech acquisition.	Thirty-four patients (28 %) of types 1.5 and 1.9 acquired comprehensible speech
Tosi et al. (2023)	Cross-sectional study	N = 15, with 12 being treated with Nusinersen, 2 receiving Zolgensma, and 1 being treated with Risdiplam	1, with 5 patients of type 1a, 4 of type 1b SMA, and 6 of type 1c.	0.47–6.78	The Griffiths III scale The Vineland Adaptive Behavior System - Second Edition (VABS-II) Survey Interview Form	The mean general development quotient was 64.8, and 9 out of 15 had a score <70. Mean language score was 83.67. The mean of adaptive IQ was 68.67, which is indicative of global difficulties in adaptive functioning
Al-Zaidy et al. (2019)	Observational study (Follow-Up)	n = 15, treated with Zolgensma during the trial	1	0.07–0.63	Follow up to determine the ability to speak after treatment.	11 out of the included 15 patients were able to speak at the end of the 2y follow-up period.
Ngawa et al. (2023)	Observational study (Longitudinal, Prospective)	(N = 18) 11 Patients were treated postsymptomatically. 7 patients were treated presymptoatically.	1	<3	The Bayley Scales of Infant and Toddler Development™ – Third Edition	On average, patients treated presymptomatically scored higher than patients treated postsymptonatically on the cognitive and communication scale.

3. Data extraction and quality assessment

3.1. Cross-sectional studies

Quality assessment of the cross-sectional studies was conducted using the AXIS tool. The studies varied in quality with Pane et al. (2018), Osmanovic et al. (2020), Mix et al. (2021), and Tosi et al. (2023) rated as high quality; Lenzoni et al. (2021) and Ball et al. (2021) as moderate due to unjustified sample sizes and potential selection bias; Kizina et al. (2021) as fair; and Hoshi et al. (2017) as low quality due to multiple areas of concern including sample justification and internal consistency (Table 2).

3.2. Observational studies

For the observational studies, the ROBINS-I tool was applied to various observational studies, each with distinct designs. The study by Al-Zaidy et al. (2019) is an observational follow-up study, which exhibited high risk in the confounding and participant selection domains. Ngawa et al. (2023) conducted a longitudinal, prospective study showing a high risk in confounding and outcomes measurement domains. Vidovic et al. (2023) carried out a monocentric longitudinal study, which presented a moderate risk in confounding factors. Each study was thoroughly assessed for bias across multiple domains (Table 3).

3.3. Retrospective study

Lastly, the retrospective study by Zappa et al. (2021) was assessed with the NIH tool and was considered of good quality, scoring 9.5 (Table 4).

Each study was included based on relevance and methodological quality, ensuring a robust synthesis of the evidence within the PRISMA guidelines.

Table 7
Measure and results of cognition and communication profiles in SMA 2, 3 and/or 4 Patients Receiving SMN Modulating Therapies.

Reference	Study design	Sample			Outcomes	Results
		Size	Type of SMA	Age range at evaluation (year)		
Osmanovic et al. (2020)	Cross-sectional study	n = 34: adults with SMA undergoing treatment with Nusinersen, including 14 with type 2, 19 with type 3, and 1 with type 4; n = 34: adults with ALS	2, 3 & 4	SMA: Median: 40.2; ALS: Median: 65.8	Edinburgh Cognitive and Behavioural ALS Screen (ECAS) German version Wortschatztest (WST): German vocabulary test	SMA patients had significantly higher ECAS total score than ALS adults ($p < 0.001$ for all). No significant difference in intelligence between SMA and ALS patients, as measured by the WST test ($p = 0.49$).
Mix et al. (2021)	Cross-sectional study	n = 31 including 27 undergoing Nusinersen treatment; n = 19 control adults	2 & 3	19.1–64.6 Median: 35.9	Edinburgh Cognitive and Behavioural Amyotrophic Lateral Sclerosis (ALS) Screen (ECAS)	SMA patients and control adults had similar ECAS score ($p = 0.28$). SMA2 and 3 had similar ECAS score and for each cognitive domain ($p = 0.46$).
Kizina et al. (2021)	Cross-sectional study	n = 32: adults with SMA undergoing Nusinersen treatment, including 15 with type 2 and 17 with type 3	2 & 3	18–58 Median: 35	Wechsler Adult Intelligence Scale fourth edition (WAIS-IV), German version	Mean IQ of SMA2 and 3 is not significantly different ($p = 0.61$).
Vidovic et al. (2023)	Observational study (monocentric Longitudinal)	N = 23, SMA2 (n = 10) SMA3 (n = 13) treatment-naive patients	2&3	Mean age of all patients was (38.1 ± 11.4) years.	The German version of the Edinburgh Cognitive and Behavioral ALS Screen (ECAS)	At baseline, No difference in the absolute ECAS scores between patients with SMA2 and 3, except for the ALS-specific domain of Language. After 14 months of Nusinersen treatment, all patients showed significant improvement of the absolute scores in both subscores (ALS-specific: $p = 0.001$; non-ALS-specific: $p = 0.006$) and in the ECAS total score ($p < 0.001$).

4. Results

4.1. Study selection

Our systematic review identified twelve studies that met the inclusion criteria, capturing a broad spectrum of cognitive and communicative outcomes in patients with spinal muscular atrophy (SMA). The literature spanned from 2017 to 2023, with one pivotal study, Hoshi et al. (2017), included for its unique insights into communication patterns in SMA1 patients despite predating 2018.

4.2. Treatment-naïve SMA1 patients

Four studies focused on the cognitive and communication profiles of treatment-naïve SMA1 patients. These studies, documented in Table 5, provided valuable baseline data on the natural history of cognitive and communicative functions in this population. Key outcomes indicated a range of cognitive abilities, from preserved to significantly impacted, which were sometimes correlated with the severity of motor dysfunction [11,15–17].

4.3. Treated SMA1 patients

In contrast, an equal number of trials, outlined in Table 6, assessed similar profiles in SMA1 patients post-treatment. These studies offered a glimpse into the potential shifts in cognitive and communicative capabilities following intervention, highlighting improvements in some areas while identifying persistent challenges in others treatment [18–21].

4.4. SMA2, SMA3, and SMA4 patients

For the less severe phenotypes, SMA2, 3, and 4, four trials provided post-treatment assessments. The summaries of these studies, as seen in Table 7, suggested that treatment modalities might have differential impacts on cognitive outcomes and communication abilities, with some patients showing marked improvements and others exhibiting subtler changes [22–25].

4.5. Synthesis of findings

Collectively, the included studies employed a variety of research designs, ranging from cross-sectional analyses to longitudinal follow-ups, encompassing a diverse patient demographic. Despite the methodological heterogeneity, a narrative synthesis of the results revealed a pattern of cognitive resilience in some patients, while others faced notable communicative hurdles, irrespective of treatment status. This variability underlines the complexity of SMA's impact on neurodevelopmental outcomes.

5. Findings

5.1. Evaluating cognitive and communication profiles in untreated SMA patients

- *SMA1*

Three studies so far have discussed the cognition and communication profile of treatment-naïve patients with SMA1 [11,15,16] (Table 5).

To evaluate the different communication milestones among untreated children with SMA1, Hoshi et al. (2017) conducted a survey using the Communication and Symbolic Behavior Scales Developmental Profile (CSBS DP) Infant-Toddler Checklist. This survey assessed the range of communication methods used by the children, including their ability to communicate through electronic devices, and catalogued the types of expressions conveyed through such means. The study found that 50 % of children aged eleven months to fifteen years could use eye movement to indicate 'yes' or 'no', 47 % primarily communicated through eye fixation, 47.2 % used electronic communication devices, 30.6 % communicated vocally, and 22.2 % utilized nonelectronic communication devices. Notably, 19.4 % were unable to use any method to convey their intentions. While this study provides valuable quantitative data on communication methods in SMA1, it does not extend to a qualitative analysis of the effectiveness or comprehensibility of communication, an area that merits further exploration to fully understand the cognitive-communication capabilities of these children [15].

To assess communication through motor patterns, and the characteristics and methods thereof, Ball et al. (2019) surveyed parents of children with SMA1. This study was initially considered to involve untreated patients, as there was no explicit mention of treatment status. Findings revealed severe impairment in communication due to motor pattern disabilities, with pronounced deficits in respiratory, speech, finger, lip, and tongue motor skills. However, participants realized that their children had greater difficulty expressing language than understanding it. Parents reported that deteriorated clarity was the most common characteristic associated with speaking (the median reported score was 4.5, indicating low clarity), while independence was the least realized characteristic (the median score was 3.4, indicating relatively high dependency). The results indicated that children with SMA1 used gestures as the most common communication method, followed by speech, and speech-generating devices. Non-technological picture or symbol boards or books were the least commonly used communication method [16].

To evaluate cognitive profiles and communication skills, Zappa et al. (2021) conducted a study involving nineteen children with

SMA1, aged between three and eleven years, who were not on any SMN-restoring treatments. These children were benchmarked against nineteen typically developing controls. The researchers employed the Raven's Colored Progressive Matrices Test (RPCM) for non-verbal IQ assessment and the 'Test di Comprensione Grammaticale per Bambini' (TCGB) to evaluate language morphosyntactic comprehension. The ALS Severity Score (ALSSS) was utilized to gauge speech disturbances, with scores ranging from 1, indicating no useful speech, to 7, which denotes detectable speech disturbances, albeit with noticeable abnormalities. Hence, the ALSSS does not measure normal speech but ranges from the absence of useful speech to speech that is discernible yet not normal. In this cohort, the median non-verbal IQ and morphosyntactic comprehension for children with SMA1 were respectively in the high or medium-high range, irrespective of age, disease severity, or phenotype. Notably, the study found a significant direct correlation between ALSSS and CHOP-INTEND scores ($p < 0.001$), suggesting a linkage between the degree of motor function impairment and speech capability. More severe SMA1 phenotypes (type 1a and 1b) scored lower, while the less severe phenotype (type 1c) scored higher on these assessments ($p < 0.001$) [11].

- *SMA3*

One study so far has discussed the cognition and communication profile of treatment-naïve patients with SMA3 [17] (Table 5).

In their exploration of cognitive functions relative to clinical factors in SMA, Lenzoni et al. (2022) examined a cohort of 22 patients with SMA3. Utilizing a comprehensive neuropsychological battery alongside assessments of motor function—such as the Hammersmith Functional Motor Scale for SMA (HFMSE), the Revised Upper Limb Module (RULM), and the Six Minute Walk Test (6MWT)—the study delineated a clear relationship between motor function and cognitive abilities. It was found that better motor skills were associated with enhanced attention spans, correcting the initial confusion; thus, motor and cognitive functions are indeed correlated. Specifically, those with more pronounced motor impairments had more attentional deficits. Paradoxically, the same patients demonstrated superior language-related abilities, verbal fluency, and memory, suggesting a compensatory mechanism. This compensatory trend was significant among male patients but was not observed in female patients. The study did not explicitly provide reasons for this sex-specific difference. Compared to healthy controls, the SMA patients exhibited lower performance in several cognitive domains, including executive functions, language, and visuospatial abilities [17].

5.2. Evaluating cognitive and communication profiles in SMA patients receiving SMN modulating therapies

- *SMA1*

Four trials evaluated the cognitive performance cognitive and/or communication profile of SMA1 patients that had received an SMN modulating therapy [18–21] (Table 6).

In the study by Pane et al. (2018), the functional capabilities, including communication skills, of 33 SMA1 patients were assessed. These patients began Nusinersen treatment at a mean age of 12.4 months, receiving four doses over sixteen weeks. The research highlights the critical nature of treatment initiation timing and subsequent assessments of cognitive, language, and motor skills to evaluate the therapeutic effects on developmental progress. Evaluations utilized the CHOP-INTEND and HINE-2 for motor function, and consistent with prior terminology used in this context, 'communication skills' were assessed alongside motor abilities, reflecting a significant enhancement post-treatment.

The results indicated that 34 of the 122 participants were able to vocalize short sentences comprehensible to the evaluators. The majority (81 %) of these communicative participants were diagnosed with the least severe form of SMA1, categorized as 1c in the Dubowitz decimal classification. Contrastingly, only a small fraction (1.9 %) of those with a more severe classification (Type 1b) could produce intelligible speech [18].

In the study by Al-Zaidy et al. (2019), the health outcomes, with a focus on motor function as measured by CHOP-INTEND, were evaluated in 15 infants with SMA1 treated with the gene replacement therapy AVXS-101 (Zolgensma). Treatment commenced when infants had a mean age of 5.6 months, followed by cognitive and language assessments over a two-year period. Speech ability, a component of communication skills, was assessed alongside motor function; however, the specific tests used were not detailed. It is implied that assessments like HINE-2 may have been utilized, as 11 infants (73 %) demonstrated the ability to vocalize words post-therapy. The exact timing of these assessments relative to the treatment initiation was not specified, an important detail for interpreting the progression of outcomes [19].

Ngawa et al. (2023) tracked the psychomotor, cognitive, and communicative development of SMA1 patients, distinguishing between those who began treatment after the onset of symptoms ($n = 11$), treated at various points from 32 to 488 days of age, and those treated presymptomatically ($n = 7$), with interventions starting as early as 37 days after birth. The Bayley Scales of Infant and Toddler Development™ – Third Edition (BSID-III) was employed to measure developmental progress. Cognitive outcomes on the BSID-III revealed that six out of seven presymptomatic patients (86 %) achieved average scores, with assessments conducted at varying ages but referenced to the last measurement for consistency. One individual was in the low average range. For postsymptomatic patients, seven (64 %) scored in the average, three in the low average, and one in the abnormal range for cognition. On the language scale, four presymptomatic patients (57 %) were average, with one each in the low average and abnormal ranges, and one not assessed. Among postsymptomatic patients, five (45 %) were average, one low average, and five abnormal. However, the study's robustness is questioned by a high risk of bias rating according to the ROBINS-I tool. This assessment tool critically examines seven domains of bias, which can significantly influence the study's conclusions [20].

Tosi et al. (2023) investigated the neurocognitive development of 15 children with SMA1, evaluated through the Griffiths III scale

and the Vineland Adaptive Behavior System - Second Edition (VABS-II) following treatment with disease-modifying therapies. The children, with a mean age of 2.6 years at assessment (range 0.47–6.78 years), had started treatment at a mean age of 6.03 months. The study reported a mean general development quotient of 64.8 from the Griffiths III scale, indicating developmental delays, with nine patients scoring below 70 ($p < 0.001$). Language development was a relative strength with variability in scores (mean 83.67, range 51–113, $p = 0.024$). The VABS-II revealed a mean adaptive behavior composite score of 68.67, reflecting overall adaptive functioning challenges. Strengths were reported in the communication domain (mean 78.60, $p < 0.001$). These assessments were integrated into the standard follow-up protocol for patients under treatment, aligning the evaluation timeline with the therapeutic interventions [21].

- *SMA2, 3, and/or 4*

Four studies evaluated the cognitive performance cognitive and/or communication profile of SMA2,3, and 4 patients that had received an SMN modulating therapy [22–25] (Table 7).

Osmanovic et al. (2021) compared cognitive functions in adults with SMA2–4 ($n = 34$, all receiving Nusinersen) and Amyotrophic Lateral Sclerosis (ALS, $n = 34$). Using the Edinburgh Cognitive and Behavioural ALS Screen (ECAS) and a German vocabulary test (Wortschatztest, WST), they assessed various cognitive domains. Contrary to the initial assertion, SMA patients performed better than ALS patients in memory, language, and executive function on the ECAS, with significant differences in the ECAS total score favoring SMA patients ($p = 0.001$). The vocabulary abilities measured by the WST were similar between the SMA and ALS groups, with no significant difference ($p = 0.502$). Notably, the study did not compare these patients to healthy controls, and specific details regarding the exact duration of Nusinersen treatment prior to assessment were not provided [22].

Mix et al. (2021) assessed the cognitive functions in a cohort of adults with SMA2 and 3 ($n = 31$; aged 19.1–64.6 years) during the early two-month loading phase of Nusinersen treatment, specifically within two weeks of initiation. Comparisons were made with matched healthy controls ($n = 19$). The study utilized the Edinburgh Cognitive and Behavioural ALS Screen (ECAS) to measure memory, visuospatial abilities, language, verbal fluency, and executive functions. The results indicated no significant differences between the SMA patients and healthy controls across all cognitive domains, with p-values as follows: memory ($p = 0.374$), visuospatial abilities ($p = 0.558$), language ($p = 0.412$), verbal fluency ($p = 0.423$), and executive functions ($p = 0.927$). Furthermore, the study reported no significant differences in ECAS scores between patients with SMA2 and 3 ($p = 0.424$). An inverse correlation was found between physical function and executive function, suggesting that individuals with decreased motor function may exhibit increased executive function ($\tau = -0.36$, $p = 0.018$). The authors propose that this may reflect an adaptive mechanism of executive function due to motor impairment, possibly through the reallocation of cognitive resources or enhanced caregiver interaction [23].

Kizina et al. (2021) studied a total of 33 adult patients, including twelve females and twenty-one males aged 18 to 58, undergoing Nusinersen treatment, to evaluate their IQ using the Wechsler Adult Intelligence Scale (WAIS). The WAIS measures verbal comprehension, perceptual reasoning, working memory, and processing speed, although processing speed was excluded due to its dependence on time-bound motor functions. In their findings, compared to the general population, the average scores for both the working memory index ($p = 0.012$) and the perceptual reasoning index ($p = 0.013$) were significantly lower in adults with SMA2 ($n = 15$), while no significant difference was observed in the verbal comprehension index. For SMA3 patients ($n = 17$), there was a non-significant trend towards decreased IQ scores compared to the general population. Additionally, there was no significant difference in mean IQ scores between SMA2 and 3 patients. It's important to note that the timing of treatment initiation in relation to cognitive assessments was not explicitly detailed in the study [24].

Vidovic et al. (2023) conducted an assessment of the cognitive profile in adult patients with SMA2 and 3 coinciding with the initiation of Nusinersen treatment. Cognitive function was measured using the Edinburgh Cognitive and Behavioral ALS Screen (ECAS) immediately before the first treatment dose and again after 14 months, which was a year after completing the treatment initiation. Initially, the study found no significant differences in the ECAS scores between the two SMA groups, aside from the Language domain where type 2 patients scored higher ($p = 0.009$), a result that warrants further investigation. Subsequent ECAS evaluations indicated improvements across all measured domains after 14 months. These observed changes in cognitive performance throughout the treatment period do not necessarily imply a direct effect of Nusinersen on cognitive or language functions, and the study does not assert causation. The significant advancements in scores were noted in ALS-specific domains (Language, Verbal Fluency, Executive Function) and the non-ALS-specific domain of Memory, as well as in the overall ECAS scores [25].

6. Discussion

The cognitive and communication profiles of SMA patients, as highlighted by Polido et al. (2019), remain a focal point in the wake of emerging treatment modalities. Their review, which stands as a key reference up to that period, suggested that SMA2 and 3 are not typically linked with cognitive impairment, while type 1 presents a complex spectrum of cognitive outcomes. It was observed that the severity of motor impairment might correlate with cognitive impairment (or deficits), particularly in SMA1 where Types 1A and 1B often show more significant cognitive deficits than the less severe type 1C [9].

Recent studies continue to substantiate the normal cognitive functioning in types 2 and 3, but with more nuance: when subjected to detailed assessments, these studies, such as Lenzoni et al. (2021), expose more nuanced cognitive issues in adult patients, including deficits in executive functions and attention, visuospatial abilities, language, and attention the last being correlated to motor function [17]. This indicates that despite the outward appearance of normal cognition, subtle yet significant challenges persist.

For SMA1, the literature is more varied. Regarding specifically cognition and language comprehension the only newer study reported normal skills in a broad aged population of untreated SMA1 patients [11]. This is in contradiction to previous studies of Polido

et al. that reported a poorer performance of SMA1 patients in more specific pair-matching tasks of increasing complexity in the context of an eye tracking setting. Interestingly these tasks required specific skills like attention, spatial location processing and executive function that may not have captured in the context of a RPCM.

Regarding expressive speech language and in communication, and in contradiction to receptive language skills, recent studies confirmed a clear impairment in treatment naïve SMA1 patients, strongly dependent on the SMA1 phenotypes (specifically Types 1A and 1B versus 1C), and on general motor function as measured by the CHOP INTEND scale [11,16].

The opposite clinical picture of well-preserved cognitive function together with impairment in expressive language and communication in SMA1 patients suggests that non-verbal cognitive abilities, potentially indicative of compensatory cognitive mechanisms, can be an asset in SMA1 patients, although they may not be immediately evident due to physical disabilities. These capacities must be considered in the management and educational planning for these children. This is particularly important as language expressive impairment very often limits the social interactions of SMA1 children only to the surrounding people of the immediate family able to understand their messages.

However, the evaluation of cognition in SMA1 is limited to the evaluation/use of tests that do not require language expressive skills and motor abilities, such as manipulating, limiting a proper comprehensive evaluation of cognition like for example the use of a complete Wechsler test.

The significant knowledge gap SMA research, particularly concerning the standardization of methodologies focused on cognition and communication, cannot be overlooked. Establishing standardized assessment tools for these domains is crucial and should be a priority for future research. This step is essential to deepen our understanding of SMA's full impact and the outcomes of various treatments. Consequently, advancing the standardization of cognitive and communication assessments will bridge this gap and foster a more comprehensive grasp of SMA's implications on patient health and recovery. In this new era, where patients are increasingly receiving treatment, it is also critical to evaluate how such interventions influence cognitive assessments. We must carefully interpret improvements in communication or cognitive scores, recognizing that they may not be direct effects of treatment. For instance, Pane et al. (2018) and Al-Zaidy et al. (2019) reported post-treatment advancements that could be attributed to patients' enhanced capacity to manifest their cognitive abilities, likely facilitated by improved motor function from treatments like Nusinersen.

The influence of disease-modifying therapies on cognitive and communication outcomes in SMA1 is a subject of ongoing research, with a focus on treatments such as Risdiplam, Nusinersen, and gene replacement therapy with Zolgensma. However, a common limitation is the lack of comprehensive baseline cognitive and communication evaluations before treatment – let alone that these are standardized -, particularly in very young patients. Notwithstanding this limitation, evidence suggests that functional communication improvements correlate with significant motor benefits from treatment, potentially leading to a better ability to express and interact, as well as better attention and executive function. This underscores the potential value of early detection and intervention, as presymptomatic treatment may result in more favorable outcomes than postsymptomatic treatment.

Lastly, when considering cognitive evolution in treated SMA2, 3, and 4 patients, the methodological variability across studies precludes definitive conclusions. Vidovic et al. (2023) offer a unique perspective, having assessed cognitive functions in SMA2 and 3 patients before and after treatment over a specified follow-up period. While their findings suggest a correlation between treatment and cognitive development, it is important to interpret these changes within the context of broader cognitive evolution over time rather than attributing them directly to the treatment effects alone.

7. Conclusion

The body of research investigating cognitive and communicative functions in spinal muscular atrophy (SMA) patients presents a complex landscape, shaped by the diversity of assessment tools and the heterogeneity of study designs. Despite these methodological variances, which challenge the formulation of definitive conclusions, emerging evidence suggests that early intervention, particularly with presymptomatic SMA1 patients, is associated with notable improvements in cognitive and communication abilities. These findings highlight the potential of disease-modifying treatments to positively influence developmental trajectories, not just in halting or slowing the progression of physical symptoms but also in supporting cognitive and communicative development.

In SMA2 and 3, where motor impairments are less severe, treatment appears to correlate with a positive developmental trend in cognitive and communication skills. This observation bolsters the argument for the effectiveness of disease-modifying therapies and underscores the necessity for early and proactive treatment approaches.

The key takeaway from this body of work is the critical importance of timely intervention and the need for consistent, standardized measures in assessing cognitive and communicative outcomes in SMA. As the therapeutic landscape continues to evolve, it is imperative to integrate robust cognitive and communicative assessments into the standard care protocol, ensuring that all SMA patients can achieve their full potential. This integrative approach is vital not only for enhancing quality of life but also for paving the way toward more personalized and effective treatment strategies for SMA.

CRediT authorship contribution statement

Sanae Akodad: Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Delphine De Smedt:** Writing – review & editing, Supervision. **Simon Baijot:** Writing – review & editing. **Hilde Stevens:** Writing – review & editing, Validation, Supervision. **Nicolas Deconinck:** Writing – review & editing, Validation, Supervision.

Declaration of competing interest

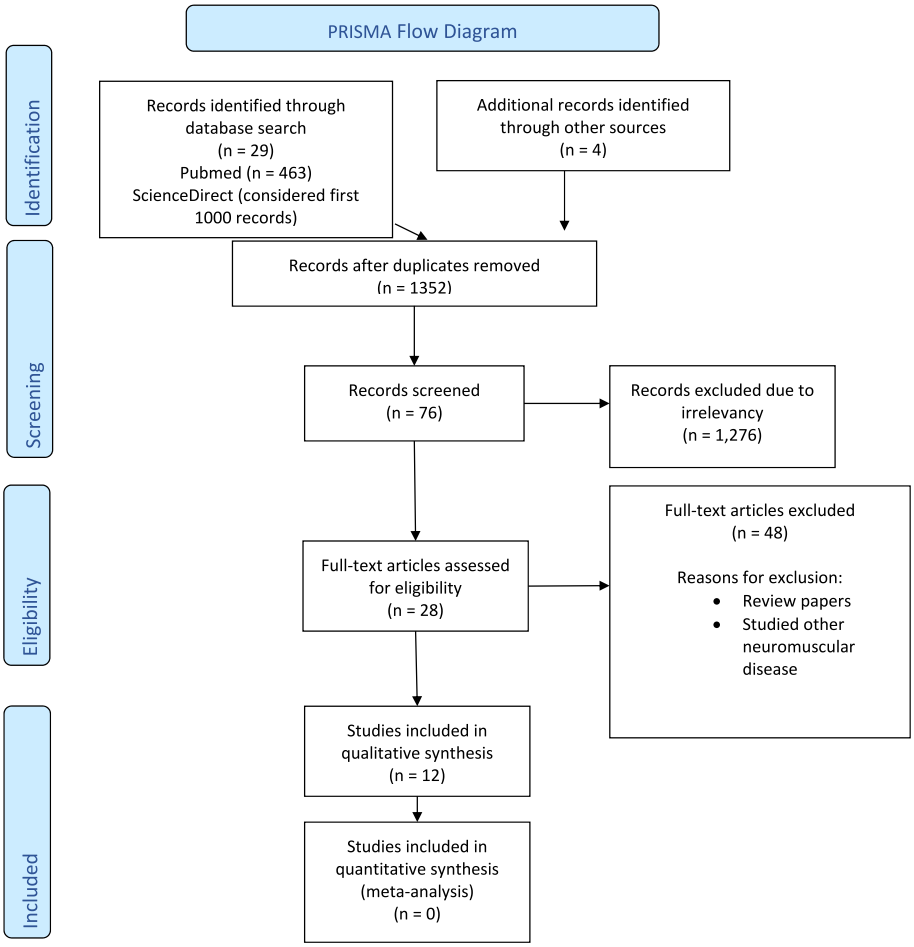
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix

Table 1(a)
Literature search strategy.

Searched Databases	PUBMED	ScienceDirect
Search strategy	(("spinal muscular atrophy" [All Fields] OR ("SMA" [All Fields]) AND ("cognition" [All Fields] OR "communication skill" [All Fields] OR "speech" [All Fields] OR "language" [All Fields]))	("spinal muscular atrophy" OR "SMA") AND (" cognition" OR "communication skill" OR "speech" OR "language")
Eligibility Criteria	- Studies published between 2015 and 2023 - Cognition assessment in individuals with SMA - Communication skills in individual with SMA	
Exclusion Criteria	- Review papers - Studies discussed other neuromuscular diseases	

Table 1(b)
Literature search strategy: PRISMA FLOW DIAGRAM.



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. https://doi.org/10.1371/journal.pmed1000097

Table 2
AXIS CRITICAL APPRAISAL TOOL FOR CROSS-SECTIONAL STUDIES.

Questions	Hoshi et al. (2017)	Pane et al. (2018)	Osmanovic et al. (2020)	Lenzoni et al. (2021)	Ball et al. (2021)	Kizina et al. (2021)	Mix et al. (2021)	Tosi et al. (2023)
Were the aims/objectives of the study clear?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the study design appropriate for the stated aim(s)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the sample size justified?	No	Yes	Yes	No	No	No	Yes	No
Was the target/reference population clearly defined? (Is it clear who the research was about?)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Was the sample frame taken from an appropriate population base so that it closely represented the target/reference population under investigation?	No	Yes	Yes	Yes	No	No	Yes	Yes
Was the selection process likely to select subjects/participants that were representative of the target/reference population under investigation?	No	Yes	Yes	Yes	No	No	Yes	No
Were measures undertaken to address and categorize non-responders?	No	Yes	Yes	Don't know	Don't know	No	No	Don't know
Were the risk factor and outcome variables measured appropriate to the aims of the study?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were the risk factor and outcome variables measured correctly using instruments/measurements that had been trialed, piloted or published previously?	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Is it clear what was used to determined statistical significance and/or precision estimates?	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were the methods (including statistical methods) sufficiently described to enable them to be repeated?	Don't know	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were the basic data adequately described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Does the response rate raise concerns about non-response bias?	No	No	No	No	No	Don't know	Don't know	Don't know
If appropriate, was information about non-responders described?	No	Yes	Yes	Don't know	Yes	No	No	No
Were the results internally consistent?	No	No	No	Yes	No	No	No	Yes
Were the results for the analyses described in the methods, presented?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were the authors' discussions and conclusions justified by the results?	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were the limitations of the study discussed?	Yes	No	Yes	Yes	Yes	No	Yes	Yes
Were there any funding sources or conflicts of interest that may affect the authors' interpretation of the results?	No	No	No	No	No	No	No	No
Was ethical approval or consent of participants attained?	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes

Table 3
ROB FOR THE OBSERVATIONAL STUDY.

Study	Study Design	Confounding	Participants selection	Classification of intervention	Deviation from intended interventions	Missing data	Outcomes measurement	Selection of the reported results
Al-Zaidy et al. (2019)	Observational Follow-Up	High Risk	High Risk	Low	Low	Low	Low	Low
Ngawa et al. (2023)	Longitudinal, Prospective	High Risk	Low Risk	Low High	Low	Low	High	Low
Vidovic et al. (2023)	Monocentric Longitudinal	Moderate Risk	Low risk	Low	Low	moderate	Low	Low

Table 4
CRITICAL ASSESSMENT OF THE RETROSPECTIVE STUDY. NIH critical appraisal tool for retrospective studies.

NIH critical appraisal tool for retrospective studies																
Study	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Scores	Quality
Zappa et al. (2021)	Y	Y	Y	Y	N	NR	Y	NA	Y	N	Y	NR	NR	Y	9.5	Good

Total scores (Yes = 1, No = 0.5, NR & NA = 0); Quality rating: good (9–14 point) or fair (7–8 point) or poor (0–7 points); NA: not applicable, NR: not reported, Y: Yes, N: No.

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