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A Further Characterisation of the Neuropsychological Profile, Social Perception, and Academic Skills in Sotos Syndrome

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ABSTRACT

Background: Sotos syndrome (SoS) is a rare genetic disorder characterised by physical overgrowth and by frequent intellectual disability and comorbidity with neurodevelopmental disorders. A recent study documented a specific cognitive profile of SoS. However, further research is needed to replicate and expand these findings to other neuropsychological domains, including social perception. Moreover, numeracy has long been considered as a weakness in SoS, but inconsistent evidence asks for a further assessment of academic skills.

Method: This single-cohort, cross-sectional study enrolled 28 participants with SoS aged 5–18 years, who underwent a comprehensive neuropsychological assessment. Moreover, a school-age subgroup was administered with standardised tests assessing academic skills.

Results: The neuropsychological profile was characterised by lowest scores in both language and visuospatial abilities and highest scores in memory for faces. Greatest difficulties were observed in rapid verbal production, visuospatial memory and graphomotor control. Neither attention and executive functions nor social perception skills were relative weaknesses or strengths of the profile. An exploratory analysis revealed that the comorbidity with autism spectrum disorder and/or attention-deficit/hyperactivity disorder did not result in a different neuropsychological profile. A large part of the sample had poor mathematics skills, and only one participant did not display any difficulties in mathematics.

Conclusions: This study extends the previous characterisation of the SoS cognitive profile and documents a prevalent difficulty in mathematics skills. Notably, social perception does not emerge as selectively impaired in SoS. The results have important implications for tailoring rehabilitative interventions, school adjustment and daily living of children and adolescents with SoS.

1 | Introduction

Sotos syndrome (SoS) is a rare congenital autosomal dominant overgrowth disorder, with an estimated prevalence of 1:14000 newborns. SoS is associated with intragenic mutations or microdeletion of the *NSD1* gene in 5q35 chromosomal region (Kurotaki et al. 2002; Tatton-Brown et al. 2005). Cardinal clinical features of this syndrome are physical overgrowth (acromegalic appearance, excessive height and/or head circumference and advanced bone age) and intellectual disability (ID) (Sotos et al. 1964; Cole and Hughes 1994). Other common features are systemic malformations, joint hyperlaxity and seizures (Brioude et al. 2019).

Even though ID is a cardinal characteristic of SoS, a wide spectrum of cognitive functioning has been reported (Lane et al. 2016). *NSD1* gene alterations exert widespread effects on neurodevelopment through epigenetic mechanisms that remain to be fully elucidated (Harris and Fahrner 2019). As observed in other genetic syndromes affecting cognitive and behavioural functioning, such as Williams syndrome (Vicari et al. 2004), Down syndrome (Ghezzo et al. 2014) and Malan syndrome (Butti et al. 2025), specific neuropsychological profiles may arise as a consequence of these genetic disruptions and the resulting cortical malformations. In SoS, such malformations were documented in most individuals, although varying in location and distribution (Neeman et al. 2024). Only recently has research started to shed light on specific cognitive features of SoS. Although the specific prevalence is unknown (Lesinskiene et al. 2024), the reported comorbidity with Attention-Deficit/ Hyperactivity Disorder (ADHD) suggests that executive functions may be specifically impaired in SoS (Lane et al. 2016; Smith et al. 2023). Moreover, most studies investigating cognitive abilities in SoS have focused only on general intellectual abilities or on a few specific neuropsychological domains, such as language or motor functioning (Finegan et al. 1994; Ball et al. 2005; de Boer et al. 2006). Since cognitive functions are strongly interdependent, especially in children with ID (Ferrari et al. 2023), the adoption of a single, co-normed battery assessing multiple domains can provide a comprehensive description of cognitive strengths and weaknesses. The cognitive profile of a UK sample that included children and adults with SoS was characterised by relative strength in verbal ability and visuospatial memory but relative weakness in non-verbal reasoning ability, based upon results on the British Ability Scales (BAS3). However, further research is needed to replicate and expand these findings, particularly by exploring additional neuropsychological domains not previously assessed.

Atypical social behaviour was previously reported in SoS (Cole and Hughes 1994; Sarimski 2003; de Boer et al. 2006), but only in recent years has the social-behavioural phenotype been systematically investigated. An increased association between SoS and autism spectrum disorder (ASD) has been proposed (Timonen-Soivio et al. 2016), with two studies reporting autistic features to be present in 70% (Sheth et al. 2015) and 83% (Lane et al. 2017) of the samples with SoS. A short report adopting the gold standard ADOS-2 tool has confirmed an increased risk of ASD in SoS, with 72.7% of SoS children showing mild to moderate levels of ASD symptoms (Riccioni et al. 2024). According to the DSM-V classification, a core criterion for ASD involves persistent deficits

in social communication and social interaction across multiple contexts (American Psychiatric Association 2013). These deficits include difficulties in social perception skills, which are a set of cognitive abilities that enable understanding others' emotions and mental states. These skills are often referred to as theory of mind and facial affect recognition in research on developmental disabilities (Baron-Cohen et al. 1985; Loukusa et al. 2014; Lozier et al. 2014). Previous literature has consistently documented deficits in social perception skills in idiopathic ASD as well as in genetic syndromes that present comorbidity with ASD (Happé and Frith 2014; Baribeau et al. 2015; Vivanti et al. 2018). Differences in social communication and responsiveness were reported in SoS by means of standardised questionnaires (Sheth et al. 2015; Lane et al. 2017). Nevertheless, no previous studies have directly tested social perception skills in individuals with SoS, which should be considered in the broader context of neuropsychological profile.

The presence of ID and cognitive impairments in children with SoS affects their learning abilities and school attainments (Sarimski 2003). In a seminal work by Cole and Hughes (1994), numeracy was pointed out by parents as the weakest area. In that study, nearly all children, even those with average intellectual abilities, presented greater difficulty with numeracy than literacy. Nevertheless, following research on this topic is scarce and results are conflicting. The study of Lane et al. (2019) reported a deficit in quantitative reasoning, measured as detection and application of rules concerning sequential patterns and relationships between pairs of numbers, as a main feature of the SoS cognitive profile. A study by the same group (Lane et al. 2019a) explored domain-specific numeracy skills through the administration of a dot comparison task to a sample of children and adults with SoS and to two healthy and clinical control groups. The findings suggested that the approximate number system, namely the rapid and intuitive sense for numbers, does not appear to be selectively impaired in SoS. This inconsistent evidence asks for a further assessment of academic skills.

The current study investigated the neuropsychological profile of Italian children and adolescents with SoS, with the aim of replicating and further elaborating on the previously identified cognitive profile (Lane et al. 2019). Participants aged 5–18 years underwent a neuropsychological assessment using the NEPSY-II, which covered multiple cognitive domains. As all subtests were standardised on a single, wide sample of children and adolescents, the NEPSY-II allows reliable comparisons between domains and subtests even without a control group (Russell et al. 2005). Similar to the BAS3, the NEPSY-II is widely employed to investigate specific profiles of cognitive functioning in developmental ages, including children with ID (Korkman et al. 2007). While both batteries evaluate comparable cognitive abilities, albeit using different terminologies (e.g., the BAS3's verbal ability cluster versus the NEPSY-II's language domain), a key difference is that the NEPSY-II includes specific subtests assessing social perception (i.e., theory of mind and affect recognition). The adoption of the NEPSY-II in this study allowed for the assessment of these abilities within the broader context of cognitive functioning in SoS. The NEPSY-II has been widely adopted to describe the neuropsychological profile of different neurodevelopmental disabilities and genetic syndromes, such as ASD (Narzisi

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et al. 2013), epileptic syndromes (Zilli et al. 2015), Joubert syndrome (Butti et al. 2023), Williams syndrome (Butti et al. 2024a) and Beckwith–Wiedemann syndrome (Butti et al. 2024b). Additionally, a subgroup of school-age participants underwent standardised tests to assess reading, comprehension, and mathematics skills. According to the previous description of the SoS cognitive profile (Lane et al. 2019), we anticipated differences across neuropsychological domains and greater difficulties in mathematics skills.

2 | Materials and Methods

2.1 | Participants and Procedure

Families affiliated with the Italian SoS Association (ASSI Gulliver) were informed of the possibility of participating in the study. All interested families were then contacted by the researcher to be further informed about aims and procedures of the study and to arrange their visit to the Scientific Institute, IRCCS E. Medea, where the assessments were carried out. Inclusion criteria were (i) genetic diagnosis of SoS confirmed through chart review and (ii) age from 5 to 18 years. Twenty-eight children and adolescents (mean age = 12.2; SD = 3.9) were recruited and underwent the neuropsychological assessment. As expected, many participants (42%) had a previous clinical diagnosis of ASD,

ADHD, or both. All participants had their intelligence quotient (IQ) assessed within the 2 years prior to recruitment. Although different tests were used (e.g., Leiter scales and Wechsler scales), preventing the inclusion of IQ in the analyses, a chart review indicated that 46% of the sample had ID (i.e., IQ < 70), 29% had borderline intellectual functioning (i.e., 70 < IQ < 84), while the remaining 25% exhibited average intellectual functioning (i.e., IQ > 84). Standardised academic skills tests were administered to a subgroup of 18 participants. Remaining participants were not able to sustain these tests since they attended the kindergarten (N = 2), they had just started the primary school and were not yet attending standard classes (N = 3), they had speech impairments (N = 3) or they presented severe ID (N = 2). As expected, this subgroup was older (mean age = 13.7; SD = 2.8) and had a lower prevalence of ID (22%) compared to the whole sample. All participants followed a differentiated and/or reduced school programme and were assisted by a special education teacher in accordance with Italian laws. Demographic and clinical features of the whole sample involved in the neuropsychological assessment and of the subgroup receiving also the academic skills assessment are reported in Table 1.

The assessment was conducted over two consecutive days. Duration and number of sessions were adapted to individual characteristics (e.g., age and behaviour). Parents were asked to sign an informed consent form and children gave their assent to

TABLE 1 | Demographic and clinical features of the whole sample administered with the neuropsychological assessment and the subgroup administered with academic skills tests.

	Neuropsychological assessment (N = 28)	Academic skills assessment (N = 18)
	N (%)	N (%)
Sex (females)	10 (36%)	6 (33%)
Genetic diagnosis		
Intragenic mutation of *NSD1*	22 (79%)	17 (94%)
Microdeletion of *NSD1*	6 (21%)	1 (6%)
Clinical features		
Macrocephaly	24 (86%)	15 (83%)
Height >2 SD above the mean	21 (75%)	13 (72%)
Advanced bone age	14 (50%)	8 (44%)
Epilepsy	5 (18%)	1 (6%)
Speech impairment	3 (11%)	0
Comorbidity		
ASD	6 (21%)	1 (6%)
ADHD	4 (14%)	1 (6%)
ASD and ADHD	2 (7%)	2 (11%)
Intellectual functioning		
Average (IQ > 84)	7 (25%)	7 (39%)
Borderline (IQ 70–84)	8 (29%)	7 (39%)
Intellectual disability (IQ < 70)	13 (46%)	4 (22%)

Abbreviations: ASD = autism spectrum disorder; ADHD = attention deficit/hyperactivity disorder.

participate before starting any procedure. All procedures were in accordance with the Declaration of Helsinki and were approved by Ethical Committee of the Scientific Institute, IRCCS E. Medea (Prot. 18/21 CE).

2.2 | Neuropsychological Assessment

A subgroup of tests belonging to the NEPSY-II battery was selected to assess multiple cognitive domains and abilities in children with SoS (Korkman et al. 2007; Urgesi et al. 2011) (Table 2).

Raw scores on NEPSY-II subtests were converted into scaled scores (mean = 10, SD = 3, range = 1–19) with respect to the normative conversion tables reported in the Italian validation manual (Urgesi et al. 2011). Scaled scores > 7 represented preserved abilities, while scaled scores falling below 2 SD from the mean (< 4) indicated weak performance. The presence of severe ID and/or speech impairments did not allow the administration of the full battery to some participants.

2.3 | Assessment of Academic Skills

Academic skills were assessed with tests appropriate to each participant's school competence as attested by their individualised education programme. The standardised tests *valutazione delle abilità di lettura e comprensione* MT-3 and *valutazione delle abilità di calcolo e del ragionamento matematico* AC-MT (Cornoldi and Carretti 2016; Cornoldi et al. 2017; Cornoldi

et al. 2020) were administered to evaluate reading, comprehension and mathematics. For reading, both speed and accuracy were measured. Mathematics tests evaluated arithmetic skills (i.e., calculation and knowledge of basic arithmetic rules), accuracy and speed of mental calculation. Calculation speed was considered only when the result was correct in at least one third of the items. On the basis of normative tables, the following four-level classification was obtained according to percentile distribution: fully achieved criterion (percentile > 75), sufficient performance (percentile 11–75), request for attention (percentile 6–10), request for immediate intervention (percentile ≤ 5). Even though these levels do not imply a diagnosis, they are widely adopted for screening children with learning difficulties (Barbiero et al. 2019).

2.4 | Data Handling and Statistical Analysis

For the NEPSY-II, a global score was computed averaging the scaled score on the subtests for each neuropsychological domain. If scaled scores were available only from a single subtest of a domain (e.g., visual attention for attention and executive functions), the global score of that domain was not calculated. Descriptive statistics and the percentage of children with weaknesses were calculated for each domain and subtest. A hierarchical analysis approach was then used for describing the neuropsychological profile. First, an RM-ANOVA was conducted inserting the six domain scores as dependent variables. As an exploratory analysis, the comorbidity with ASD/ADHD was inserted as categorical factor in a mixed-model ANOVA with domain as within-subject variable. Please note that since

TABLE 2 | Domain and subtests of the NEPSY-II.

Domain	Subtest	Main assessed abilities
Attention and executive functions	*Visual attention*	Visual, selective attention
	Inhibition	Inhibitory control of verbal response
Language	*Comprehension of instructions*	Receptive language
	Speeded naming	Rapid semantic access and production
Memory and learning	*Memory for faces*	Encoding and immediate/delayed retrieval of facial stimuli
	Memory for designs	Visual–spatial memory
Sensorimotor functions	*Fingertip tapping*	Rapid motor programming
	Imitating hand positions	Imitation
	Manual motor sequences	Encoding and retrieval of rhythmic motor programmes
Social perception	*Theory of mind*	Understanding others' emotional and mental states
	Affect recognition	Facial affect recognition
Visuospatial processing	*Design copying*	Graphomotor control and visual-perceptual analysis
	Block construction	Visuospatial construction skills
	Geometric puzzles	Mental rotation

some participants did not complete the full battery, 23 participants were included in the between-domain analysis. Since this was a convenience sample, a sensitivity analysis was performed with G*Power 3.1 (Faul et al. 2007). The analysis showed that, given a power of 0.80 and alpha set at 0.05, this sample size allowed us to detect moderate-to-large between-domain differences ($f = 0.35$, corresponding to $n^2_p = 0.11$). Then, a series of paired-sample t tests or RM-ANOVAs were run within each domain, inserting scaled scores of each subtest as within-subject variable.

The percentage of participants for each of the four levels of performance was calculated with regard to academic skills.

All analyses were performed with Statistica 8.0 (Statsoft, Tulsa, OK), with alpha set at $p < 0.05$ for all effects. Significant effects in the RM-ANOVAs were analysed with Bonferroni-corrected tests. Effect sizes were estimated and reported as partial eta squared (n^2_p) for ANOVA designs, and as Cohen's d for pairwise comparisons, adopting conventional cut-offs (Lakens 2013).

3 | Results

Table 3 reports the number of participants that completed each subtest and domain, the corresponding scaled scores and the number and percentage of participants showing weak performance in each subtest and domain of the NEPSY-II.

The analysis highlighted significant differences between domains ($F_{5,110} = 4.16$, $p = 0.002$, $n^2_p = 0.16$). Bonferroni-corrected post hoc tests clarified that the memory and learning domain had higher scores than language ($p = 0.011$) and visuospatial processing ($p = 0.036$). It is noteworthy that the mean score was lower than the normative range (scaled scores <7) across all domains and that the percentage of participants with weak performance was higher than 25%. A representation of the neuropsychological profile at domain level is reported in Figure 1.

Regarding comorbidity with neurodevelopmental disorders, the exploratory analysis indicated that neither its main effect ($F_{1,21} = 1.39$, $p = 0.252$, $n^2_p = 0.06$) nor the interaction with domain ($F_{5,105} = 0.88$, $p = 0.498$, $n^2_p = 0.04$) were significant. The

TABLE 3 | Scaled scores and participants with weak performance for each domain and subtest of the NEPSY-II. Scaled scores are reported as mean (SD).

| Domain	Subtest	Tested participants (N)	Scaled score Mean (SD)	Range	Participants with individual weakness (%)
Attention and executive functions		23	5.1 (2.8)	1–10.8	30
	Visual attention	26	5 (4.4)	1–13	54
	Inhibition	23	4.1 (2.7)	1–8.7	48
Language		23	4.5 (2.5)	1–10	48
	Comprehension of instructions	28	4.6 (3.3)	1–11	39
	Speeded naming	23	3.9 (2.5)	1–10	52
Memory and learning		24	6.1 (3.2)	1–11.8	29
	Memory for faces	28	7.8 (4.7)	1–16	21
	Memory for designs	24	3.8 (3.4)	1–11.5	63
Sensorimotor functions		27	5.5 (3.2)	1–11	37
	Fingertip tapping	28	6.8 (4.5)	1–13	32
	Imitating hand positions	27	4.3 (3.7)	1–10	56
	Manual motor sequences	27	5.4 (3.3)	1–10	33
Social Perception		26	5.2 (3.1)	1–10.5	38
	Theory of mind	26	4.9 (3.5)	1–12	42
	Affect recognition	28	5.4 (3.6)	1–13	36
Visuospatial processing		26	4.4 (2.6)	1–10.3	42
	Design copying	23	2.9 (2.5)	1–7	61
	Block construction	28	5 (3.5)	1–11	39
	Geometric puzzles	25	5.1 (3.4)	1–13	32
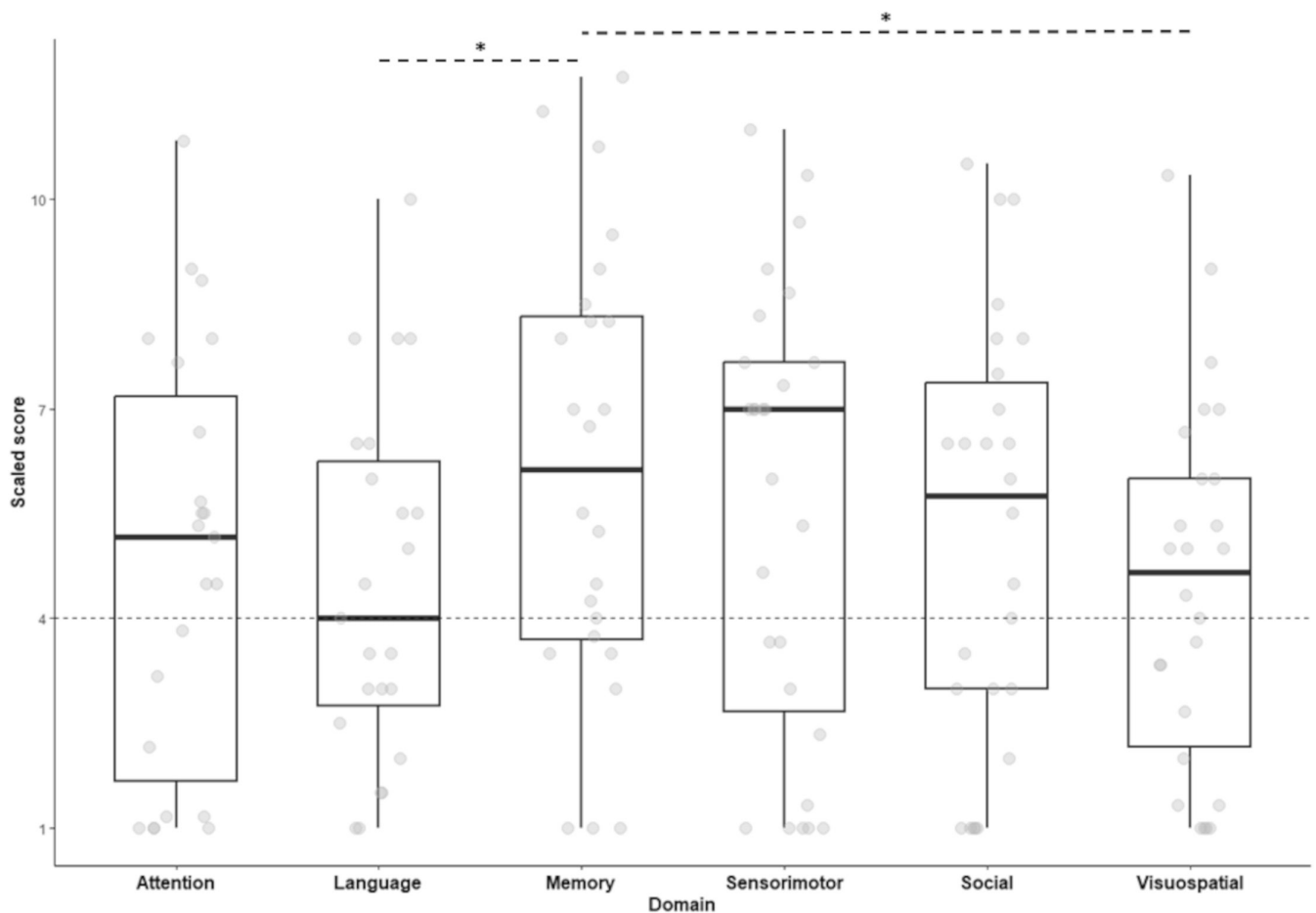
FIGURE 1 | Boxplot of the domain scores. The boxes represent the middle 50% of the data for each subtest. The upper and lower whiskers represent scores outside the middle 50% (i.e., the lower 25% of scores and the upper 25% of scores). The horizontal line within each box represents the median score. The score of 4, signalled by the thinner dotted black line, represents the threshold of weak performance (2 SD below the mean). Grey dots represent individual observations; asterisks over the thicker dotted black lines represent significant between-domain comparisons.

within-subject effect of domain was still significant ($F_{5,105} = 3.73$, $p = 0.004$, $n^2_p = 0.15$). These results suggest that the differences between neuropsychological domains were observed regardless of ASD and ADHD.

For attention and executive functions, no difference between visual attention and inhibition ($t_{22} = 1.79$, $p = 0.088$, Cohen's $d = 0.42$) was revealed. In the linguistic domain, higher scores were obtained in comprehension of instructions compared to speeded naming ($t_{22} = 2.12$, $p = 0.045$, Cohen's $d = 0.56$). For memory and learning, better performance emerged in memory for faces than in memory for designs ($t_{23} = 4.78$, $p < 0.001$, Cohen's $d = 1.16$). In sensorimotor functions ($F_{2,52} = 7.49$, $p = 0.001$, $n^2_p = 0.22$), higher scores were recorded in fingertip tapping than in imitating hand positions ($p = 0.001$). No significant differences with the other sensorimotor subtests emerged for manual motor sequences (all $p > 0.076$). Comparable scores were observed in the two subtests of social perception ($t_{25} = 0.85$, $p = 0.406$, Cohen's $d = 0.17$). Significant differences emerged in the visuospatial processing domain ($F_{2,42} = 9.86$, $p < 0.001$, $n^2_p = 0.32$), with lower scores in design copying than in block construction ($p < 0.001$) and in geometric puzzles ($p = 0.003$). Conversely, the comparison between block construction and

geometric puzzles was non-significant ($p > 0.99$). Furthermore, both participants with and without ID showed higher scores in memory for faces, while obtaining lower scores in inhibition, speeded naming, memory for designs, and design copying (Table 4).

On an individual level, the lowest percentage of participants with weak performance was observed in memory for faces (21%). In all other subtests, more than 25% of participants showed weaknesses, with percentage over 50% in memory for designs, design copying, imitating hand positions, visual attention and speeded naming. It is important to note that all participants with average intellectual functioning showed weak performance in at least one of the subtests.

For academic skills, the number and percentage of participants for each performance classification is reported in Table 5.

Consistent with the prevalence of cognitive impairments in the sample, the percentage of children with difficulties in academic skills was relatively high across all tests (50% in comprehension, 63% in reading accuracy and/or speed, 72% in arithmetic facts, 89% in mental calculation accuracy and/

TABLE 4 | Scaled scores obtained in each subtest and domain by participants with and without intellectual disability (ID). Scaled scores are reported as mean (SD).

Domain	Subtest	Scaled score	
		Participants with ID	*Participants without ID*
Attention and executive functions		2.9 (2.4)	6.2 (2.3)
	Visual attention	2.7 (3.5)	6.7 (4.3)
	Inhibition	2.1 (1.6)	5.1 (2.6)
Language		2.6 (1.6)	5.5 (2.4)
	Comprehension of instructions	2.3 (1.9)	6.5 (3.1)
	Speeded naming	2.6 (2.1)	4.5 (2.5)
Memory and learning		4.4 (2.7)	7 (2.4)
	Memory for faces	4.4 (3.6)	10.7 (3.4)
	Memory for designs	3.4 (2.8)	4 (3.7)
Sensorimotor functions		3.7 (3.2)	7 (2.5)
	Fingertip tapping	5.1 (5.4)	8.2 (3.1)
	Imitating hand positions	2.8 (3)	5.5 (3.6)
	Manual motor sequences	2.8 (2.7)	7.4 (2.3)
Social Perception		3.3 (3.2)	6.6 (2.1)
	Theory of mind	2.6 (2.9)	6.5 (2.9)
	Affect recognition	3.9 (3.8)	6.7 (3.1)
Visuospatial processing		2.7 (2.2)	5.6 (2.6)
	Design copying	1.6 (1.8)	3.5 (2.7)
	Block construction	2.8 (2.5)	7 (3)
	Geometric puzzles	3.7 (2.6)	6.1 (3.6)

Abbreviation: ID = intellectual disability.

TABLE 5 | Performance on the academic skills tests. The number and percentage of participants for each performance classification is reported.

	Tested participants—*N*	Fully achieved	Sufficient	Request for attention	Immediate intervention
Word reading					
Accuracy	16	0	13 (81%)	1 (6%)	2 (13%)
Speed	16	0	6 (37%)	3 (19%)	7 (44%)
Reading comprehension	18	0	9 (50%)	6 (33%)	3 (17%)
Mathematics					
Arithmetic skills	18	1 (6%)	4 (22%)	2 (11%)	11 (61%)
Mental calculation					
Accuracy	18	1 (6%)	5 (28%)	0	12 (66%)
Speed	6	0	2 (33%)	3 (50%)	1 (17%)

or speed). Nevertheless, half of the tested participants showed sufficient reading comprehension abilities, and 81% of children were sufficiently accurate in reading. Conversely, in each mathematics test more than 60% of the sample showed difficulties. Notably, only one participant displayed adequate performances across mathematics tests.

4 | Discussion

The main aim of the current study was to provide a further characterisation of the cognitive profile of SoS in developmental age as proposed by Lane et al. (2019). Observing the profile of performance at the six cognitive domains assessed by NEPSY-II, the lowest mean scores were found in both language and visuospatial abilities, while the best performance was observed in the memory and learning domain. The analyses within these domains clarified that the greatest difficulties regarded rapid verbal production, visuospatial memory and graphomotor control. Memory for faces was the subtest with the highest score at both group and individual levels. Neither attention and executive functions nor social perception skills emerged as relative strengths or weaknesses of the profile, although difficulties in attention subtests were shown by many participants. An exploratory analysis indicated that the comorbidity with ASD and ADHD did not result in a different neuropsychological profile, suggesting that the between-domain differences were detected regardless of secondary neurodevelopmental disorders. In a similar vein, despite the expected impact of ID on overall performance, participants with and without ID showed similar strengths and weaknesses across the same subtests. At individual level, participants with average intellectual functioning showed a weak performance in at least one subtest. These results study provide new insights into the cognitive profile of SoS, and suggest that the genetic and epigenetic alterations associated with SoS impact neurocognitive development even in absence of evident ID (Harris and Fahrner 2019).

Overall, this study confirms the previous characterisation of the SoS cognitive profile as proposed by Lane et al. (2019), with the exception of visuospatial memory, and extends it by assessing social perception. Whereas that previous study indicated visuospatial memory as a strength in SoS, the current study found it to be weak in 63% of the sample. These discrepant results may at least partially depend on the use of different tests. The BAS3 recognition of designs test assesses short-term memory for geometric forms, mainly measuring visual memory for geometric stimuli. Conversely, the NEPSY-II memory for designs subtest requires immediate and delayed recall of both visual stimuli and their positions on a grid, thus evaluating both content and spatial memory. Additionally, the current study included a memory for faces subtest to assess content memory for social stimuli, which was found to be a relative strength in SoS. Considering that the lowest mean score was observed in the visuospatial processing domain, our findings suggest that visual rather than spatial memory may be more preserved in SoS.

Apparently in contrast with the previous description of the SoS cognitive profile (Lane et al. 2019), the language domain seemed particularly affected in our sample. Still, this inconsistency may depend on the use of different batteries. In the previous description, the school-age BAS3 involved two tests assessing word definitions and verbal similarities. Although the word definitions test primarily assesses expressive language, it also involves verbal comprehension abilities to explain word meaning. Conversely, the NEPSY-II speeded naming subtest focuses on the rapid naming of geometric figures and/or single letters and numbers, while also engaging executive function skills.

Crucially, it does not require comprehension of the presented items. In the current study, the within-domain analysis indicated that verbal comprehension abilities were relatively spared compared to rapid semantic access and linguistic production. The findings from this study thus clarify that, while verbal reasoning and comprehension may be a relative strength, greater difficulties are present in rapid speech production (Finegan et al. 1994; Ball et al. 2005).

Graphomotor control (assessed by design copying) was the most affected ability in the visuospatial domain. Similarly, in the sensorimotor domain, 56% of participants showed weaknesses in imitation of hand position, a subtest that requires fine integration of proprioceptive and visual–spatial information. Although not conclusive, these findings hint at a specific difficulty in integrating sensory and motor information to control fine movements. This was also suggested by a recent study reporting differences of sensory processing and proprioception in SoS (Smith et al. 2023).

The results in social perception subtests suggest that children and adolescents with SoS display abilities to understand others' emotions and mental states are consistent with their general intellectual functioning. As mentioned above, memory for faces was relatively preserved in most individuals. The same ability is considered to be strongly impaired in ASD, manifesting a lack of interest towards socially relevant information (Riby and Hancock 2009; Weigelt et al. 2012). Globally, these results suggest that social perception skills are not specifically impaired as observed in idiopathic ASD, although there is a relatively frequent autistic-like symptomatology (Lane et al. 2017; Riccioni et al. 2024). While social perception was not a relative weakness per se, it is important to note that more than a third of the sample showed performance below the age-expected mean in this domain, with greater challenges observed in children with ID. Furthermore, real-world social interactions demand a broader set of skills than those assessed by the paper-pencil tests used in this study. In dynamic social contexts, other cognitive and behavioural issues, such as attention problems, speech impairments, aggressive behaviours and anxiety, may further impact on the psychosocial adaptation of individuals with SoS (Lesinskiene et al. 2024). Social functioning in SoS should be further examined in ecological contexts, taking into account not only social perception skills but also other cognitive and behavioural features that may contribute to social difficulties.

In regard to academic skills, difficulties in reading speed are consistent with the slowness in rapid verbal production that emerged in the neuropsychological assessment. Nevertheless, reading accuracy was preserved in most of the tested participants. Conversely, a large part of the sample had poor mathematics skills, and only one participant did not display any difficulty in mathematics. By using specific standardised tests, these results clarify previous evidence of difficulties in quantitative reasoning and numeracy (Cole and Hughes 1994; Lane et al. 2019; Lane et al. 2019a). Although it has to be confirmed in wider samples, a deficit of mathematics and calculation skills should be considered for assessment, rehabilitation and school attainment purposes of children and adolescents with SoS.

Limitations should be acknowledged in interpreting the findings of this study. The small sample size and the high age variability ask for caution in generalising our results. This caveat is particularly relevant for the exploratory analysis on comorbidity with ADHD and ASD, as well as for the assessment of academic skills, which involved only subgroups of the sample. Although the analyses revealed large differences between neuropsychological domains, the relatively small sample size may have masked other potential differences with smaller effect size, which should be explored in larger and more homogeneous samples. Moreover, the study adopted a cross-sectional design. Longitudinal data are needed to define the specific developmental trajectories of cognition in SoS, as it has been recently done for the adaptive and behavioural profile (Siracusano et al. 2024). The small sample size also prevented the investigation of specific genotype-cognitive phenotype associations (Siracusano et al. 2023). While the adoption of a co-normed battery provided reliable measures of performance for each neuropsychological skill, the direct comparison with other clinical populations could offer a more complex picture of the SoS neuropsychological profile (Morel et al. 2018; Lane et al. 2019b). Three participants with severe ID and comorbidity with ASD exhibited floor performance across subtests. Although two of these participants were excluded from the analyses, their observed floor performance suggests that severe ID may potentially blur differences between cognitive domains. However, we could not disentangle the distinct contributions of ID severity and ASD comorbidity to floor performance in these individuals, given the unclear role of associated ID in ASD in genetic syndromes (Jenner et al. 2023) and the reduced sensitivity and specificity of autism assessment tools in individuals with ID (Sappok et al. 2013). Similarly, while the use of standard scaled scores was consistent with the expected medium-to-large differences between cognitive domains and subtests, as indicated by the previous characterisation of the SoS cognitive profile (Lane et al. 2019), it may have partially masked other differences due to floor effects across different tests of children with ID. Additionally, although the results were broadly consistent and indicated a similar profile, we cannot exclude the possibility that linguistic and cultural differences between the Italian sample in the present study and the UK sample in the previous study may have contributed to some of the observed variations. Future cross-national research is needed to confirm and extend the SoS cognitive profile. Lastly, the limited sample size and the adopted tests did not allow us to test associations between learning difficulties and specific neuropsychological skills (Lane et al. 2019a).

5 | Conclusions

This study provides new insights into the SoS cognitive profile in developmental age. These findings may pave the way for tailoring syndrome-specific rehabilitative interventions, which should consider weaknesses as well as strengths of the profile of SoS. Notably, despite the relatively frequent comorbidity with ASD, social perception was not specifically impaired in this sample. This study documented also a specific difficulty in mathematics skills, which may have important implications for school adjustment and daily living (e.g., use of money autonomously) of people with SoS.

Ethics Statement

Parents/guardians were asked to sign an informed consent form and children gave their assent to participate before starting any procedure. All procedures were in accordance with the Declaration of Helsinki and were approved by the Ethical Committee of the Scientific Institute, IRCCS E. Medea (Prot. 18/21 CE).

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are openly available in OSF at https://osf.io/yta7c/, reference number 10.17605/OSF.IO/YTA7C.

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