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Communicative competence, behavioural difficulties, and caregiver burden in children with Angelman syndrome: a cross-sectional study

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Abstract

Purpose

To examine whether caregiver-rated communicative competence in children and adolescents with Angelman syndrome (AS) is associated with behavioural difficulties and caregiver burden, and to explore differences by genotype, epilepsy status, sex, and age.

Methods

Caregivers of participants aged 1–18 years completed questionnaires between 2022 and 2024 at the Angelman Centre Munich (ethics approval 23–0511 1 V). Behaviour was assessed using the German Aberrant Behavior Checklist (ABC), caregiver burden using the PedsQL™ Family Impact Module, and communication using the Observer-Reported Communication Ability (ORCA)–Angelman. Associations and group differences were tested using dummy-coded ordinary least squares regression with Šidák correction for multiple testing.

Results

After multiple-testing correction, ORCA domain and global scores were not associated with ABC subscales or PedsQL Family Impact outcomes. Communication differed by aetiology: compared with 15q11.2–q13 deletions, non-deletion aetiologies showed higher expressive (B = 0.49), receptive (B = 0.41), pragmatic (B = 0.74) and global (B = 0.55) scores (all $p < .001$). Children without epilepsy had higher ORCA domain and global scores (B = 0.35–0.54; $p \leq .003$). Receptive communication increased with age (B = 0.034 per year; $p = .004$); no sex differences were observed.

Conclusions

In this cohort, caregiver-rated communication was not linked to behavioural difficulties or family impact, but varied systematically with genotype, epilepsy status and age. Larger, stratified AS cohorts are needed to validate domain-specific communication profiles.

Introduction

Angelman syndrome (AS) is a rare neurogenetic disorder with an estimated prevalence of approximately 1 in 12,000 to 1 in 20,000 children (Kolevzon et al. 2021; Markati et al. 2021; Sarimski 2014; Oberlack and Wagner 2025; Manssen et al. 2025). AS results from deficient or abnormal function of the maternally inherited UBE3A gene on chromosome 15. UBE3A encodes three E6AP protein isoforms via differential splicing (Yamamoto et al. 1997), and loss of maternal UBE3A expression can occur through several molecular mechanisms (Markati et al. 2021). In about 70–75% of cases, AS is caused by a de novo maternal deletion of 15q11.2–q13; approximately 15% are due to a pathogenic variant in the maternal UBE3A gene. Paternal uniparental disomy of chromosome 15 is identified in 2–7% of cases, and an imprinting defect on chromosome 15 in 2–3% (Markati et al. 2021).

Clinically, AS is characterised by severe developmental delay and a profound impairment of expressive speech, while receptive skills and nonverbal communication are relatively better preserved (Gentile et al. 2010; Sarimski 2014). Importantly, the phenotype is not uniform but shows genotype–phenotype correlations: clinical severity and, in particular, communicative abilities differ between molecular subtypes, with non-deletion aetiologies (e.g., UBE3A variants, paternal uniparental disomy, imprinting defects) typically showing relatively stronger receptive and pragmatic communication than individuals with a maternal 15q11.2–q13 deletion, whereas profound limitations in expressive speech are common across subtypes (Lossie et al. 2001; Pearson et al. 2019; Sarimski 2014). Further features include disturbances of movement and balance and a distinctive behavioural phenotype (frequent laughter, marked cheerfulness, hyperactivity, and short attention span). Seizures and characteristic EEG abnormalities (high-amplitude activity with spikes) occur in more than 80% of affected individuals.

Deficits in expressive language and communication are core characteristics of AS. During the first two years of life, vocal production is reduced in both frequency and variability (Sarimski 2014). Over time, many children learn to express needs through simple gestures, whereas word imitation and spoken word production remain largely absent. Between 71% and 90% of individuals with AS never or rarely produce speech (Calculator 2013; Pearson et al. 2019). Among those who develop spoken language, vocabulary is typically extremely limited, often ranging from two to 15 words (mean ≈ five) (Alvares and Downing 1998; Andersen et al. 2001; Clayton-Smith 1993; Pearson et al. 2019), and articulated words are reported to be rarely used for communicative purposes (Didden et al. 2009).

Accordingly, many individuals rely on alternative communication modalities such as gestures, manual signs, or picture-based systems. In a cohort of 82 individuals, none used more than six words, yet 20% employed specific manual signs and others communicated by pointing to objects or pictures (Clayton-Smith 1993). In children aged 1.5–14 years, approximately 50% used specific manual signs, 25% communicated via picture cards, and 15% used electronic communication devices (Alvares and Downing 1998). A German parent survey likewise reported substantial nonverbal competencies: 79% communicated via facial expression, 61% used simple signs/gestures, and 56% indicated needs by pointing; 50% led caregivers to desired objects, 31% used screaming/crying/laughter to gain attention, 19% used standardised signs, 17% used picture cards, and 4% used a technical communication device (Holz 2022).

In observational work across four social contexts, including choice-making, commenting on events, requesting desired objects, and directing others' attention, frequently displayed communicative behaviours included moving away, crying, laughing, taking someone by the hand, touching objects, pointing, vocalizing, and touching the interaction partner (Didden et al. 2009).

Clinical experience and the emerging literature suggest that children's communicative competence may be a key predictor of caregiver quality of life and problem behaviour. Therefore, we examined associations between communicative abilities, problem behaviour, and caregiver-reported family impact.

Methods

Aberrant Behavior Checklist (ABC)

We assessed the patients' behavioural phenotype using the German version of the Aberrant Behavior Checklist (ABC; Aman et al. 1985) outside the originally validated age range. Although the ABC was originally developed for children aged ≥ 5 years, evidence suggests it can also be applied in younger children (Schmidt et al. 2013). The ABC comprises five subscales: irritability/agitation, lethargy/withdrawal, stereotypic behaviour, hyperactivity/noncompliance, and inappropriate speech (Aman and Singh 1986).

Subscale scores were calculated as the sum of the corresponding items. To account for unequal item numbers across subscales, subscale means were additionally computed. The total score was reported both as the sum across subscales and as the mean of the subscale means to ensure equal weighting across domains (Table 1). This mean of means composite is a common research scoring approach to ensure equal domain weighting when subscales contain different numbers of items (Erickson et al. 2009; Lake 2002). (Table 1)

Table 1
Descriptive statistics (minimum, maximum, mean, SD) for the Aberrant Behavior Checklist (ABC) subscales and total score.

Aberrant Behavior Checklist					
Subscale	*N*	Minimum	Maximum	Mean value	*SD*
Irritability/agitation	42	0.070	0.870	0.313	0.210
Social withdrawal	42	0.000	0.690	0.261	0.166
Stereotypic behaviour	42	0.000	1.290	0.432	0.284
Hyperactivity/noncompliance	42	0.190	1.500	0.830	0.432
Inappropriate speech	42	0.000	0.750	0.149	0.184
Total score (mean of subscale means)	42	0.088	0.714	0.397	0.175

Pediatric Quality of Life Inventory (PedsQL)

Parental impact was assessed using the PedsQL™ Family Impact Module (Varni et al. 2004), a standardised measure designed to capture the effects of a child's chronic health condition on parents and overall family functioning. The module comprises 36 items rated on a 5-point Likert scale (0 = never to 4 = almost always). It assesses parent functioning across six domains (physical, emotional, social, and cognitive functioning, communication, and worry; 28 items) and family functioning across two domains (daily activities and family relationships; 8 items) (Varni et al. 2004). Subscale scores were calculated as the sum of the corresponding items. Additionally subscale means were computed. A Total Score was computed as the mean of the subscale means (mean of means across domains) to ensure equal weighting across domains, which is common in research settings when subscales differ in item count. To date, no Angelman syndrome–specific PedsQL module is available (Table 2).

Table 2
Descriptive statistics (minimum, maximum, mean, SD) for the PedsQL™ Family Impact Module subscales and total score.

PedsQL Family Impact Module					
Subscale	*N*	Minimum	Maximum	Mean value	*SD*
Physical functioning	42	0.000	2.170	1.155	0.574
Emotional functioning	42	0.000	2.600	1.156	0.712
Social functioning	42	0.000	3.000	1.302	0.725
Cognitive functioning	42	0.000	2.400	0.913	0.580
Communication	42	0.000	3.670	1.494	0.828
Worry	42	0.400	3.800	2.029	0.827
Daily activities	42	0.000	4.330	1.791	0.964
Family relationships	42	0.000	2.800	0.974	0.747
Total score (mean of subscale means)	42	0.270	2.615	1.352	0.524

Observer-Reported Communication Ability (ORCA) – Angelman Version

Communicative functioning was assessed using the Observer-Reported Communication Ability–Angelman Version (ORCA; Zigler et al. 2023), an instrument developed to capture the characteristic communication profile of individuals with Angelman syndrome. The ORCA focuses on the population's distinct strengths and challenges, including predominant nonverbal communication, limited spoken language, and reciprocal interaction skills.

The measure comprises expressive, receptive, and pragmatic communication domains, from which a Global Communication Score is derived. Items are rated based on the observed frequency or adequacy of communicative behaviours in naturalistic settings. To ensure comparability across scales with differing item counts, both sum scores and corresponding arithmetic means of the domains were computed; the overall score was derived as the mean of the domain means (mean of means; Table 3).

Table 3
Descriptive statistics (minimum, maximum, mean, SD) for Observer-Reported Communication Ability (ORCA) domain and global scores.

ORCA					
Subscale	*N*	Minimum	Maximum	Mean value	*SD*
Expressive communication	42	1.307	2.574	1.765	0.346
Receptive communication	42	1.030	2.710	1.880	0.368
Pragmatic communication	42	1.100	3.000	1.879	0.470
Global communication	42	1.180	2.688	1.841	0.365

Statistical analyses

An a priori power analysis for a fixed-model linear regression with a single predictor (G*Power 3.1) indicated that a total sample size of N = 42 would be required to detect a large effect ($f^2 = 0.35$; corresponding to $R^2 \approx .26$) at $\alpha = .05$ with $1 - \beta = .95$ (Faul et al. 2009). The a priori sample size calculation for analyses involving binary predictors was based on the equivalence to a dummy-coded simple linear regression (i.e., an independent-samples t test). Assuming a large effect (Cohen's d = 0.80), two-sided testing with $\alpha = .05$ and $1 - \beta = .80$ yielded a required sample size of approximately n = 26 per group (total $N \approx 52$) under balanced group allocation. This sample size, however, could not be achieved in the present study due to the rarity of Angelman syndrome.

We considered using Mann–Whitney-U tests because isolated outcomes showed skewed distributions and group sizes were unequal in a few cases, which can potentially affect parametric assumptions. However, we ultimately retained dummy-coded linear regression models because, for continuous outcomes, they are typically more statistically efficient (i.e., provide higher power than rank-based tests under standard conditions) and support valid inference with unequal group sizes and moderate non-normality, particularly when using heteroskedasticity-robust standard errors (Lumley et al. 2002; Wilcox 2017). Accordingly, switching to Mann–Whitney U would not have addressed the study's main constraint, namely limited power due to the small sample size.

Data were analysed using the computer program "SPSS® Statistics 31.0.2" (Statistical Package for the Social Sciences, 31st version). The probability of error of the statistical analyses was set at an α level of .05. To counteract α-error accumulation in the calculation of the analyses performed, a Šidák adjustment of the α-level was carried out (Eid et al. 2010; Field 2013).

Assumption checks

Across all OLS models, diagnostic checks suggested overall adequate model fit. Although isolated outcomes were skewed and group sizes were unequal in very few comparisons, residual-based diagnostics indicated that core OLS assumptions were largely satisfied, with at most minor, isolated departures. Linearity in continuous predictors was examined via scatterplots and partial/added-variable plots (Samantaraya 2024). Breusch–Pagan/Koenker tests together with residual–fitted plots were used to assess heteroskedasticity (Kumar 2024). Residual normality was evaluated using Q–Q plots and, where informative, Shapiro–Wilk tests (Adhikari 2022). For ordered observations, Durbin–Watson statistics (≈ 2) and residual–order plots were inspected to rule out autocorrelation (Kumar 2024). Multicollinearity was negligible (low VIFs), and reference-category coding prevented perfect collinearity (Osemeke et al. 2024). Influence diagnostics (Cook's distance, leverage, studentized residuals) indicated no influential cases (Fox and Weisberg 2019). Together with the design-based justification of exogeneity ($E[\varepsilon|X] = 0$), these checks support the appropriateness of the OLS framework for the present analyses, consistent with methodological standards (Eid et al. 2010; Field 2013).

Results

Demographic data

A total of 42 patients with AS (24 males, 57.1%, and 18 females, 42.9%) and their parents were included in this study. The mean age was 7.8 years (SD 4.7; range 1–18). The majority had a maternal deletion (n = 30, 71.4%). Thirty patients (71.4%) were diagnosed with epilepsy. Detailed demographic information is provided in Table 4.

Table 4
Demographic data (age, sex, genotype, and epilepsy).

Demographic data (age, sex, genotype, and epilepsy)	
Age	
Mean age (SD); range	7.8 (4.7); 1–18
Gender n = (%)	
Male	24 (57.1)
Female	18 (42.9)
Genotype n = (%)	
Deletion	30 (71.4)
Non-deletion	12 (28.6)
Epilepsy n = (%)	
Yes	30 (71.4)
No	12 (28.6)

Influence of the communication on the quality of life and the child's behaviour

After adjustment for multiple testing, no significant associations were found between ORCA communication domains and family impact (PedsQL) or behavioural impairments (ABC). The detailed regression results for these analyses are presented in Table 5 (family impact) and Table 6 (behavioural impairments). Detailed descriptive statistics, including means and standard deviations, are provided in Tables 1–3.

Table 5
Standardised regression coefficients (β) and p-values from OLS regression models examining associations between ORCA domain/global scores and PedsQL™ Family Impact Module subscales and total score. (Šidák: α' = 1 − (1 − α)^(1/m) = 1 − 0.95^(1/9) ≈ 0.006)

Family Impact									
ORCA domain	Physical functioning β (p)	Emotional functioning β (p)	Social functioning β (p)	Cognitive functioning β (p)	Communication β (p)	Worry β (p)	Daily activities β (p)	Family Relationships β (p)	Total score β (p)
Expressive communication	-0.099 (.531)	0.096 (.547)	-0.036 (.823)	0.177 (.261)	-0.083 (.601)	0.088 (.581)	0.151 (.339)	0.178 (.258)	0.089 (.577)
Receptive communication	-0.130 (.411)	-0.020 (.898)	-0.066 (.680)	0.260 (.096)	-0.205 (.192)	0.204 (.196)	0.138 (.384)	0.237 (.131)	0.077 (.628)
Pragmatic communication	-0.037 (.815)	0.222 (.159)	0.022 (.890)	0.254 (.104)	-0.051 (.747)	0.099 (.531)	0.180 (.254)	0.167 (.289)	0.152 (.335)
Global communication	-0.091 (.567)	0.118 (.455)	-0.024 (.881)	0.252 (.107)	-0.117 (.460)	0.139 (.381)	0.171 (.278)	0.208 (.187)	0.119 (.452)

Table 6
Standardised regression coefficients (β) and p-values from OLS regression models examining associations between ORCA domain/global scores and Aberrant Behavior Checklist (ABC) subscales and total score. (Šidák: α' = 1 − (1 − α)^(1/m) = 1 − 0.95^(1/6) ≈ 0.009)

Behavioural Impairments						
ORCA domain	Irritability β (p)	Social withdrawal β (p)	Stereotypic behaviour β (p)	Hyperactivity β (p)	Inappropriate speech β (p)	Total score β (p)
Expressive communication	0.132 (.404)	-0.094 (.553)	-0.001 (.995)	0.090 (.573)	0.083 (.602)	0.075 (.637)
Receptive communication	0.083 (.601)	-0.109 (.491)	-0.085 (.595)	0.103 (.516)	0.178 (.259)	0.060 (.706)
Pragmatic communication	-0.013 (.935)	-0.116 (.464)	-0.086 (.588)	-0.029 (.857)	0.231 (.141)	-0.019 (.907)
Global communication	0.064 (.687)	-0.116 (.464)	-0.066 (.680)	0.051 (.751)	0.185 (.240)	0.036 (.822)

Influence of genotype, epilepsy, age and sex

Genotype

In dummy-coded linear regression models, genotype showed a clear effect across all three ORCA subdomains and the ORCA global communication score in favour of children of the non-deletion subgroup. Expressive communication differed significantly between groups (B = 0.492, SE = 0.091, β = .650, t(40) = 5.407, p < .001; R^2 = .422, F(1, 40) = 29.241, p < .001), corresponding to an average advantage of + 0.49 points. Receptive communication showed a similar pattern (B = 0.407, SE = 0.110, β = .506, t(40) = 3.709, p < .001; R^2 = .256, F(1, 40) = 13.756, p < .001; +0.41 points). The strongest effect was observed for pragmatic communication (B = 0.738, SE = 0.113, β = .717, t(40) = 6.514, p < .001; R^2 = .515, F(1, 40) = 42.437, p < .001; +0.74 points). Global communication showed a similar pattern (B = 0.545, SE = 0.092, β = .683, t(40) = 5.914, p < .001; R^2 = .466, F(1, 40) = 34.975, p < .001; +0.55 points). Detailed results are provided in Table 7 and graphically illustrated in Figs. 1a and 1b.

Table 7
Standardised regression coefficients (β) and p-values from linear regression models examining associations of genotype, epilepsy status, sex, and age with ORCA domain/global scores. (Šidák: α' = 1 − (1 − α)^(1/m) = 1 − 0.95^(1/4) ≈ 0.013)

Predictor	Expressive communication β (p)	Receptive communication β (p)	Pragmatic communication β (p)	Global communication β (p)
Genotype (non-deletion vs deletion)	**0.650 (< .001)**	**0.506 (< .001)**	**0.717 (< .001)**	**0.683 (< .001)**
Epilepsy (no vs yes)	**0.460 (.002)**	**0.454 (.003)**	**0.528 (< .001)**	**0.524 (< .001)**
Sex (male vs female)	0.100 (.529)	0.068 (.668)	0.215 (.171)	0.147 (.354)
Age (years)	0.320 (.039)	**0.434 (.004)**	0.309 (.047)	0.379 (.014)

Epilepsy

In the dummy-coded linear regression models, epilepsy was significantly associated with lower scores across all three ORCA subdomains and the ORCA global communication score, favouring children without epilepsy. Significant group differences emerged for expressive communication (B = 0.348, SE = 0.106, β = .460, t(40) = 3.281, p = .002; R^2 = .212, F(1, 40) = 10.762, p = .002; +0.35 points), receptive communication (B = 0.365, SE = 0.113, β = .454, t(40) = 3.220, p = .003; R^2 = .206, F(1, 40) = 10.366, p = .003; +0.37 points), and pragmatic communication (B = 0.543, SE = 0.138, β = .528, t(40) = 3.932, p < .001; R^2 = .279, F(1, 40) = 15.460, p < .001; +0.54 points). Global communication was also significantly higher in children without epilepsy (B = 0.418, SE = 0.108, β = .524, t(40) = 3.891, p < .001; R^2 = .275, F(1, 40) = 15.140, p < .001; +0.42 points). Detailed results are provided in Table 7 and graphically illustrated in Figs. 2a and 2b.

Age

In linear regression models with age as the predictor (n = 42; df = 40), only receptive communication remained significant after correction: age predicted higher receptive scores (B = 0.034, SE = 0.011, β = .434, t(40) = 3.050, p = .004; R^2 = .189, F(1, 40) = 9.301, p = .004), corresponding to an increase of + 0.034 points per year of age. Expressive, pragmatic, and ORCA global communication scores showed no significant associations with age. Detailed results are provided in Table 7 and graphically illustrated in Fig. 3.

Gender

No statistically significant sex-related differences were observed in any ORCA subdomain (expressive, receptive, pragmatic) or in the global communication score.

Discussion

In the present cohort, ORCA domain scores provided a differentiated picture of communication ability: genotype and epilepsy status were associated with expressive, receptive and pragmatic communication in dummy-coded OLS models, and the only developmental association that remained significant after multiple-testing correction was the age-related increase in receptive communication. By contrast, the ORCA global composite score (computed as the equal-weighted mean of the expressive, receptive, and pragmatic domain means) summarised overall communication ability but did not capture this domain-specific age association. This pattern is consistent with the ORCA's domain-based structure and with standard psychometric considerations: averaging across correlated domains can reduce variance and attenuate domain-specific subgroup differences and developmental trends, thereby potentially reducing sensitivity at the level of a single global score (Zigler et al. 2023; Chen et al. 2024; Embretson and Reise 2000). Moreover, given the small and partly unbalanced subgroup sizes, effect estimates from binary contrasts should be interpreted cautiously; in analyses that jointly model correlated predictors, reference-category choices and suppression effects can further influence regression coefficients (MacKinnon et al. 2000; Gelman and Hill 2007). Power calculations indicated that the available sample size was below that required for robust detection of effects in binary contrasts (e.g., epilepsy, genotype, sex), whereas analyses involving a continuous predictor (age) were comparatively better powered. Accordingly, findings for dummy-coded predictors warrant replication in larger cohorts, while the observed age-related effect—restricted to receptive communication—may be relatively more stable within the present sample size.

In a previous study, we demonstrated clear associations between behavioural problems and family burden. In contrast, the present study indicates that communicative impairments – contrary to common assumptions in the current literature – do not significantly contribute to family impact or behavioural difficulties. This suggests that behavioural problems, rather than communicative deficits, mainly impact families of children with Angelman syndrome. The prevailing view in the literature that communication difficulties are the main source of family burden might reflect the limited involvement of psychological perspectives in previous research.

These findings are consistent with several studies demonstrating that language and communicative competencies vary between different genetic subtypes in Angelman syndrome (Gentile et al. 2010; Pearson et al. 2019; Sarimski 2014). Individuals in the non-deletion group tend to display a wider range of communicative functions (Didden et al. 2009). Pearson et al. (2019), for example, reported significantly stronger receptive-language abilities in individuals with non-deletion aetiologies compared with those with deletions (Pearson et al. 2019). By contrast, the markedly reduced expressive-speech abilities appear comparatively homogeneous across genetic subtypes. Pearson et al. (2019) suggest that UBE3A may be more relevant for speech production than for the development of receptive language.

In the study by Lossie et al. (2001), 71% of individuals with a deletion produced no words, while the remaining 29% produced a maximum of three words; 53% were able to follow simple instructions (Lossie et al. 2001). In the non-deletion subgroup the proportion of individuals able to articulate multiple words was substantially higher. Differences between genetic subgroups have also been shown regarding prelinguistic skills (Didden et al. 2009; Sarimski 2014). Didden et al. (2009), for instance, reported that individuals with uniparental disomy used manual signs more frequently than individuals with a deletion.

With respect to the association between molecular subtype and gesture use, the literature is mixed. While Jolleff et al. (2006) concluded that individuals in the non-deletion group produced gestures more frequently than individuals with deletions, Calculator (2013) reported that 76% of individuals with non-deletion aetiologies and 83% of individuals with deletions used specific gestures. Regarding the use of enhanced natural gestures, signing, and speech, Calculator (2013) found a significant group difference between deletion and non-deletion groups, such that these communicative patterns were more frequently observed in individuals with non-deletion aetiologies. Similar conclusions were also reported by Didden et al. (2009).

Regarding epilepsy, all three ORCA subdomains showed an epilepsy effect, favouring children without epilepsy. Our findings comparing epilepsy versus non-epilepsy likewise align with prior evidence suggesting that the presence of epilepsy adversely affects language and communicative competencies. However, in the present sample we could not clearly disentangle epilepsy effects from genotype, and the available cell sizes did not permit more fine-grained stratified comparisons (e.g., deletion with epilepsy vs deletion without epilepsy) or formal genotype × epilepsy interaction analyses. Consequently, the observed epilepsy-group differences should be interpreted cautiously, and future studies should aim to recruit sufficiently large and balanced cohorts to allow stratified analyses and joint modelling of genotype and epilepsy. In the study by Didden et al. (2009), individuals without epilepsy displayed certain communicative behaviours—such as pointing gestures to request an object or manual signs to comment on events—significantly more often than individuals with epilepsy. The authors reported similar patterns for the use of symbolic communication forms (Didden et al. 2009). Complementing these findings, Parkinson (2002) reported in the general population that epilepsy is associated with the presence of language disorders. Pearson et al. (2019) noted in this context that Didden et al. (2009) did not include level of intellectual impairment as a covariate. They emphasised that, in other genetic syndromes associated with high epilepsy rates, a relationship between epilepsy severity and the severity of cognitive impairment has been demonstrated—for example in tuberous sclerosis (Jansen et al. 2008).

No significant associations with age were observed for expressive communication, pragmatic communication, or the ORCA global communication score. This finding is consistent with results reported by Didden et al. (2009), where age—apart from one exception—did not influence the repertoire of communicative competencies. The authors noted that adults, compared with children and adolescents, showed social smiling less frequently.

Many children with Angelman syndrome can attract caregivers' attention through nonverbal means, express wishes for objects, make choices between alternatives, or comment on events. Nearly all parents in the present sample reported that they generally understand their child's communication well, whereas unfamiliar observers experience difficulties. At the same time, it is plausible that children and adolescents themselves experience substantial distress related to the absence of speech and that limited expressive capacity contributes to frustration. There may also be a discrepancy between parents' perception that they understand the child's wishes well and the child's own perception. Thus, behavioural problems may plausibly be driven, at least in part, by communication deficits.

Children and adolescents with better communicative competencies tend to have a higher overall cognitive level (Didden et al. 2009) and may therefore reflect more strongly on their own limitations, which could in turn contribute to more pronounced behavioural difficulties. Behavioural problems such as hyperactivity and aggressive behaviour appear to have a substantial impact on parental burden. Future research could use a purpose-designed questionnaire to more specifically examine the contribution of language impairments to caregiver strain.

As with most findings reported in the literature, the results of the present study are based on parent ratings. To capture the contexts in which communicative forms are used, future studies should place greater emphasis on methods of direct observation.

It should be noted, however, that assembling large samples in Angelman syndrome research is inherently challenging, given the rarity of the condition and the logistical demands of international recruitment. Previous multicentre efforts have demonstrated that sufficiently powered studies are only

feasible through extensive collaboration across sites and patient registries (Pelc et al. 2008; Tan et al. 2011; Wheeler et al. 2017). Therefore, while our findings highlight meaningful domain-specific profiles, future research will need coordinated international data collection to establish the robustness of these effects.

In summary, despite the limitations imposed by sample size, our analyses suggest that communication in Angelman syndrome is best conceptualised as a domain-specific profile rather than a single global construct, with meaningful variation by genotype, epilepsy status, and age. At the same time, we did not find evidence, after correction for multiple testing, that caregiver-rated communication domains are robustly associated with behavioural difficulties or family impact in this cohort. Harmonised, registry-enabled international studies with longitudinal follow-up and complementary observational measures will be essential to confirm the stability and clinical relevance of these effects and to inform stratified outcome assessment in future trials and care pathways.

Abbreviations

AS: Angelman syndrome

d: deletion

nd: non-deletion

PedsQL: Pediatric Quality of Life Inventory

ABC: Aberrant Behavior Checklist

AAC: Augmentative and Alternative Communication

ORCA: Observer-Reported Communication Ability–Angelman Version

Declarations

Ethics approval: The study was approved by the Ethics Committee of Ludwig Maximilian University (LMU) Munich (approval no. 23-0511 1 V). All data were processed in pseudonymised form by assigning each participant a unique study code. Personal identifiers and the re-identification key (code list) were stored separately from the research dataset on a restricted-access, password-protected institutional system; access was limited to authorised study personnel. Statistical analyses were conducted on the pseudonymised dataset and results are reported in aggregate form only.

Consent to participate: Informed consent was obtained from parents or legal guardians prior to participation.

Consent for publication: Not applicable.

Data availability: The datasets generated and/or analysed during the current study are not publicly available due to data protection and privacy restrictions, but are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Figures

Figure 1a

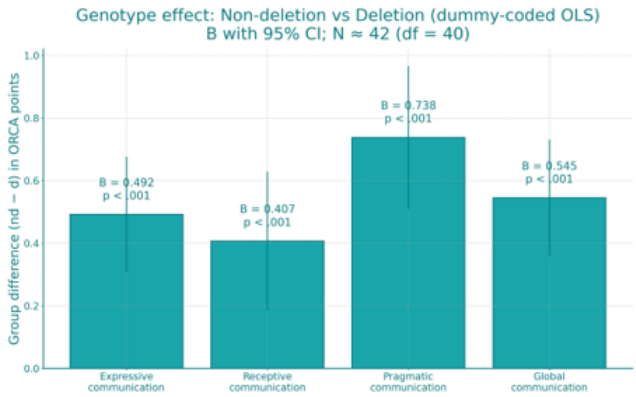


Figure 1b

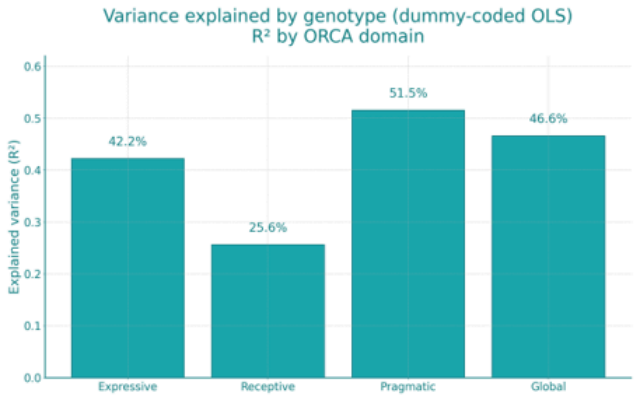


Figure 1

a. Genotype effect on ORCA domain scores (dummy-coded OLS).
Bars show unstandardised group differences (Non-deletion − Deletion) with 95% confidence intervals; positive values indicate higher scores for the non-deletion group. Coefficients: Expressive B = 0.492 (SE = 0.091), Receptive B = 0.407 (SE = 0.110), Pragmatic B = 0.738 (SE = 0.113), Global B = 0.545 (SE = 0.092); all p < .001; residual df = 40.

Figure 1b. Variance explained by genotype (dummy-coded OLS).
Bars depict R^2 for the ORCA domains: Expressive R^2 = .422, Receptive R^2 = .256, Pragmatic R^2 = .515, Global R^2 = .466.

Figure 2a

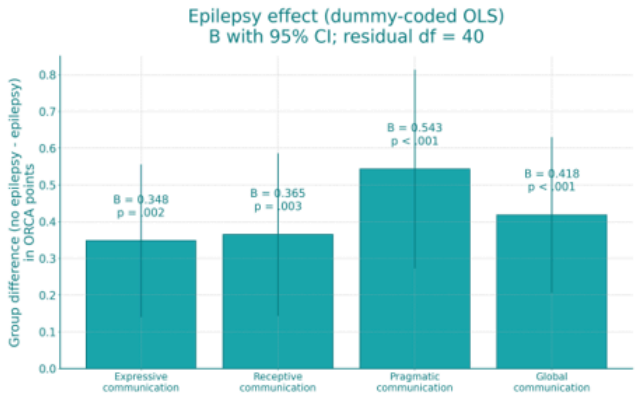


Figure 2b

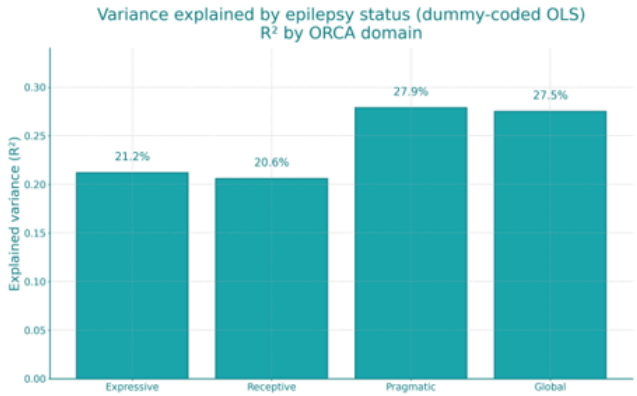


Figure 2

a. Epilepsy effect on ORCA domain scores (dummy-coded OLS).
Bars show unstandardised group differences (No epilepsy − Epilepsy) with 95% confidence intervals; positive values indicate higher scores for the no epilepsy group. Coefficients: Expressive B = 0.348 (SE = 0.106, p = .002); Receptive B = 0.365 (SE = 0.113, p = .003); Pragmatic B = 0.543 (SE = 0.138, p < .001); Global B = 0.418 (SE = 0.108, p < .001); residual df = 40.

Figure 2b. Variance explained by epilepsy status (dummy-coded OLS).
Bars depict R^2 for the ORCA domains: Expressive R^2 = .212; Receptive R^2 = .206; Pragmatic R^2 = .279; Global R^2 = .275.

Figure 3

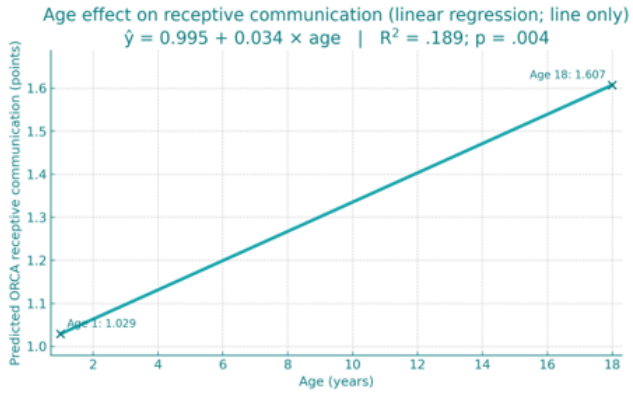


Figure 3

Age effect on ORCA receptive communication (linear regression; line only).
The line shows the predicted absolute score across ages 1–18 based on y = 0.995 + 0.034 × age. Predicted values range from 1.029 (age 1) to 1.607

(age 18); $R^2 = .189$, $p = .004$.