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ORIGINAL PAPER

The Cerebellar Cognitive Affective Syndrome in Ataxia-Telangiectasia

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Abstract

Ataxia-telangiectasia (AT) is an autosomal recessive, multisystem disease causing cerebellar ataxia, mucocutaneous telangiectasias, immunodeficiency, and malignancies. A pilot study reported cognitive and behavioral manifestations characteristic of the cerebellar cognitive affective / Schmahmann syndrome (CCAS). We set out to test and further define these observations because a more comprehensive understanding of the spectrum of impairments in AT is essential for optimal management. Twenty patients (12 males; 9.86 ± 5.5 years, range 4.3 to 23.2) were grouped by age: AT-I (toddlers and preschoolers, $n = 7$, 4.3–5.9 years), AT-II (school children, $n = 7$, 5.9–9.8 years), AT-III (adolescents/young adults, $n = 6$, 12.6–23.2 years). Standard and experimental tests investigated executive, linguistic, visual-spatial, and affective/social-cognitive domains. Results were compared to standard norms and healthy controls. Cognitive changes in AT-I were limited to mild visual-spatial disorganization. Spatial deficits were greater in AT-II, with low average scores on executive function (auditory working memory), expressive language (vocabulary), academic abilities (math, spelling, reading), social cognition (affect recognition from faces), and emotional/psychological processing. Full Scale IQ scores were low average to borderline impaired. AT-III patients had the greatest level of deficits which were evident particularly in spatial skills, executive function (auditory working memory, sequencing, word/color interference, set-shifting, categorization errors, perseveration), academic achievement, social cognition (affect recognition from faces), and behavioral control. Full Scale IQ scores in this group fell in the impaired range, while language was borderline impaired for comprehension, and low average for expression. Cognitive deficits in AT at a young age are mild and limited to visual-spatial functions. More widespread cognitive difficulties emerge with age and disease progression, impacting executive function, spatial skills, affect, and social cognition. Linguistic processing remains mildly affected. Recognition of the CCAS in children with AT may facilitate therapeutic interventions to improve quality of life.

Keywords Cerebellar cognitive affective syndrome · CCAS · Ataxia-telangiectasia · Cognition · Behavior

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Ataxia-telangiectasia (AT) is a rare, autosomal recessive, multisystem neurodegenerative disease that causes cerebellar ataxia, telangiectasias of the conjunctiva and skin, immunodeficiency, radiation sensitivity, and lymphoid, hematologic, and solid malignancies [1–3]. Classic AT affects children in their first to fourth year of life. In younger patients (toddlers), it manifests with cerebellar ataxia, whereas older patients (adolescents and young adults) may develop other motor signs including limb dystonia, myoclonic jerks, and choreoathetoid movements [4–6]. In non-classic AT, the disease phenotype may be milder, presenting later in school age children, adolescents, and young adults, with motor features such as dystonia (for review [3, 6]).

AT is caused by partial or total mutational inactivation of the ATM gene, coding for a (PI3K) serine/threonine-kinase. The hallmark neuropathology of the disease is

cerebellar degeneration, particularly of the cerebellar cortex, with loss of the internal granular layer, and severe Purkinje cell loss and dislocation [7]. There is relative preservation of the deep cerebellar nuclei, and inferior olivary and pontine nuclei. Spinal cord changes include degeneration of the posterior columns, notably the gracile fascicle, and prominent loss of anterior horn cells. Peripheral nervous system pathology includes axonal degeneration and neurogenic muscular atrophy [7].

The literature on neurological manifestations of AT has generally focused on motor phenomenology. Against this background, a convergence of anatomical, physiological, clinical, and functional neuroimaging studies indicate that the cerebellum is integrally involved also in cognition and emotion. The cerebellar cognitive affective syndrome (CCAS) [8] is characterized by deficits in executive functioning, linguistic processing, spatial cognition, and affect regulation, resulting in overall intellectual impairment. Together with the cerebellar motor syndrome and the vestibular cerebellar syndrome, the CCAS has been regarded as the third cornerstone of clinical ataxiology (Schmahmann's syndrome [9]). The impact of cerebellar pathology on intellectual and social-emotional functioning in children is also now recognized. Children develop the CCAS following excision of cerebellar tumors [10–12], in the setting of perinatal disruptions, and in developmental disorders [13–15]. Cognitive impairments in children have also been described in acquired or congenital cerebellar disorders [16], and cerebellar dysfunction is linked with cognitive and emotional deficits in early infantile autism [17].

Given that there is widespread pathology of the cerebellum in AT, we aimed to determine whether the neurological manifestations of this disorder include not only cerebellar motor ataxia but also the intellectual and neuropsychiatric impairments that characterize the CCAS. In a preliminary study of AT in children from Germany [18], we found cognitive and behavioral symptoms that are characteristic of the CCAS. That study also suggested that patients with mutations allowing for some transcription of ATM protein performed better on selected cognitive tasks implicating a milder cognitive phenotype than patients with ATM mutations leading to a truncated protein [18]. Similar genotype-phenotype relationships have been reported for motor and other clinical manifestations in AT, but not for the cognitive and the behavioral symptoms [6].

In the present investigation, we set out to examine these observations in a US cohort of AT patients in a more comprehensive manner in order to define the nature and severity of the cognitive, behavioral, and social-emotional changes in children with AT. We also explored the relationship between the genotype and cognitive/motor phenotype in this patient population.

Participants and Methods

Participants

We studied 20 individuals (12 male, 8 female) ages 4–23 years (9.86 ± 5.5 years) with a clinical and genetic diagnosis of AT recruited through the Massachusetts General Hospital Ataxia Unit (Table 1). Clinical diagnosis was according to World Health Organization and expert guidelines [2, 19, 20]. Exclusion criteria were perinatal incidents, neurological or non-neurological illness unrelated to AT, and previous or current radiotherapy or chemotherapy.

The AT patients were divided by convention into three age groups: AT-I, toddlers and preschoolers; AT-II, school age; and AT-III, adolescents and young adults. The age ranges of the patients in these groups in this cohort were AT-I ($n = 7$) 4.10–5.9 years; AT-II ($n = 7$) 7.11–9.9 years, and AT-III ($n = 6$) 12.6–23.2 years.

Most attend regular schools with integrated special care and one-on-one attendants, with Individualized Education Programs (IEP) and individual accommodations such as writing boards, computers with adapted mouse, and more recess and break time when tired. Some patients attend schools for children with special needs.

Thirty typically developing children matched for age, handedness, and gender were recruited as healthy controls from the panel of volunteers at Massachusetts General Hospital for the experimental measures used in this study. This study was approved by the institutional review board of the Massachusetts General Hospital. Informed consent was obtained from all parents as well as from patients older than 14 years, and assent was obtained from all patients younger than 14.

Methods

All subjects completed the following protocol:

(1) Complete history, clinical, developmental, and neurological examination, including administration of the Brief Ataxia Rating Scale (BARS) [21], (2) standard comprehensive neuropsychological test battery, (3) experimental tests shown to be associated with cerebellar activation on neuroimaging studies [22, 23], (4) assessment of disease stage [24] defined as follows: Stage 0 = no gait difficulties, Stage 1 = onset of gait disorder, Stage 2 = walking aid required, Stage 3 = wheelchair-bound, and (5) analysis of genetic results previously obtained during routine clinical care.

Neurological Examination Protocol and Documentation of Ataxia

Detailed history and neurological examination was performed (F.H. and J.D.S.) and video-taped in each case. The BARS

Table 1 Patient characteristics, demographic features, age/clinical disease. * = monozygotic twins. BARS = Brief Ataxia Rating Scale (Schmahmann et al. 2009), F = female, M = male, m = months, N/D = not done, y = years

Patient number	Age (y/m)-gender (M/F)	BARS Score (/30)	Ataxia severity stage (0–4)	Age group	Behavioral and cognitive problems reported by parents
1	4/10.9–M	16	Walks unassisted, broad based gait (Stage 1)	AT-I	Fatigue, temper tantrums when frustrated, expressive language delays
2	12/5.9–M	23	Two person assisted gait < 25 ft, wheelchair at all other times (Stage 3)	AT-III	Fatigue, easily frustrated, depressed
3	9/7.2–F	11	One person assist, walker at home (Stage 2)	AT-II	Fatigue
4	5/7.2–F	7	Walks unassisted, broad based (Stage 1)	AT-I	Fatigue
5	18/3.5–F	N/D	Two person assisted gait < 25 ft, wheelchair at all other times (Stage 3)	AT-III	Fatigue, difficult to calm once upset (worse when younger; 9/10 on severity scale). Needs more "comforting" and "hugs" to calm her down than healthy 18 y/o teens, gets frustrated easily, does not get excited about jokes compared to her same age peers, seems withdrawn
6	9/0.4–F	18	One person assist (Stage 2)	AT-II	Fatigue, frustration when trying to keep up with peers
7	15/6.9–M	23	Two person assisted gait < 25 ft, wheelchair at all other times (Stage 3)	AT-III	Fatigue, very slow to process cognitive tasks, sometimes immature (more than peers), since high school more trouble getting socially involved
8*	5/9.2–M	12	Walks unassisted, broad based, staggering gait (Stage 1)	AT-I	Fatigue, easily distractible, clingy, wants a lot of attention, gets upset if rules or structures are not followed, difficult to calm down when upset. Stranger anxiety, separation anxiety. Lack of expressive speech (does not talk)
9*	5/9.2–M	12	Walks unassisted, broad based, staggering gait (Stage 1)	AT-I	Fatigue, easily distractible, defiant, clingy, at times out of normal range aggressive (hits brother or mother) when frustrated or if daily structures change, lack of expressive speech (points if he wants things)
10	8/2.4–M	11	Walks unassisted, broad based, staggering gait (Stage 1)	AT-II	Distractible, fatigue
11	5/3.7–F	5	Walks unassisted, staggering gait, arm sway (Stage 1)	AT-I	Fatigue
12	4/3.3–M	8	Walks unassisted, staggering gait, arm swing (Stage 1)	AT-I	Working memory (forgets easily), strong opposition to certain textures of food or smells, easily upset
13	9/1.2–F	21	One person assist, uses walker at home/ wheelchair for longer distances (Stage 2)	AT-II	Aggression (hits teachers, mother) had to change classes/school, bossy, screams when upset, no insight into disrespectful behavior. Fatigue
14	9/8.6–M	16	Walks with assistance of wall (1 person assist) (Stage 2)	AT-II	Fatigue, arousal, difficulties expressing himself (word finding), better with shorter phrases
15	9/3.9–M	10	No walking aid, broad based, dystonic posturing. No walking aid at home. Plays in soccer team (Stage 1)	AT-II	None reported
16	15/0.8–F	3	No walking aid, broad based, dystonic posturing. No walking aid at home, does karate (Stage 1)	AT-III	Fatigue (increases throughout day). No other signs reported
17	20/1.2–F	25	Wheelchair (Stage 3)	AT-III	Uncomfortable at initiating conversations in new social settings
18	5/1.7–M	9	Walks unassisted, staggering gait, arm swing (Stage 1)	AT-I	Sensitive, easily frightened by loud noises, at times restless (fidgety)
19	23/2.4–M	21		AT-III	

Table 1 (continued)

Patient number	Age (y/m)-gender (M/F)	BARS Score (/30)	Ataxia severity stage (0–4)	Age group	Behavioral and cognitive problems reported by parents
			Two person assisted gait 25 ft, wheelchair at all other times (Stage 3)		Short term memory difficulties, aversion to certain textures of food
20	7/11.0–M	11	Walks unassisted, staggering, broad based gait (Stage 1)	AT-II	Difficulty with multitasking, fatigue

detects and quantifies the cerebellar motor syndrome, assessing gait (0 to 8 points), heel-to-shin test for decomposition of lower extremity movement (0 to 4, scored left and right), finger-to-nose test for decomposition and dysmetria of the upper extremities (0 to 4 points scored left and right), dysarthria (0 to 4), and oculomotor abnormalities, namely observation of the eyes in primary position, detection of nystagmus, and the presence of degraded pursuit and saccadic eye movements (0 to 2). Perfect cerebellar motor performance scores 0, maximal impairment scores 30. Motor performance was also evaluated using 25-ft timed walk**.** Additional motor symptoms and signs were documented, including dystonia, myoclonic jerks of limbs, choreoathetosis, resting tremor, bradykinesia, hypomimia, and drooling. Disease stage was determined as part of the neurological examination.

Early infant/child development was assessed retrospectively using the Denver Developmental Screening Test (DENVER II) [25]. A subset of families provided IEPs of school age children, which provided information regarding cognitive, behavioral, academic, and adaptive functioning in the educational setting.

Genotype Analysis

ATM-mutational genotypes were available from standard diagnostic procedures in 9 of the 21 patients and retrospectively evaluated [26]. In some patients clinical ATM kinase assays were available (Dr. Richard A. Gatti, University of California, Los Angeles, UCLA). All other patients provided radioimmunoassays that were used to confirm the clinical diagnosis of AT [2]. Using Ensembl 69 (NCBI 37) build, the pathogenicity of each variant was analyzed using MutationTaster2 [26]. All ATM variants were compared to transcript ID ENST00000278616 (NM_000051.3). The mutations we identified are as described in Table 2.

Neuropsychological Assessment

All subjects completed a comprehensive neuropsychological assessment designed to evaluate major areas of cognitive and behavioral function, including the domains that characterize the CCAS (executive functioning, linguistic processing, visuospatial skills, and social-emotional functioning). Tasks were administered following standardized procedures (M.D.). See Supplementary Table 1 for details of tests administered and citations.

Social cognition was assessed in groups AT-II and AT-III using the Social Perception scale of the Developmental Neuropsychological Assessment Scale (NEPSY-II) [27] that measures affect recognition from photographs of children's faces (happy, sad, fear, anger, disgust, neutral), and verbal and contextual Theory of Mind tasks. Group AT-III was also assessed on the Advanced Clinical Solutions (ACS) Social Cognition subtests [28].

Parents/guardians completed standardized measures of emotional, behavioral, social, and adaptive functioning: the Behavior Rating Inventory of Executive Function (BRIEF) [29], Behavior Assessment System for Children (BASC-2) [30], ADHD Symptom checklist [31], Gilliam Autism Rating Scale (GARS-2) [32], Vineland Adaptive Behavior Scales (VABS) [33], and a Social and Communication Disorder Checklist (SCDC) [34].

Experimental Measures

Metalinguistic skills were assessed in a subset of patients using the Test of Language Competence-Expanded (TLC-E) [35]. The TLC-E has four subtests: ambiguous sentences, making inferences, recreating speech acts, and figurative language. Due to time constraints, only the first five items of each subtest were administered. Answers were evaluated using the scoring key of the standard norms. Answers were summarized for total correct answers per subtest.

Older patients were also asked to solve 12 math problems from verbal and visual presentation. There were six addition problems (two 1-digit additions, two 2-digit additions < 20, two 2-digit additions < 50) and six subtraction problems (two 1-digit subtractions, two 2-digit subtractions < 20, and two 2-digit subtractions < 50). Performance on experimental tests was compared to control subjects. There was no time limit.

Experimental tests of social cognition included a test of affect recognition (Reading the Mind in the Eyes Test-Child Version, RMET-C) [36], acted-out Theory of Mind (TOM) stories [37–41] (Supplement 2), and an Empathy Rating Scale [42]. AT-I patients were tested only on experimental measures of social cognition because standard tests did not

Table 2 Results of genetic analysis. Abbreviations: AA/aa = amino acid, dbSNP = data base for single nucleotide polymorphism (https://www.ncbi.nlm.nih.gov/projects/SNP/), ExAC = Exome Aggregation Consortium (http://exac.broadinstitute.org/), fs = frame shift, 1000G = 1000 Genome Database (http://www.internationalgenome.org/), Het = heterozygous, nt = nucleotide, PTC = premature termination codon, ‡ = highly conserved

Patient	DNA changes	Mutant stop codon nucleotide	AA residues	AA changes (mutation)	Splice site change	Frameshift	PTC	Known variant in database		Known disease mutation (dbSNP)	ATM protein
		Full length = 9171 nt	Full length = 3057 aa					ExAC	1000G		
1	c.7915A > T	7917	2639	K2639*	No	No	Yes	No	No		
2	c.3369_3369delA	3375	1125	Y1124Tfs*2	No	Yes	Yes	No	No	rs587781752	
	c.3754_3756delinsCA	3765	1255	Y1252Qfs*4	No	Yes	Yes	No	No	rs786201886	
3	Same as patient 2 (sibling)										
4	c.2250G > A	N/A	N/A	N/A	Donor lost	N/A	N/A	1 Het Carrier	No	rs1137887	
	g.109394A > C (c.7630-2A > C)	N/A	N/A	N/A	Acceptor lost	N/A	N/A	2 Het Carrier	No	rs587779866	
	c.8122G > A	9171	3057	D‡2708 N	N/A	No	Yes	No	No	rs587782719	
6	g.48664G > A (c.2921 + 1G > A)	N/A	N/A	N/A	Donor lost	N/A	N/A	3 Het Carrier	No	rs587781558	No detectable ATM protein
8	g.50048G > A (c.3154-1G > A)	N/A	N/A	N/A	Acceptor lost	N/A	N/A	1 Het Carrier	No	rs750663117	No detectable ATM protein
	c.8364 T > G	9171	3057	H‡2788Q PI3K/PI4K domain lost	N/A	No	N/A	No	No		
9	Same as patient 08 (identical twins)										
10	c.6997_6998insA	7116	2372	T2333Nfs*40 Several domains lost	N/A	Yes	Yes	No	No		No detectable ATM protein
	g.131398G > A (c.8786 + 1G > A)	N/A	N/A	N/A	Donor lost	N/A	N/A	2 Het Carrier	No	rs17174393	
11	Same as patient 10 (sibling to 10)										
13	c.8146G > T	9171	3057	V‡2716F PI3K/PI4K domain lost	N/A	No	No	No	No		
	g.142841G > C (c.8988-1G > C)	N/A	N/A	N/A	Acceptor lost	N/A	N/A	No	No	rs730881386	
15	c.4432C > T	4434	1478	Q1478*	N/A	N/A	Yes	No	No		No detectable ATM protein
	c.2610C > T	9171	3057	No	No	No	No	2 Het Carriers	No	rs587780618	
	c.3489C > T	9171	3057	No	No	No	No	No	No		

Table 2 (continued)

Patient	DNA changes	Mutant stop codon nucleotide	AA residues	AA changes (mutation)	Splice site change	Frameshift	PTC	Known variant in database		Known disease mutation (dbSNP)	ATM protein
								ExAC	1000G		
		Full length = 9171 nt	Full length = 3057 aa								
16	c.8147 T > C	9171	3057	V‡2716A PI3K/PI4K domain lost	No	No	No	5 Het Carriers	No	rs587782652	
	c.8494C > T	9171	3057	R‡2832C PI3K/PI4K domain lost	No	No	No	1 Het Carrier	No	rs587779872	
19	Exon 64–65 deletion										
20	c.1027_1030delGAAA	1032	344	E343Ifs*2	N/A	Yes	Yes	No	No		No detectable ATM protein

provide age-matched norms. AT-II and AT-III patients received the experimental tests in addition to the standard tests.

Parents completed the Cerebellar Neuropsychiatric Rating Scale (CNRS) [43, 44] (for details, see Supplementary Table 1). The CNRS is an experimental questionnaire that targets neuropsychiatric symptoms described in cerebellar patients [43]. A score of 0 indicates absence of symptoms. Parents rated their child's behavior on a four-point Likert Scale indicating whether symptoms occurred never (0 points), sometimes (1 point), often (2 points), or always (3 points). They also were interviewed for behavioral and emotional concerns in their children, such as emotional dysregulation, atypical behaviors, frustration, and sadness.

Statistical Analysis

Behavioral data were analyzed using SPSS v20/Graph Pad Prism (SPSS Inc.) (Graph Pad Software, La Jolla, CA, USA). In order to obtain data comparable to previous studies, statistical approaches were adapted from earlier studies [8, 10, 18]. Standard scores were obtained by comparing raw scores with the mean score for individuals of the same age, and when provided for the test, the same gender. Test scores are based on a mean and standard deviation but are expressed differently for different tests. Some provide Standard Scores (as for IQ scores with mean = 100 and standard deviation (SD) = 15), scaled scores (mean = 10, SD = 3), or percentile scores, whereas others provide means and SDs for age-matched samples with which a patient's raw score is compared (see Supplement 3). Given the need to compare patients' performances on tests across different functional domains as well as with results from previous studies, all scores were converted to *z* scores. The *z* score provides a standard from which all other scores can be derived and reflects the amount that a score deviates from the mean of that population. Z scores are obtained by the formula [(subject) − (population mean) / (SD for the population)]. Scores are stated in standard deviation units that reflect their distance from the mean (with mean *z* score = 0). Consistent with accepted classifications regarding score interpretation, scores ≤ − 1 SD below the mean were considered in the middle of the low average range, scores < − 1.5 SD were considered mildly impaired, and those < − 2.0 SD were considered impaired [8, 10, 18]. Two-tailed tests of significance were applied to Pearson correlations between BARS total score and the major categories of neuropsychological data.

Results

Genetic Confirmation

Among the 14 patients whose genetic studies were available for analysis, we identified 20 genetic variants. These included

single nucleotide variants (15) and Indels (insertion deletion mutations) (4) predicted to have deleterious effects on the function of ATM kinase through mutations in highly conserved amino acid residues (5), nonsense/frameshift mutations leading to premature termination codons (PTC) (6), loss of splice donor (3) or splice acceptor (3) sites or seemingly silent mutations of unknown significance. As summarized in Table 2, 12 of these variants are reported in the dbSNP database.

Two of the 14 confirmed AT patients presented with unusually mild phenotypes. Patient 15 (P15, Tables 1 and 2) had no detectable ATM protein on Western blot analysis and a nonsense mutation leading to a truncated transcript on one allele which would make a polypeptide composed of only 1478 amino acid (aa) residues (full length—3057 aa). This patient also has two putatively silent mutations of unknown significance. The second, patient 16, was a compound heterozygote with single nucleotide variation on each allele (P16, Tables 1 and 2) resulting in missense mutations at the highly conserved Valine and Arginine residues at aa residues 2716 and 2832, respectively. These changes were predicted to have deleterious effect on the PI3K/PI4K domain (aa 2712–2962) of the ATM kinase.

Motor Abilities

The cerebellar motor syndrome measured by the BARS revealed that AT-I patients scored 9.5 ± 3.7, AT-II patients 12.4 points ± 4.3, and AT-III patients 23 points ± 1.6. Severity of BARS scores correlated with increasing age ($r > 0.93$, $p < 0.001$), consistent with the neurodegenerative nature of this disease. Total BARS score correlated with Full Scale IQ ($p < 0.05$), the Beery VMI visual motor test which has a motor component ($p < 0.0001$), and the EOWPVT ($p < 0.02$) which fell in the borderline low normal range.

Disease State and Neurological Presentation

All seven AT-I patients presented with ataxia severity stage 1 (onset of gait ataxia but no walking aid required), and cerebellar motor findings of gait ataxia, upper limb dysmetria with dysdiadochokinesis, lower limb dysmetria, and oculomotor abnormalities. Some patients had drooling. The seven AT-II patients presented with ataxia severity stages 1–3 (no walking aid/walking aid/wheelchair-bound). Neurological findings included cerebellar motor features as well as bradykinesia, dystonia, myoclonus, and drooling. Five of the six AT-III patients were in ataxia severity stage 3 (wheelchair-bound), with cerebellar ataxia and other motor findings including bradykinesia, hypomimia, dystonia, and myoclonus. Dysphagia and urinary urgency were identified in two AT-III patients. See Table 1.

The two patients with mild disease as part of their variant/non-classic AT phenotype were assigned by age to groups AT-II (P15, male, age 9.8 years) and AT-III (P16, female, age 15.0 years). Both walked independently without assistance and participated in sports (soccer, karate). Parents reported dystonic gait and posturing of hands and feet when walking at a young age, bradykinesia and drooling, and myoclonic jerks in school age/teenage years. Traditional cerebellar motor signs of ataxia and dysmetria were less prominent, as were their cognitive phenotypes.

Parental Report of Behavioral Symptoms

Parents of all subjects completed behavioral rating scales. Behavioral symptoms were reported by the parents of 10 of the 20 children (50%). These included difficulties in the executive domain (8/10 patients; attention, arousal, multitasking, processing speed), social skill set (2/10 patients; immature behaviors, difficulties engaging in social interactions), and emotion regulation (5/10 patients; easy frustration, temper tantrums, difficulties calming after emotional upset, defiant, oppositional or passive aggressive behaviors, verbally and physically aggressive behavior, hypometric or flat affect, internalization of frustration and anger). Autism spectrum symptoms in two patients manifested as a strict need to adhere to daily routines, stranger anxiety beyond the normal age expectation, clinginess, lack of expressive verbal communication with use of pointing, body language, and vocalization to express wishes, strong opposition to certain textures and smells, fixation on objects such as ice cubes, and easy sensitive overload to noise, social settings, and school. Parents stated that these behaviors were not present continuously but came in bursts. No patient was reported to have overt signs of psychosis, such as hallucinations or delusions.

Fatigue was reported to be a major cause of disability in daily life activities by the parents of 66% of the patients.

A wide range of behavioral symptoms seemed to be reported more frequently in the older patients, but the small number of patients in each group precluded statistical analysis. A higher frequency in older children may be related to progression of the disease itself, although it is possible that these may not have been reported in younger patients because temper tantrums or other indicators of emotion dysregulation may have been interpreted as a normal behavior in younger children.

Cognitive Measures

The following test results are reported by age group and in comparison to standard norms.

Overall Cognitive Ability

AT-I Mean performance fell within the average range on standard tests of verbal and nonverbal intelligence (Full Scale IQ z score = − 0.44, nonverbal IQ z score = − 0.28). Similar performance was found on standard tests of general ability and fluid reasoning where the AT-I patients' mean and individual scores fell within the average range on standard norms.

AT-II Mean performance was in the low average range on standard tests of intelligence (Full Scale IQ z score = − 1.13), particularly on a test of visual pattern reasoning (Matrix Reasoning z score = − 1.49).

AT-III The mean Full Scale IQ z score = − 1.48 was in the borderline range. Matrix Reasoning was mildly impaired compared to standard norms (mean z score = − 1.83), not significantly different than the performance of the AT-II group ($p = 0.5$).

Confirmation of CCAS in AT Patients

AT patients demonstrated impaired or borderline impaired performance in visual-spatial, executive, linguistic, social cognitive, and affective domains, the defining features of the CCAS. For a summary of results, see Table 3. Here we present standard and experimental measures of cognition and behavior by cognitive domain, although we recognize that many cognitive tests tap more than one domain.

Visual-Spatial Skills

AT-I patients performed in the average range on visual-spatial tasks, including the Motor-Free Visual Perception Test (MVPT-3) which measures visuospatial abilities without any motor demands (MVPT-3, z score = − 1.06). Performances were in the lower end of the average range on visuomotor integration tasks including the Beery Visual Motor Integration test (z score = − 0.8), and the Block Design subtest of the WPPSI-IV (z score = − 0.9).

AT-II patients' mean performance fell in the low average range on the MVPT-3, with subjects in this group obtaining scores that ranged from low average to average (mean z score = − 0.9). Their mean score was mildly impaired on the Wechsler Abbreviated Scale of Intelligence (WASI-II) perceptual reasoning index (z score = − 1.83) which is influenced by motor abilities. Mean performance on the block design subtest (z score = − 1.8) was mildly impaired. Mean performance on a task of design copy (Beery Visual Motor Integration test) was impaired (z score = − 2.4). All AT-II patients completed the Rey-Osterrieth Figure Copy Test (ROCFT), with copies characterized by marked fragmentation, and individual scores falling < 1st percentile (Fig. 1). Five patients obtained a perfect score when copying a 2D-star or 2D-interlocking pentagons, but no patient could reconstitute the 3D shape of a cube, producing either 2D or fragmented cubes, or they attempted a 3D copy with missing lines or perseverative errors (Fig. 2). It should be noted that developmental norms (Beery Visual Motor Integration Test [45]) indicate that children do not succeed in producing an integrated copy of a 3D cube until after the age of 8 years. However, the copies produced by the AT children in this study lack the beginning stages of integration that are typically observed at this age.

AT-III patients were impaired on all visual-spatial tests. Impairments were most pronounced on the Perceptual Reasoning Index of the WASI-II (z score = − 2.11), and mild impairment was also observed on the Motor Free Perceptual Reasoning Test (MVPT-3, z score = − 1.69). Children in this group evidenced severe impairment on block design (z score = − 2.58) and the Beery Visual Motor Integration Test (z score = − 3.67). Only three patients were able to perform the block design test due to motor deficits (Table 3). AT-III patients were too motorically impaired to copy the Rey Complex figure, except for one patient with variant disease whose copy accuracy fell below the 1st percentile. Two AT-III patients copied the 2D-star and 2D-interlocking pentagons but drew a 2-D or fragmented copy of the cube (Fig. 2).

Executive Functions

AT-I patients' mean performance fell within the average range on most standard tests of executive function (visual working memory total mean z score = − 0.17). Zoo Locations subtest revealed an average group mean score, although some patients' scores fell within the low end of performance (z score = − 0.58). Auditory working memory (Digit Span) was not tested in this age group due to lack of age-matched norms. Tests of processing speed are based on timed fine motor skills. AT-I patients showed low average performance (WPPSI Processing Speed Index z score = − 1.44, Bug Search z score = − 1.2, Cancellation subtest z score = − 1.4).

AT-II patients' mean performance was low average on tests of auditory working memory: Digit Span total (mean z score = −1.2), forward (z score = −0.9), backwards (z score = −1.0), and sequencing (z score = −0.73). Immediate recall of visual information was tested by means of the immediate recall condition on the ROCFT [46] (see Supplement 1). All AT-II patients were able to complete this task with individual scores below the 1st percentile. This likely reflects difficulty encoding the complex figure in the copy condition. Tests of processing speed were not administered because of motor incapacity.

Six AT-II patients completed a standard test of sustained and divided attention, impulsivity and motor control (Quotient® ADHD System) (http://www.quotient-adhd.com). Five received a diagnosis of likely-ADHD based on this

Table 3 Results of standard tests in AT patients

Cognitive domain/test	Toddlers and preschoolers (group AT-I, $n = 7$)		School age (group AT-II, $n = 7$)		Adolescents and young adults (group AT-III, $n = 6$)	
	Mean (range)	Test	Mean (range)	Test	Mean (range)	Test
Overall cognitive ability						
Full Scale IQ (S)	93 (78–115)	WPPSI-IV	**83** (75–96)	WASI-II	**78** (66–85)	WASI-II
Nonverbal IQ (S)	96 (80–107)		107[a]		96[a]	
General Ability (S)	90.6 (79–111)					
Language						
Expressive vocabulary (ss)	12 (6–16)	EOWPVT	8 (3–10) 14[a] and 10 (7–12) 10[a]	WASI-II and EOWPVT, respectively	9 (6–11) 10[a]	EOWPVT
Comprehension (ss)	10 (2–14)	WPPSI-IV	9 (5–14)	WASI-II	**7** (5–9) 10[a]	WASI-II
Similarities (ss)	11 (4–16)	WPPSI-IV	11 (7–15) 11[a]	WASI-II	8 (6–9) 10[a]	WASI-II
Receptive language (ss)	12 (10–16)	ROWPVT	11 (9–15) 14[a]	ROWPVT	11 (6–14) 10[a]	ROWPVT
Information (ss)	**8** (1–11)	WPPSI-IV	*n/a*	*n/a*	*n/a*	*n/a*
Formulated sentences (ss)	n/a	n/a	n/a	n/a	9 (9) 9[a]	CELF-4
Ambiguous sentences						
Composite score	n/a	TLC-E	74.6%	TLC-E	75.3%	TLC-E
Picture points			92.9%		72.5%	
Interpretation points			68.5%		72.3%	
Making inferences						
Composite score (% correct)	33%[b]	TLC-E	93.4%	TLC-E	86.6%	TLC-E
Recreating speech acts						
Composite score	n/a	TLC-E	74.1%	TLC-E	95.5%	TLC-E
Holistic score			81.25%		91.1%	
Word count			97.9%		100%	
Figurative language						
Composite score	n/a	TLC-E	53.3%	TLC-E	82%	TLC-E
Interpretation points			42%		81.1%	
Picture points			80%		86.6%	
Executive functions						
Digit span total score (ss)	*n/a*	*n/a*	**6** (3–11) 7[a]	WISC-VI	**6** (4–10) 8[a]	WAIS
Forward span (ss)	*n/a*	*n/a*	**7** (4–10) 9[a]	WISC	**7** (5–10) 7[a]	WAIS

Table 3 (continued)

Cognitive domain/test	Toddlers and preschoolers (group AT-I, $n = 7$)		School age (group AT-II, $n = 7$)		Adolescents and young adults (group AT-III, $n = 6$)	
	Mean (range)	Test	Mean (range)	Test	Mean (range)	Test
Backward span (ss)	*n/a*	*n/a*	**7** (3–10) 7[a]	WISC	**7** (6–8) 10[a]	WAIS
Digit span sequencing (ss)	*n/a*	*n/a*	8 (2–14) 7[a]	WISC	**6** (4–11) 8[a]	WAIS
Visual working memory composite (ss)	9 (7–13)	WPPSI-IV	*n/a*	*n/a*	*n/a*	*n/a*
Picture memory (ss)	11 (7–17)	WPPSI-IV	*n/a*	*n/a*	*n/a*	*n/a*
Zoo locations (ss)	**8** (3–15)	WPPSI-IV	*n/a*	*n/a*	*n/a*	*n/a*
WCST-4 errors	*n/a*	*n/a*	*n/a*	*n/a*	**7** (4–10) 14[a]	WCST-4
WCST-4 perseverations	*n/a*	*n/a*	*n/a*	*n/a*	**6** (2–9) 15[a]	WCST-4
Stroop Test[b]	*n/a*	*n/a*	*n/a*	*n/a*	**3**	Stroop
Words						
Colors	*n/a*	*n/a*	*n/a*	*n/a*	**3**	Stroop
Color/word	*n/a*	*n/a*	*n/a*	*n/a*	**3**	Stroop
Interference	*n/a*	*n/a*	*n/a*	*n/a*	**3**	Stroop
Processing speed	6 (3–7)	WPPSI	*n/a*	*n/a*	*n/a*	*n/a*
Total score (ss)						
Bug search (ss)	5 (1–9)	WPPSI	*n/a*	*n/a*	*n/a*	*n/a*
Cancellation (ss)	6 (3–8)	WPPSI	*n/a*	*n/a*	*n/a*	*n/a*
Visual-spatial functions						
Matrix reasoning (ss)	11 (8–14)	WPPSI-IV	**6** (3–9) 11[a]	WASI-II	**5** (3–9) 11[a]	WASI-II
Picture concepts (ss)	13 (11–15)	WPPSI-IV	*n/a*	*n/a*	*n/a*	*n/a*
Block design (ss)	**7** (3–11)	WPPSI-IV	**5** (4–9) 9[a]	WASI-II	**2** (1–4) 7[a]	WASI-II
Object assembly (ss)	9 (6–10)	WPPSI-IV	*n/a*	*n/a*	*n/a*	*n/a*
Visual-spatial composite	**7** (5–8)	WPPSI-IV	*n/a*	*n/a*	*n/a*	*n/a*
Visual motor integration	8 (6–9)	VMI-6	**3** (0–5) 6[a]	VMI-6	**< 1** (< 1) 5[a]	VMI-6
Perceptual reasoning	**7** (4–11)	MVPT-3	**7** (5–12) 12[a] **and 4**	MVPT-3 and PRI of WASI-II, respectively	**5** (1–7) 11[a] **and 4**	

Table 3 (continued)

Cognitive domain/test	Toddlers and preschoolers (group AT-I, $n = 7$)		School age (group AT-II, $n = 7$)		Adolescents and young adults (group AT-III, $n = 6$)	
	Mean (range)	Test	Mean (range)	Test	Mean (range)	Test
			(4–8) 10[a]		(2–6) 9[a]	MVPT-3 and PRI of WASI-II, respectively
ROCFT-copy (ss)	*n/a*	*n/a*	**2** (2)	ROCFT	*n/a*	*n/a*
ROCFT-immediate RC (ss)	*n/a*	*n/a*	**< 2** ($n = 3$) **< 5** ($n = 2$) **< 6** ($n = 1$)	ROCFT	*n/a*	*n/a*
Copy star	*n/a*	*n/a*	Correct ($n = 5/5$)	See supplement 1	Correct ($n = 2/2$)	See supplement 1
Copy interlocking pentagons	*n/a*	*n/a*	Correct ($n = 5/5$)	See supplement 1	Correct ($n = 2/2$)	See supplement 1
Copy 3D cube	*n/a*	*n/a*	**Incorrect** ($n = 5/5$)	See supplement 1	**Incorrect** ($n = 2/2$)	See supplement 1
Attention						
ADHD Quotient System Index	Likely	Quotient System®	Likely	Quotient System®	*n/a*	*n/a*
Motion Index	Likely	Quotient System®	Likely (1 probable)	Quotient System®	*n/a*	*n/a*
Attention	Likely	Quotient System®	Likely	Quotient System®	*n/a*	*n/a*
Global	Likely	Quotient System®	Likely	Quotient System®	*n/a*	*n/a*
Academic performance						
Math (ss)[b]	*n/a*	*n/a*	**7**	WRAT-IV	**3**	WRAT-IV
Spelling (ss)[b]	*n/a*	*n/a*	**5**	WRAT-IV	**5**	WRAT-IV
Reading (ss)[b]	*n/a*	*n/a*	**6**	WRAT-IV	**7**	WRAT-IV
School readiness (ss)	13 (8–17)	Bracken	*n/a*	*n/a*	*n/a*	*n/a*
Motor function tests						
BARS total score	9.8	BARS	14	BARS	23	BARS
25 ft timed walk (sec)	15.52	n/a	24.55	n/a	35.94	n/a

Bold font indicates test results 1 SD below mean (e.g., mean standard score 100, 1 SD is 15; scaled score mean = 10, 1 SD is 3. Items in italics = test was not performed in this age group. For detailed test information, see Supplement 1

Abbreviations: *BARS* Brief Ataxia Rating Scale, *Bracken* Bracken School Readiness Assessment, *CELF-4* Clinical Evaluation of Language Fundamentals, *EOWPVT* Expressive One-Word Picture Vocabulary Test, *MVPT-III* Motor-Free Visual Perception Test, *PRI* Perceptual Reasoning Index of WASI-II, *ROCFT* Rey-Osterrieth Copy Figure Task, *ROWPVT* Receptive One-Word Picture Vocabulary Test, *S* Standard score, *s* seconds, *SD* Standard Deviation, *ss* scaled score, *Stroop* Stroop Color and Word Test, *TLC-E* Test of Language Competence-Expanded, *VMI-6* Beery Visual Motor Integration test, *WASI-II* Wechsler Abbreviated Scale of Intelligence, *WISC* Wechsler Intelligence Scale for Children, *WPPSI-IV* Wechsler Preschool and Primary Scale of Intelligence, *WRAT-IV* Wide Range Achievement Test

[a] Test result of the patients with variant disease presentation (P15 and P16, respectively)

[b] Test was performed by ≤ 3 patients

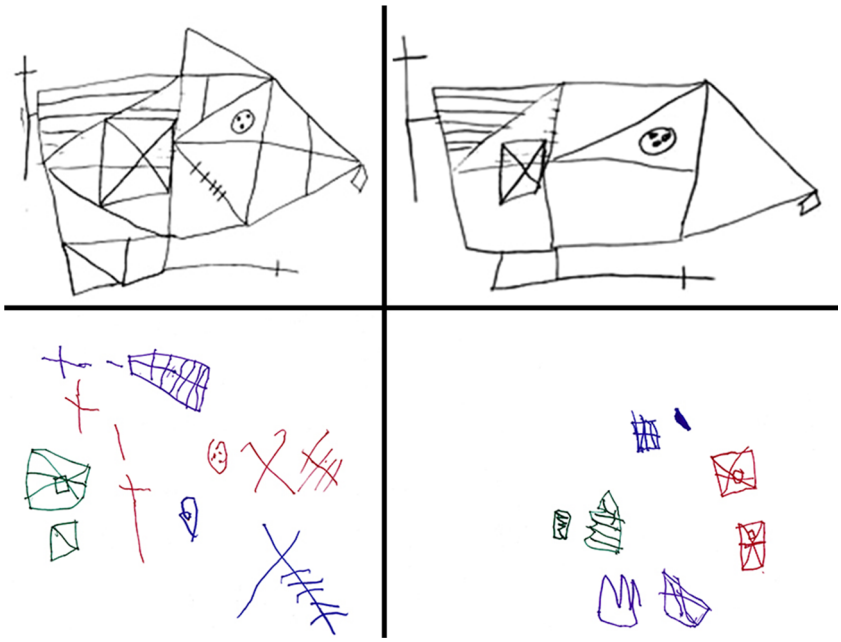

Fig. 1 Rey-Osterrieth Complex Figure drawings by a female AT patient age 9.7 years (bottom row) and a typically developing age matched control (top row). The Copy condition is on the left, and the Immediate Recall condition is on the right. Color coding for the AT patient was first red, followed by blue, green, and purple

test, and one a diagnosis of probable-ADHD. This was a timed test that required motor skill, which may have affected performance.

The mean auditory working memory scores for AT-III patients were no different than the AT-II group ($p = 0.4$). Observed differences were also not significant ($p = 0.5$) for forward digit span (mean raw score 8.2), backwards digit span (mean raw score = 6.6), and auditory sequencing (mean z score = − 1.33). One patient with variant AT was able to complete the ROCF test, scoring < 1st percentile for accuracy. Tests of processing speed were not administered due to motor difficulties. One was tested on the Stroop Color and Word Test of executive function, with a z score of − 2.5 in the impaired range. Six patients administered the Wisconsin Card Sorting test (Card Version 4) performed in the low average range for overall accuracy (mean z score = − 0.92) and perseverative errors (mean z score = − 1.4).

Language

AT-I patients' mean scores were within the average range on standard tests of language. They performed above average on tests of expressive language (Expressive One-Word Picture Vocabulary Test [EOWPVT]; z score = 0.83) and receptive language (Receptive One-Word Picture Vocabulary Test [ROWPVT]; z score = 0.83), and achieved average scores in the verbal domain on the information subtest (z score = − 0.6).

AT-II patients' mean scores on tests of language were also within the average range, and no different than those of AT-I patients (EOWPVT z score = 0.07; ROWPVT z score = 0.32,

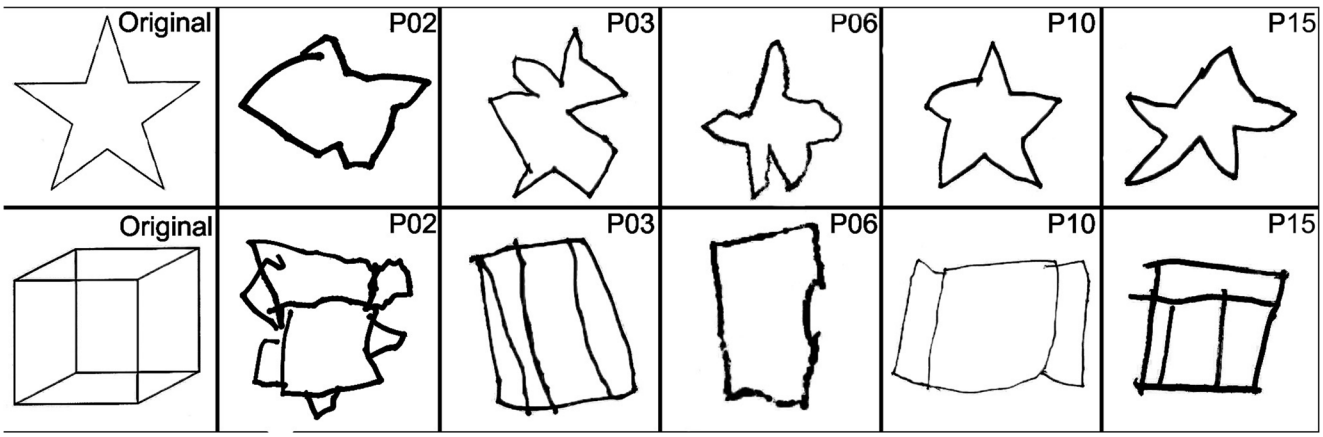

Fig. 2 Performance on the Copy a Star condition versus Copy a Cube in older AT patients. Patient ages at time of assessment (years/months): P02: 12/6; P03: 9/7; P06: 9/0; P10: 8/2; P15: 9/4. Patients showed mild difficulties copying the two-dimensional star, but were markedly impaired in their attempt to reproduce the three-dimensional cube

$p = 0.3$). Performance on a test of expressive verbal language was in the low average range (WASI-II, vocabulary subtest, z score = − 0.71). Patients were also mostly unimpaired on the metalinguistic (TLC-E) task, scoring 74.6% correct on ambiguous sentences, 93.4% on making inferences, 53.3% correct on figurative language, and 74.1% on creating grammatically correct sentences.

AT-III patients' mean z score (z = − 0.78) on the EOWPVT was lower than AT-I ($p = 0.03$), while scores on the receptive vocabulary measure (ROWPVT) were similar to those of AT-II patients (z score = 0.38; $p = 0.5$). AT-III patients' mean score was in the lower end of the average range for the Verbal Comprehension Index (WASI-II, z score = − 0.87) and on a verbal concept formation test (WASI-II Similarities, mean z score = − 0.83). On the TLC-E, AT-III patients ($n = 4$) were similar to AT-II, achieving 75.3% correct on ambiguous sentences, 86.6% correct on making inferences, 82.0% correct on figurative language, and 95.5% correct on creating grammatically correct sentences. Three AT-III patients also completed the formulated sentences subtest of the Clinical Evaluation of Language Fundamentals (CELF-4), with average scores compared to standard norms (z score = − 0.4).

Academic Achievement Tests

Due to time constraints, academic performance was tested in only a subset of patients. The findings are presented to provide examples of these patients' performances on school-related measures.

AT-I Four patients completed the Bracken School Readiness Assessment, scoring in the high average range (z score = 0.83). One excelled at the Word Reading (z score = 2.53) and Spelling subtests (z score = 1.33) of the Wide Range Achievement Test (WRAT-IV).

AT-II Two patients were in the lower end of the range of normal for the Word Reading subtest of the WRAT-IV (z score = − 1.44), one was mildly impaired on the spelling subtest (z score = − 1.67), and one scored in the average range on the math subtests of the WRAT-IV (z score = − 0.93). Five performed the experimental addition and subtraction task, receiving a perfect score on 1-digit addition. Two failed 2-digit addition with numbers < 20, and all failed one or both the 2-addition tasks with numbers < 50. Similarly, all but one AT-II patient completed the 1-digit subtraction. Four failed one or both the 2-digit subtractions < 20, and three failed the 2-digit subtraction task with numbers < 50.

AT-III One patient was able to complete the WRAT-IV, with an average score on reading (z score = − 1.1) but impaired on spelling (z score = − 1.6) and more so with math (z score = − 2.5). AT-III patients received highest scores adding and subtracting 1- and 2-digit numbers < 20, and lowest scores on 2-digit addition of numbers < 50 and 2-digit subtraction of numbers < 20 and < 50.

General Knowledge and Learning

AT-I General knowledge and ability to learn were assessed using the Information subtest of the WPPSI-IV. Scores fell in the average range (z score = − 0.61), although the distribution of scores ranged from very low to superior.

AT-II Visual memory was tested in all seven patients using the 5-min recall condition of the ROCFT. Five scored in the 2nd percentile or below, one in the 4th and one in the 12th percentile, possibly reflecting poor copying and encoding.

AT-III One patient completed the immediate recall condition on the ROCFT and scored below the 1st percentile, also possibly reflecting poor copying and encoding.

Cognitive Results in Patients with Mild Phenotype

Two AT patients (P15 and P16) with unusually mild phenotypes were analyzed separately for their cognitive performance. Their individual scores fell either above or within average range based on standard norms and are shown in Table 3.

Behavioral and Emotional Assessments

The following test results are reported by age group and in comparison to the experimental control cohort unless stated otherwise.

Social Cognition

AT-I Four patients were tested on experimental acted-out TOM stories (see Supplement 2). All passed a second order false belief question, emotional consistency questions, and emotional inference based on reality. Two failed the second order belief question, a deceptive content question testing for the other's false belief understanding, and an emotional inference question based on false belief [37–41]. On a parent informed questionnaire on empathy (Empathy Quotient, EQ) and systemizing skills (Systemizing Quotient, SQ) [42], AT-I patients scored an average of 31.8 (SD 13.7) on the EQ and 20.8 (SD 5.4) on the SQ.

AT-II Three patients assessed using standard tests of affect recognition (NEPSY-II) scored within the average range (z score = − 0.33). Five performed the TOM subtest of the NEPSY-II, three of whom scored above the 51st percentile, one below the 50th percentile, and one below the 2nd

percentile on standard norms (Table 4). On the TOM verbal task, two were impaired (percentile < 2 and < 25), one below average (26–50th percentile), and two in the normal range (percentile > 51). On the experimental RMET-C test, AT-II patients scored significantly lower ($p = 0.006$) than matched healthy controls, missing positive emotions more than controls ($p = 0.03$), but they passed all subtests of the experimental acted-out TOM stories (see Supplement 2). AT-II patients scored an average of 37.6 (SD 9.4) points on the EQ, and 25.1 (SD 9.4) points on the SQ.

AT-III patients scored in the low average range on the affect recognition subtest of the NEPSY-II (z score = − 1.33) and were mildly impaired on the Wechsler ACS Social Perception subtest (z score = − 1.67) and affect naming (z score = − 1.67) (Table 4). Prosody (z score = − 0.66) and recognition of social pairs (z score = − 0.56) fell within normal range. All of the latter were compared to standard norms. On the experimental RMET-C, AT-III patients scored lower than controls ($p < 0.001$) and missed more positive emotions ($p < 0.001$). All six AT-III patients passed the subtests of experimental acted-out TOM stories (e.g., second order belief tasks, emotional inference tasks), but three were impaired on the TOM composite portion of the standard NEPSY-II (< 25th percentile on standard norms), and three were below average on the verbal component of the TOM task (one < 5th percentile, two 25–50th percentile on standard norms). The scores for EQ and SQ were all within published experimental norms [42], averaging 36.5 (SD 9.9) points on the EQ and 22.2 (SD 7.5) points on the SQ.

Table 4 Standard social cognition test results

	School age (group AT-II, $n = 7$)		Adolescents and young adults (group AT-III, $n = 6$)	
Cognitive domain	Mean score	*Test*	Mean score	*Test*
Social cognition standard tests				
Affect recognition (ss)	9[a]	NEPSY-II	**6**	NEPSY-II
TOM composite (%ile)	**1, < 2%**	NEPSY-II	**1, < 5%**	NEPSY-II
	1, < 50%		**1, < 10%**	
	3, 51–75%		**1, < 25%**	
TOM verbal (%ile)	**1, < 2%**	NEPSY-II	**1, < 5th%**	NEPSY-II
	1, < 25%		**2, 25–50%**	
	1, 26–50%			
	1, 50–75%			
	1, >75%			
Social perception (ss)	*n/a*	*n/a*	**5**[a]	ACS
Social perception affect naming (ss)	*n/a*	*n/a*	**5**	ACS
Social perception prosody (ss)	*n/a*	*n/a*	8	ACS
Social perception pairs (ss)	*n/a*	*n/a*	8	ACS
Social cognition experimental tests				
Emotion recognition from faces	***P* = 0.006**	RMET-C	***p* < 0.001**	RMET-C
Total correct (patient mean score/control mean score)	(16.5/21.8)		(16.3/21.2)	
Positive emotions	***p* = 0.03** (1.8/4.6)	RMET-C	***p* = < 0.001** (2.3/1.2)	RMET-C
Negative emotions	*p* = n.s. (6.6/7.6)	RMET-C	*p* = n.s. (6.6/7.2)	RMET-C
Neutral emotions	*p* = n.s. (8.0/9.5)	RMET-C	***p* < 0.5** (7.3/8.9)	RMET-C

Bold font = significant difference compared to controls, or scores > 1SD below mean on standard norms. Items in italics = test not available for age group. Note: Patients in age group AT-I were not administered standard tests of social cognition. Results of experimental TOM stories are in the manuscript. For test details see Supplement 1

Abbreviation: *ACS* Wechsler Advanced Clinical Solutions Social Perception test, *n/a* not available, *NEPSY* Developmental Neuropsychological Assessment Scale, *n.s.* not significant, *RMET-C* Reading the Mind in the Eyes Test-Child Version, *ss* scaled score, *TOM* Theory of Mind

[a] Test was performed by ≤ 3 patients

Neuropsychiatry

On the CNRS, 85% of parents ($n = 17$) indicated presence of symptoms in the attention domain followed by difficulties with emotion regulation (75%; $n = 15$), social skills (70%; $n = 14$), psychosis spectrum symptoms (55%; $n = 9$), and autism spectrum (33%; $n = 7$). Whereas there were no reports of hallucinations or delusions, the CNRS psychosis spectrum includes hypermetric behaviors such as illogical thoughts, irrational concerns or false beliefs, and hypometric behaviors including impaired empathy, aloofness or lack of emotional responsiveness, and indifference to self or others. When analyzed for the direction of impairment (overshoot/hypermetria vs undershoot/hypometria) in each domain of the CNRS [43], parents indicated the highest range of severity for social skills undershoot (severity range 1–10; maximum score 12), social skills overshoot (range 1–9; maximum score 12), followed by attention control overshoot (range 1–7, maximum score 12), emotion control overshoot (range 1–7, maximum score 12), autism spectrum undershoot (range 1–3; maximum score 6), and attention control undershoot (range 1–5, maximum score 12). As outlined in Supplement Table 1, we conceptualize the polarity of the symptoms within each domain of the CNRS along the lines of the Positive and Negative Syndrome Scale of Schizophrenia (PANNS [47]). We regard these polarities as potentially important phenomenological descriptors of cerebellar psychopathology, the neurobiology of which remains to be established.

Communication and Social Interaction

Parents completed the SCDC, a three-point Likert Scale questionnaire assessing frequency of social and communication problems. Eighty percent of parents ($n = 17$) indicated some difficulties with social skills or social communication, ranging from minor to moderate scores (range 1–16, maximum score 24).

Standard Behavior Inventories

On the BRIEF, GARS-2, and ADHD Symptom Checklist, parents rated all patients as falling within the normal ranges. Only the adaptability domain on the BASC-2 fell in the at-risk range in AT-III patients (see Supplements 3 for test details).

Developmental Milestones and Individual Education Programs

Parents of five patients reported delayed expressive language development before age 3, and three patients presented with early onset stereotypical behaviors, avoidance of certain textures, and difficulties with social play.

Most attend regular schools with integrated special care and 1-1s, IEP plans, and individual adjustments (e.g., writing boards, computers with adapted mouse, more recess and break time when tired). Some patients (the minority) attend schools for children with special needs only.

When we reviewed the IEP reports for 18 of the 20 patients, it was apparent that there was considerable variability in reporting cognitive measures administered and cognitive domains covered. Fatigue, difficulties with arousal, and "slow thinking" were noted frequently by parents and teachers, but few reports addressed cognitive and behavioral challenges in a systematic and comprehensive manner. This deficit in appreciation of the non-motor challenges faced by AT children was a motivating reason for embarking on this study.

Discussion

This comprehensive study of cognition and emotion in a US cohort of patients with AT replicates and extends our earlier findings in a German cohort [18]. The present investigation provides greater depth and breadth to the understanding of the cognitive and emotional profile in children with AT, with assessments of social cognition, affect, visual-spatial function, and new and broader tests of executive function. We also tested all the domains of the CCAS and considered the issue of school readiness.

Cognitive and Emotional Phenotype in AT

AT-I (Toddlers and Preschoolers)

Cognitive changes in toddlers and preschoolers (group AT-I) were mild and limited to visual-spatial skills. Patients demonstrated borderline impaired scores for perceptional reasoning as well as visual motor integration. Visual memory fell in the low average range. In contrast, the fluid reasoning index (FRI) was unaffected, indicating that these children can apply logic and reasoning to problem -solving and novel situations. Patients performed comparably across both FRI subtests (matrix reasoning, MR; and picture concepts, PC) and showed a particular strength for PC, supporting and complementing results of the perceptual reasoning tasks showing that perceptual visual skills were more of a challenge than visual categorical reasoning tasks. Visual-spatial impairments have been reported previously in children with cerebellar diseases, including difficulties on tasks of visual perception, incomplete appreciation of figural completeness and configuration, and deficits with planning and organization of visual stimuli [10].

The cerebellar vermis (I–IV, and IX) and fusiform gyrus are functionally connected [48], and a PET neuroimaging study in AT reported lower metabolism in the fusiform gyrus (encompassing Brodmann area 36) [49]. These findings are

germane to our AT cohort because vermis dysfunction may impair visually relevant cerebrocerebellar circuits, resulting in the visual perceptual impairments we observed.

In line with results on our previous study [18], patients were also impaired on the Bug Search and Cancellation subtests of the WPPSI-IV, measures of visual search and attention within the executive domain. However, both tests are motor dependent and timed which likely influenced test performance.

AT-II (School Age Children)

Cognitive changes in school age children with AT (group AT-II) were more widespread, with deeper and broader deficits particularly in the visual-spatial domain. They performed in the low average range compared to healthy controls on tests of expressive language (vocabulary), executive function (auditory working memory), and academic abilities (math, spelling, reading). The sum of impairments led to Full Scale IQ scores that were in the lower range of average or bordered on the impaired range. Tests of social cognition (affect recognition from the RMET-C) were impaired in comparison to healthy controls, particularly for positive emotions, and affective dysregulation was reported in some patients.

The deficits in the visual-spatial domain were characterized by problems with visual construction, integration, and reasoning. They had difficulty with the ROCFT copy, producing copies with preservation of basic details drawn in a segmented fashion with loss of overall and internal configuration (Fig. 1) [50, 51] as details were drawn first and placed out of context. These findings are similar to prior descriptions of ROCFT performance in children [10] and adults [8] with cerebellar lesions. The copies of the 3D cube by the AT-II children were also similar to adult cerebellar patients [52] as they were able to copy 2D figures well, but their copies of a 3D cube lacked dimensionality, and were characterized by addition of lines, loss of perspective and perseveration (Fig. 2), a skill generally acquired after the age of 8 years [45]. The distinction between intact performance on the 2D tasks versus impaired 3D copy may be explained by damage to the cerebellar posterior lobe which is linked with cerebral posterior parietal association cortices [53] concerned with internal representations of spatial maps, and with the dorsal premotor cortices [54–56] concerned with motor imagery [57, 58]. Both these cerebral cortical areas are involved in spatial transformation and mental rotation tasks [58, 59].

While not crossing the threshold of impaired performance in this study, executive function deficits have been described repeatedly in children and adults with cerebellar disorders [8, 10, 11, 18], and we previously reported auditory working memory deficits in our study of German AT patients [18]. Cerebellar activation is consistently reported during working memory paradigms (e.g., [23, 60–63].

The AT-II patients were impaired on a task of social cognition (affect recognition from faces) with a significant deficit on decoding positive emotions. These findings were similar to those in our previous study [44] in which adults with cerebellar disorders were impaired in their ability to decode positive emotions from faces. Processing of emotions from faces is subserved by higher order cortices in the temporal lobe, the ventromedial prefrontal cortex (VMPFC) and in the amygdala [64]. The cerebellum is incorporated into all these associative and paralimbic circuits by way of feed forward connections from these cerebral cortical areas to cerebellum via the pons, and by feedback connections from cerebellum through thalamus back to the cerebral cortex [53, 54, 65–67].

Deficits in emotion attribution are believed to be at the core of neuropsychiatric disorders such as schizophrenia and autism spectrum disorder (ASD) [68, 69]. AT parents noted select behavioral changes in their children on an experimental questionnaire designed to detect behavioral symptoms in the cerebellar cohort (CNRS) [43], e.g., attentional control (distractibility, difficulty shifting focus of attention, inattentiveness), emotional control (lability, anxiety, disinhibition, sadness, and dysphoria), and social skills (anger, aggression, oppositional behavior, immaturity, childishness, difficulties with social cues), and some parents indicated symptoms associated with autism spectrum disorder (avoidant behaviors, easy sensory overload).

Standard behavioral questionnaires did not detect the changes indicated on the CNRS. This is in line with findings in our earlier study which showed that the CNRS was able to reveal behavioral changes not reported on standard questionnaires [52]. Patients were also tested on a standardized computer test of attention (Quotient® ADHD System) (http://www.quotient-adhd.com). Scores in comparison to standard norms raised the likelihood of attention deficits not apparent on the BRIEF, GARS-2, or ADHD Symptom Checklist. The Quotient is a timed task, however, and it requires motor skill and was not designed to test AT patients whose motor deficits were likely a confounding factor.

Language remained an area of relative strength, with borderline impaired receptive language scores (comprehension) and expressive language scores in the low average range compared to AT-I patients. These findings stand in contrast to results in our German AT cohort [18] where older AT patients were impaired on expressive and receptive language tests. These differences may be explained by different tests used in the two studies. In addition, our AT patients fared better than expected on the metalinguistic tasks of the TLC-E. Language difficulties are consistently reported in children and adults with diseases of the cerebellum [8, 10–16, 18], children surviving resection of cerebellar tumors have impairments in fluency and narrative [10], and converging evidence indicates that the cerebellum is part of the language network [23, 61–63]. It is possible that our vocabulary tests were not

searching enough in the younger children, and our tests were too limited in the older patients because of time constraints, but this relative sparing in AT will need to be revisited in future studies.

AT-III (Adolescents and Young Adults)

Impairments further deepened and widened for patients in the oldest age group (adolescents, young adults). They showed more severe deficits on the visual-spatial domain, executive dysfunction (auditory working memory and sequencing, word/color interference, set-shifting, categorization errors, perseveration), greater social cognitive deficits (affect recognition from faces), academic impairments, and behavioral difficulties resulting in overall IQ scores falling in the impaired range. Only language remained a relative area of strength, with borderline impaired receptive (comprehension) and low average expressive language scores.

Deficits in Children with AT Conform to the Cerebellar Cognitive Affective Syndrome

AT patients exhibit progressive impairments in spatial cognition, executive function, and affect regulation including deficits in social cognition, with relatively less impairment of linguistic processing. These are the hallmark features of the CCAS described in both adults and children [8–10]. The CCAS arises from damage to the cognitive/limbic regions of the cerebellar posterior lobe, thought to reflect disruption of the cerebellar contribution (the universal cerebellar transform [70, 71]) to distributed neural circuits linking cerebellum with associative and paralimbic regions in the cerebral hemispheres [54, 65, 72, 73].

The deficits in AT evolve over time, coincident with progression of the cerebellar motor syndrome and with more extensive pathology in the cerebellum. The present findings are in line with our previous report in German AT patients [18], with the exception of better performance on language tasks in the older US patients, possibly reflecting differences in test batteries.

Whereas neuroimaging studies in older AT patients show signal alterations outside the cerebellum [18 and 49 for reviews], autopsy studies in genetically confirmed AT cases do not report extra-cerebellar pathology [5, 7]. The few available autopsy studies in patients with genetic confirmation or with decreased levels of AFP combined with increased radiosensitivity radiation assays point to the major neuropathological findings being confined to the cerebellum. These include degeneration of the cerebellar cortex with loss of the internal granular layer, severe Purkinje cell loss, and dislocation as well as empty baskets, with relatively well-preserved deep cerebellar nuclei and inferior olives. There is also degeneration of the posterior columns, specially of the gracile fascicle, and prominent anterior horn cell loss, with axonal degeneration of the peripheral nerves with subsequent muscle atrophy [5, 7]. Given that neuropathology studies in confirmed AT cases to date do not demonstrate extra-cerebellar pathology, it is possible that signal alterations on neuroimaging may be the result of upstream pathology secondary to primary cerebellar degeneration. It therefore seems reasonable to conclude that the cognitive impairments we describe are primarily related to cerebellar injury, particularly since they conform to the definition of the CCAS, the syndrome resulting from pathology in the cerebellum.

There were correlations between total BARS score—a marker of cerebellar motor disability, with FSIQ, visual motor integration (VMI), and expressive vocabulary skills (on the EOWPVT), but the number of patients is small, and calculations were not corrected for multiple comparisons. It may be expected that more widespread cerebellar pathology involving cerebellar motor as well as cognitive areas may result in correlations between cognitive measures and motor skill, but this will need to be explored in future studies with larger numbers of patients and detailed morphometric brain imaging analysis.

Cognitive Phenotype-Genotype Relationship

The clinical presentation in patients with classic AT is not always homogeneous [20]. Affected siblings with identical mutations may experience different rates of disease progression and symptom severity including cognitive symptoms. Approximately 75–85% of patients present with the severe, classic form of AT, defined by either absence or dysfunction of the ATM protein leading to a complete lack of ATM kinase activity [6]. Patients with the mild, variant form of AT retain some ATM kinase activity resulting from either a low level of normal or mutant ATM [2, 5, 6]. The exclusive relationship of ATM kinase activity to disease severity has recently been questioned by reports of patients with mild, atypical AT but absence of ATM protein, no detectable ATM kinase activity, and radiosensitivity comparable to that of patients with severe AT [74, 75].

One of the two AT patients (P15) investigated in this study with variant, mild disease phenotype showed a truncating mutation and no detectable ATM protein, and the other (P16) had a mutation that putatively allowed for some residual ATM kinase transcript. The reason for the partial rescue of the clinical AT phenotype in patients with absence of ATM kinase activity is not known but modifying genes or epigenetic regulation may contribute to this phenomenon [76]. In patients with residual ATM kinase activity, lower ATM kinase activity levels may be sufficient to delay the overall disease progression and result in a milder phenotype. It is also possible that non-genetic factors may contribute to inter-individual differences, such as environmental stimulation and education.

Both our patients with mild motor phenotypes scored well above the mean on the majority of cognitive tasks compared to their age-matched disease cohort (i.e., AT-II and AT-III). This finding suggests that cognitive symptoms are integral to the clinical presentation of AT and, like the motor manifestations, also influenced by the genotype-phenotype relationship.

Environmental Cognitive Impact

In addition to genetic influences, motor impairments in AT may contribute to cognitive deficits because patients are raised in environments that focus on development of their motor abilities, with cognitive training receiving relatively less attention.

Other environmental factors include varying levels of cognitive training in each patient. Some received extensive in-home math, spelling and other cognitive enhancement over and above their school work. It is possible that these additional cognitive interventions may have had a beneficial impact on cognitive performance.

Conclusion

This is the first study of cognition and behavior in a cohort of North American AT patients. We confirm and extend our earlier findings in a German cohort that children with AT manifest the CCAS. We show that cognitive challenges at the outset are mild and reflect visual-spatial difficulties. Deficits deepen and broaden as patients grow older including impairments in the executive, affective, and social cognitive domains, with language variably involved. Our findings suggest that both the motor and the cognitive symptoms conform to a genotype-phenotype relationship. Our patients' families emphasized to us that the CCAS is a source of frustration in the educational and personal setting. Recognition is a prerequisite to intervention and rehabilitation in the school and home setting to maximize compensatory strategies and enhance quality of life. Our results provide empirical evidence for the importance of cognitive and behavioral testing in clinical practice and in the scientific exploration of AT. Further investigations into genotype-phenotype interactions and the mechanisms of motor and cognitive-emotional impairments in AT may open the way to novel therapeutic strategies in this neurodegenerative childhood disorder.

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Compliance with Ethical Standards

Conflict of Interest Dr. Schmahmann consults for Bayer, Biogen, Biohaven, Cadent and Pfizer, and receives royalties for book publications from Elsevier, Oxford, MacKeith, and Springer. The authors declare that they have no conflict of interest.

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